EXECUTIVE SUMMARY

Uniform Formulary Beneficiary Advisory Panel (BAP)

September 27, 2018

UNIFORM FORMULARY DRUG CLASS REVIEWS

I. UF CLASS REVIEWS

A. CORTICOSTEROIDS-IMMUNE MODULATORS: ATOPIC DERMATITIS

1. Atopic Dermatitis—UF Recommendation

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) the following, based on clinical and cost effectiveness:

- UF
  - pimecrolimus (Elidel)
  - dupilumab (Dupixent)
  - tacrolimus (Protopic, generics)
- NF
  - crisaborole (Eucrisa)

2. Atopic Dermatitis—Manual Prior Authorization (PA) Criteria

Manual PA criteria for both crisaborole ointment and dupilumab injection were recommended at the May 2017 P&T Committee meeting.

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) updating the current PA criteria for dupilumab (Dupixent), to require a trial of phototherapy, if feasible, in all new users, due to the AAD 2017 consensus statement on systemic therapies. The Committee also recommended maintaining the current manual PA criteria for crisaborole (Eucrisa), which requires a two-week trial of at least two formulary medium to high potency topical corticosteroids or a TCI first.

a. Eucrisa

<u>No changes from the November 2017 meeting</u>

Manual PA criteria apply to all new users of Eucrisa.

<u>Manual PA criteria</u>: Coverage is approved if all of the following criteria are met:

- Patient has mild to moderate atopic dermatitis

- Prescribed by a dermatologist, allergist, or immunologist

- Patient has a contraindication to, intolerability to, or failed treatment with a two-week trial of at least one medium to high potency topical corticosteroid

AND

- Patient has a contraindication to, intolerability to, or failed treatment with a two-week trial of a second agent including
  - An additional medium - high potency topical corticosteroid OR
  - Topical calcineurin inhibitor (i.e., tacrolimus, Elidel)

Non-FDA-approved uses are NOT approved.

PA does not expire.

b. Dupixent

August 2018 updates are in BOLD.

Manual PA criteria apply to all new users of Dupixent.
Manual PA criteria: Coverage will be approved for initial therapy for 6 months if all criteria are met:

- Patient has moderate to severe or uncontrolled atopic dermatitis

- Patient must be 18 years of age or older

- Prescribed by a dermatologist, allergist, or immunologist

- Patient has a contraindication to, intolerability to, or failed treatment with at least ONE high potency/class 1 topical corticosteroid

- Patient has a contraindication to, intolerability to, or failed treatment with at least ONE systemic immunosuppressant

- **Patient has a contraindication to, intolerability to, inability to access treatment, or failed treatment with Narrowband UVB phototherapy**

Non-FDA-approved uses are NOT approved.

PA expires after 6 months.

Renewal PA criteria: coverage will be approved indefinitely for continuation of therapy if:

- The patient has had a positive response to therapy, e.g., an Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1)

3. Atopic Dermatitis—UF and PA Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) an effective date upon the first Wednesday two weeks after the signing of the minutes in all points of service.

Summary of Physician's Perspective:

Although this is the first formulary review for the class, both Eucrisa and Dupixent were previously reviewed as new drugs in 2017. There are no formulary changes recommended, so patients will be paying the same co-pay.

Eucrisa is currently non-formulary. A survey of Military Health System (MHS) providers felt Eucrisa is marginally effective, and it is appropriate to have a prior authorization (PA) requiring a trial of topical corticosteroids and TCIs (topical calcineurin inhibitors). This requirement is in the current PA.

MHS providers felt Dupixent was effective for severe cases, and acknowledged that a PA requiring a trial of other immunosuppressives would be appropriate. The PA was updated to also include the trial of phototherapy.

Summary of Panel Questions and Comments:

Mr. Hostettler requested the total cost of this therapeutic category to the Department of Defense or Military Health System.

Lt Col Khoury said that total cost was approximately 25-30 million. He later amended that to 25.5 million.

Mr. Hostettler inquired about the reasoning for the 2-week implementation period.

Lt Col Khoury said there were no changes. Those drugs on UF stayed on the UF and NF drugs are staying NF so there are no real changes to patients. The PA criteria only affects new users.

There were no more questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, and UF and PA Implementation Plan for Atopic Dermatitis.

- **Atopic Dermatitis—UF Recommendation**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

  _____ These comments were taken under consideration prior to my final decision

- **Atopic Dermatitis—Manual PA Criteria**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

  _____ These comments were taken under consideration prior to my final decision

- **Atopic Dermatitis— UF and PA Implementation Plan**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

  _____ These comments were taken under consideration prior to my final decision

B. HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS (DAAS)

1. HCV DAAs—UF Recommendation

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) the following, based on clinical and cost effectiveness:

- UF
  - sofosbuvir/velpatasvir (Epclusa)
  - ledipasvir/sofosbuvir (Harvoni)
  - glecaprevir/pibrentasvir (Mavyret)
  - paritaprevir/ritonavir/ombitasvir (Technivie)
  - paritaprevir/ritonavir/ombitasvir/dasabuvir tablets pak (Viekira Pak)
  - paritaprevir/ritonavir/ombitasvir/dasabuvir XR tablets (Viekira XR)
  - sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

- NF
  - daclatasvir (Daklinza)
  - simeprevir (Olysio)
  - sofosbuvir (Sovaldi)
  - grazoprevir/elbasvir (Zepatier)

- Note that as part of this recommendation, the current requirement for a trial of Harvoni prior to another HCV DAA ("step therapy") has been removed. Additionally, no HCV DAA products were recommended for Extended Core Formulary (ECF) addition. For the HCV drug class, ribavirin 200 mg capsules and peginterferon alfa-2a (Pegasys) were designated ECF in November 2012.

2. HCV DAAs—Manual PA Criteria

Manual PA criteria is currently required for all the HCV DAAs, including the use of Harvoni as the step-preferred product. The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) revising the manual PA criteria for new users of Daklinza, Epclusa, Harvoni, Mavyret, Olysio, Sovaldi, Technivie, Viekira XR, Viekira Pak, and Zepatier, to remove the Harvoni step therapy requirement, and simplify the PA criteria by having these drugs on the same PA form.

Additionally, the P&T Committee recommended maintaining separate PA criteria for Vosevi, since it is reserved for treatment-experienced patients. Minor updates to the Vosevi PA criteria were also recommended for new users, including removal of the Harvoni step. Coverage for any HCV DAA is only allowed for the FDA-approved indications or as outlined in the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD/IDSA) HCV guidelines (www.HCVguidelines.org).

a) Daklinza, Epclusa, Harvoni, Mavyret, Olysio, Sovaldi, Technivie, Viekira XR, Viekira Pak, and Zepatier

Changes from the August 2018 meeting will replace current PA criteria in place for the HCV DAAs. Note that the Harvoni step therapy requirement has been removed.

Manual PA criteria apply to all new users of Daklinza, Epclusa, Harvoni, Mavyret, Olysio, Sovaldi, Technivie, Viekira Pak, Viekira XR, and Zepatier.

Manual PA criteria: The HCV DAA is approved if all of the following criteria are met:
- ≥ 18 years of age

- Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious disease physician, or a liver transplant physician

- Patient has laboratory evidence of hepatitis C virus infection

- The HCV genotype is documented (Check box – GT1a, GT1b, GT2, GT3, GT4, GT5, GT6)

Coverage for the HCV DAA is only allowed for the FDA-approved indications or as outlined in the AASLD/IDSA HCV guidelines.

PA expires in 1 year.

b) Vosevi

Changes from the November 2017 meeting are in strikethrough; August 2018 updates are in BOLD and strikethrough.

Manual PA criteria apply to all new users of Vosevi.

Manual PA criteria: Vosevi is approved if all the following criteria are met:

- ≥ 18 years of age and diagnosed with chronic hepatitis C virus (HCV)

- Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician

- Laboratory evidence of chronic hepatitis C

- The HCV genotype is documented. (Check box – GT1a, GT1b, GT2, GT3, GT4, GT5, GT6)

- The patient does not have estimated glomerular filtration rate (eGFR) ≤ 30 mL/min or end-stage renal disease (ESRD) requiring hemodialysis

- The patient will not be receiving concomitant therapy with other hepatitis C drugs or rifampin

- The treatment course will not exceed the maximum duration of treatment of 12 weeks

- **Patient has one of the following:**

  - **Patient has HCV GT 1, 2, 3, 4, 5, or 6 and was previously treated with an HCV regimen containing an NS5A inhibitor (for example, daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, or velpatasvir).**

    OR

- **Patient has HCV GT 1a or 3 and has previously been treated with an HCV regimen containing sofosbuvir with or without an NS5A inhibitor (for example, daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, or velpatasvir).**

~~• Patient cannot use Harvoni (due to HCV GT2 or GT3) other agents (due to decompensation, etc.)~~

~~AND~~

~~• Previously treated with an NS5A inhibitor~~ OR

~~• HCV GT-1a or-3 and treated with sofosbuvir without an NS5A inhibitor~~

Coverage for the HCV DAA is only allowed for the FDA-approved indications or as outlined in the AASLD/IDSA HCV guidelines.

PA expires after 1 year; complete original PA form for renewal of therapy.

3. HCV DAAs—UF and PA Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) DHA send letters to beneficiaries who are affected by the UF decision.

Summary of Physician's Perspective:

This is the fourth time we've reviewed the class, because the treatment guidelines and therapies have been updated frequently. Now that there are single tablet regimens available that target all the HCV genotypes, we are not expecting any major advances in therapy going forward.

The four products recommended for non-formulary placement will be subject to the copay increase. The Committee felt that these drugs should be non-formulary since they are outdated drugs. However, there are fewer than 15 patients on these drugs currently, and it is likely that the patients will have completed their course of therapy by the time the implementation date occurs, which will be in January 2019.

Also, after the meeting we became aware that the manufacturer has voluntarily discontinued production of Technivie and Viekira, however we don't have any patients on these drugs right now.

Since these drugs first came on the market, there has been several improvements in therapy. The drugs that are most commonly used are all on the uniform formulary. Removing the

step therapy for Harvoni ensures that the newer therapies can be used in the appropriate patients.

This is an excellent example of competition bringing improved agents to market, with better outcomes for patients, reduced toxicities, all the while seeing reduced overall costs amongst those agents.

Summary of Panel Questions and Comments:

Mr. Hostettler wanted to understand how the P&T Committee's decision affects the implementation timeframe. Most current users would have completed therapy before the changes are in place. There is also an impact to new patients who may start treatment before the 60-day implementation. He asks if it feasible to put the PA in place "now" for new patients and delay the implementation for current users. This would allow current users to complete their therapy.

Lt Col Khoury believes it will be hard to avoid impacts to patients because it is a phased process. As the information states in the handouts, there are 11 patients on the NF designated agents. There will be no impact to current patients because they will have completed their course of treatment prior to the implementation period. Although he does not believe it is feasible to implement the PA immediately for new patients and delay the implementation for current patients, without an impact to current or new patients at some point, he will take the suggestion back for further review. The problem predicting when a new patient begins therapy and figuring out how to implement your recommendation.

Mr. Hostettler suggested implementing the new PA as soon as the Director, DHA signs the minutes. Then, new patients would not be required to pay the increase in co-pay for the 3rd Tier drugs. Current patient would complete his or her treatment within the 60 days with no negative impact or interruption to treatment.

Lt Col Khoury asked if Mr. Hostettler was suggesting a faster implementation.

Mr. Hostettler replied yes for the actual PA. As previously stated, he is concerned it will affect the treatment of current users. If a faster implementation is problematic, grandfather current users and allow them to complete their therapy.

Lt Col Khoury stated there are significant changes with the PA as well as limitations that will take time to coordinate with our stakeholder.

There were no more questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, and UF and PA Implementation Plan for HCV DAAs.

- **HCV DAAs —UF Recommendation**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

  _____These comments were taken under consideration prior to my final decision

- **HCV DAAs —Manual PA Criteria**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

  _____These comments were taken under consideration prior to my final decision

- **HCV DAAs— UF and PA Implementation Plan**

  Concur: 4 Non-Concur: 1 Abstain: 0 Absent: 1

  Director, DHA:

  _____These comments were taken under consideration prior to my final decision

Additional Panel Questions and Comments

There was additional discussion regarding this drug class.

Mr. Hostettler repeats his suggestion of delaying implementation of the PA for current users to ensure that their therapy is complete and putting the PA in place earlier for new patients to avoid any impact. Conversely, pursue the 60-day implementation but grandfather any patients who start therapy during the 60-days and allow them to complete their therapy under the old PA.

Lt Col Khoury wants to ensure he understands the question. He asked if Mr. Hostettler is recommending DoD grandfather the co-pay for new and current users.

Mr. Hostettler replied yes.

Lt Col Khoury stated historically we do not grandfather the co-pay when there is a change. The historical precedence is when the status changes the co-pay changes as well. However, I will take your recommendation back for further discussion.

C. CORTICOSTEROIDS-IMMUNE MODULATORS: ADRENOCORTICOTROPIC HORMONES (ACTH)

1. Corticosteroids-Immune Modulators: Adrenocorticotropic Hormones (ACTH)—Maintain Current UF Status and PA Criteria.

Background—The P&T Committee previously evaluated the ACTH subclass at the February 2018 meeting. The ACTH subclass is comprised solely of injectable corticotropin (H.P. Acthar Gel). The Committee designated H.P. Acthar with UF status, with manual PA allowing use exclusively for infantile spasms or exacerbation of multiple sclerosis (MS) and only after failure of or intolerance to a course of corticosteroids.

At this meeting, the P&T Committee reviewed additional information received from providers and the FDA as it relates to the clinical effectiveness and safety of H.P. Acthar. There was no change to the cost effectiveness conclusion, Uniform Formulary recommendation, or PA criteria from the February 2018 P&T Committee meeting.

A comprehensive review of the evidence for H.P. Acthar Gel's efficacy for infantile spasms, multiple sclerosis exacerbation, other uses, and safety and tolerability across all indications and usages was performed for the February 2018 P&T Committee meeting. That comprehensive body of evidence guided the P&T's decision-making in that meeting.

The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 0 absent) the following:

- Infantile Spasms
    - New information was presented that reaffirms and strengthens the clinical conclusions reached by the P&T Committee at the February 2018 meeting, including the following:
        - Patients with infantile spasms require urgent treatment that is better facilitated by oral corticosteroids, which are widely available, rather than the administratively burdensome H.P. Acthar Gel, due to the limited distribution requirements by the manufacturer.
        - High-dose oral corticosteroids were reaffirmed as a frontline treatment alongside H.P. Acthar Gel and vigabatrin (Sabril).
- MS Exacerbation

- Fundamentals of inflammation were reviewed, reaffirming the appropriateness of the requirement that patients try and fail the safer and more effective corticosteroid treatment option prior to approval of H.P. Acthar Gel for each multiple sclerosis exacerbation.

- Other Uses

  - There was no new data to support changing the original recommendation that uses other than infantile spasms and MS exacerbation be excluded from TRICARE coverage.[1]

- Safety

  - No new information was presented that helped allay the concerns of the Committee regarding the safety profile of H.P. Acthar Gel. New data, however, did cause the Committee to have more safety concerns than previously concluded.

- Other Factors

  - A review of coverage of H.P. Acthar Gel by several commercial health care plans performed for the February 2018 P&T Committee meeting found significant limitations or outright exclusions of H.P. Acthar Gel.

  - For the August 2018 meeting, the P&T Committee reviewed an update to several national health care plans and health systems' coverage policies. Of the 50 pharmacy benefit managers (PBMs) reviewed in the update, 9 health care plans did not cover H.P. Acthar Gel for any indication for their respective beneficiaries.

  - Several prominent health care plans and health systems require a trial of oral corticosteroids prior to using H.P. Acthar Gel for infantile spasms. These include Intermountain Health System in Utah and leading Academic Centers of Excellence in Pediatric Neurology, such as Johns Hopkins and UCLA.

  - The P&T Committee reviewed prior decisions in other drug classes where the recommendation was to require a trial of a drug lacking FDA approval for a particular diagnosis prior to use of a drug that carries FDA approval for that particular diagnosis. One example is that patients with Duchenne's Muscular Dystrophy are required to try or have intolerance to prednisone prior to using deflazacort (Emflaza) [February 2017 DoD P&T Committee Meeting].

- Overall, the Committee evaluated the additional information presented and agreed that no new evidence was presented that would change the clinical conclusions reached by the P&T Committee at the February 2018 meeting. In fact, additional information for

[1] As with any drug, an appeal is available for an eligible covered beneficiary or network or uniformed provider on behalf of the beneficiary to establish clinical justification for the use of a pharmaceutical agent that is not on the Uniform Formulary. See 10 U.S.C. § 1074g.

treatment of infantile spasms further confirmed the appropriateness of a trial of corticosteroids and the importance of early treatment, before using H.P. Acthar Gel. Additional safety concerns for H.P. Acthar Gel were raised by the new information. No changes to the existing manual PA criteria for H.P. Acthar Gel were recommended.

Summary of Physician's Perspective:

The Committee did another review of the clinical data with Acthar. There were no changes to the cost conclusion, UF recommendation, or PA criteria. The PA criteria for Acthar cover both infantile spasms and MS exacerbation, but do require a trial of steroids first.

Summary of Panel Questions and Comments:

Mr. Hostettler thanked the P&T Committee for going back and re-reviewing the information to confirm their recommendation.

There were no more questions or comments from the Panel. The Chair called for a vote for the Corticosteroids-Immune Modulators: Adrenocorticotropic Hormones (ACTH) to maintain current UF Status and PA Criteria

- **ACTH—Maintain Current UF Status and PA Criteria**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

Director, DHA:

These comments were taken under consideration prior to my final decision

II. NEWLY APPROVED DRUGS PER 32 CFR 199.21(G)(5)

A. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF Recommendation

The P&T Committee recommended (group 1 and group 3: 14 for, 0 opposed, 0 abstained, 0 absent and group 2: 13 for, 0 opposed, 0 abstained, 1 absent) the following:

- UF:
  - abiraterone acetate micronized (Yonsa) – Oral Oncologic Agent for Prostate Cancer
  - avatrombopag (Doptelet) – Hematological Agent: Platelets for Thrombocytopenia in Chronic Liver Disease
  - baricitinib (Olumiant) – Targeted Immunomodulatory Biologic (TIB) for Rheumatoid Arthritis
  - binimetinib (Mektovi) – Oral Oncologic Agent for Metastatic Melanoma
  - encorafenib (Braftovi) – Oral Oncologic Agent for Metastatic Melanoma

- epoetin-alfa-epbx (Retacrit) injection – Hematological Agent: Red Blood Cell Stimulant for Erythropoiesis
- erenumab-aooe (Aimovig) injection – Migraine Agent (calcitonin gene-related peptide [CGRP]) for Migraine Headache Prophylaxis
- fostamatinib (Tavalisse) – Hematological Agent: Platelets for Chronic Immune Thrombocytopenia
- hydroxyurea (Siklos) tablets – Hematological Agent: Sickle Cell Anemia Agent for Sickle Cell Anemia in Pediatrics
- pegvaliase-pqpz (Palynziq) injection – Miscellaneous Metabolic Agent for Phenylketonuria
- tolvaptan (Jynarque) – Miscellaneous Nephrology Agent for Rapidly Progressing Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- NF:
  - amantadine extended release tablets (Osmolex ER) – Parkinson's Agent
  - estradiol (Imvexxy) vaginal insert – Miscellaneous Gynecological Agent for Dyspareunia
  - levonorgestrel/ethinyl estradiol/ferrous (Balcoltra) – Oral Combined Contraceptive Agent
  - lofexidine (Lucemyra) – Alpha 2 Antagonist for Mitigation of Symptoms of Opioid Withdrawal
  - oxycodone IR (Roxybond) – Narcotic Analgesic Abuse Deterrent Formulation for Pain

B. Newly Approved Drugs per 32 CFR 199.21(g)(5)—PA Criteria

The P&T Committee recommended (group 1 and group 3: 14 for, 0 opposed, 0 abstained, 0 absent and group 2: 13 for, 0 opposed, 0 abstained, 1 absent) the following:

- Applying manual PA criteria to new users of Yonsa, Osmolex ER, Doptelet, Olumiant, Imvexxy, Mektovi, Braftovi, Lucemyra, Aimovig, Siklos, and Palynziq.

- Applying manual PA criteria to new and current users of Tavalisse and Jynarque.

Full PA Criteria for the Newly Approved Drugs per 32 CFR 199.21(g)(5)

a) abiraterone acetate micronized (Yonsa)

Manual PA criteria apply to all new users of Yonsa.

Manual PA criteria: Yonsa is approved if all criteria are met:

- Provider is aware that Yonsa may have different dosing and food effects than other abiraterone acetate products, due to the risks of medication errors and overdose

- Patient has documented diagnosis of metastatic castration-resistant prostate cancer (mCRPC)

- Patient must receive concomitant therapy with methylprednisolone
- The patient is concomitantly receiving a gonadotropin-releasing hormone (GnRH) analog or has had bilateral orchiectomy

Non-FDA-approved uses are NOT approved, with exception for treatment in patients with metastatic high-risk castration-sensitive prostate cancer (mHRCSPC).

PA does not expire.

b) amantadine extended release tablets (Osmolex ER)

Manual PA criteria apply to all new users of Osmolex ER.

Manual PA criteria: Osmolex ER is approved if all criteria are met:

- Patient is aged 18 years and older
- Patient has a diagnosis of either Parkinson's disease or drug-induced extrapyramidal symptoms
- Patient has had therapeutic failure of a trial of amantadine 300 mg per day given in divided doses using immediate release tablets.

Non-FDA-approved uses are NOT approved.

PA does not expire.

c) avatrombopag (Doptelet)

Manual PA criteria apply to all new users of Doptelet.

Manual PA criteria: Avatrombopag (Doptelet) is approved if all criteria are met:

- Age $\geq$ 18
- Patient is diagnosed with liver disease that has caused severe thrombocytopenia (platelet count less than 50 x 10^9/L)
- Patient is scheduled to undergo a procedure with a moderate to high bleeding risk within 10-13 days after starting avatrombopag
- Patient has no evidence of current thrombosis
- The drug is prescribed by or in consultation with a gastroenterologist

Non-FDA-approved uses are NOT approved.

PA expires in 60 days.

d) baricitinib (Olumiant)

Manual PA criteria apply to all new users of Olumiant.

Manual PA criteria: Baricitinib (Olumiant) is approved if all criteria are met:

- Provider acknowledges that Humira is the preferred TIB to treat rheumatoid arthritis
- Provider acknowledges that if a JAK inhibitor is desired, Xeljanz/Xeljanz XR is an alternative to baricitinib (Olumiant) without the black box warning risk of thrombosis
- Age ≥ 18
- Has diagnosis of moderate to severe active rheumatoid arthritis
- Has a contraindication, inadequate response, or had an adverse reaction to adalimumab (Humira)
- Has a contraindication, inadequate response, or had an adverse reaction to methotrexate
- Has no history of thromboembolic disease
- Is not receiving other potent immunosuppressants (e.g., azathioprine or cyclosporine)
- May not be used concomitantly with other TIB agents except for Otezla
- Must be prescribed by or in consultation with a rheumatologist

Non-FDA-approved uses are NOT approved.

PA does not expire.

e) binimetinib (Mektovi)

Manual PA criteria apply to all new users of Mektovi.

Manual PA criteria: Mektovi is approved if all criteria are met:

- Age ≥ 18 years
- Has unresectable or metastatic melanoma
- Has confirmed BRAF V600E or BRAF V600K mutation by an FDA-approved test
- Mektovi is being taken in combination with Braftovi
- Patient is not on concurrent dabrafenib (Tafinlar), trametinib (Mekinist), vemurafenib (Zelboraf), nor cobimetinib (Cotellic)
- Prescribed by or in consultation with an oncologist

Non-FDA-approved uses are NOT approved.

PA does not expire.

f) encorafenib (Braftovi)

Manual PA criteria apply to all new users of Braftovi.

Manual PA criteria: Braftovi is approved if all criteria are met:

- Age ≥ 18 years
- Has unresectable or metastatic melanoma
- Has confirmed BRAF V600E or BRAF V600K mutation by an FDA-approved test
- Braftovi is being taken in combination with Mektovi
- Patient is not on concurrent dabrafenib (Tafinlar), trametinib (Mekinist), vemurafenib (Zelboraf), nor cobimetinib (Cotellic)
- Prescribed by or in consultation with an oncologist

Non-FDA-approved uses are NOT approved.

PA does not expire.

g) erenumab-aooe (Aimovig) injection

Manual PA criteria apply to all new users of Aimovig.

Manual PA criteria: Aimovig is approved if all criteria are met:

- Patient ≥ 18 years old and not pregnant
- Must be prescribed by or in consultation with a neurologist
- Patient has a migraine diagnosis with at least 8 migraine days per month for 3 months
- Patient has a contraindication to, intolerability to, or has failed a 2-month trial of at least ONE drug from TWO of the following migraine prophylactic drug classes:
    - Prophylactic antiepileptic medications: valproate, divalproic acid, topiramate
    - Prophylactic beta-blocker medications: metoprolol, propranolol, atenolol, nadolol
    - Prophylactic antidepressants: amitriptyline, venlafaxine

Non-FDA-approved uses are NOT approved.

PA expires after 6 months.

Renewal criteria: coverage will be approved indefinitely for continuation of therapy if:

- The patient has shown improvement in migraine prevention (e.g., reduced migraine headache days, reduced migraine frequency, reduced use of acute abortive migraine medication)

h) estradiol (Imvexxy) vaginal insert

Manual PA criteria apply to all new users of Imvexxy.

Manual PA criteria: Imvexxy is approved for 1 year if all criteria are met:

- Patient is a postmenopausal woman with a diagnosis of moderate to severe dyspareunia due to vulvar and vaginal atrophy
- Patient has tried and failed or has a contraindication to a low dose vaginal estrogen preparation (e.g., Premarin vaginal cream, Estrace vaginal cream, Estring, Vagifem)
- Patient does not have any of the following:

- Undiagnosed abnormal genital bleeding
- Pregnant or breastfeeding
- History of breast cancer or currently has breast cancer
- History of thromboembolic disease or currently has thromboembolism

Non-FDA-approved uses are NOT approved.

PA expires in 1 year.

Renewal criteria: Coverage is approved for an additional year if:

- Patient has an improvement in dyspareunia symptom severity

i) fostamatinib (Tavalisse)

Manual PA criteria apply to all new and current users Tavalisse.

Manual PA criteria: Fostamatinib (Tavalisse) is approved if all criteria are met:

- Age ≥ 18
- Has diagnosis of chronic primary idiopathic thrombocytopenic purpura (ITP) whose disease has been refractory to at least one previous therapy (including IVIG, thrombopoietin(s), corticosteroids, and/or splenectomy)
- Has laboratory evidence of thrombocytopenia with average [platelet] count less than 30 x 10^9/L over three discrete tests
- Has no evidence of active or chronic infection
- Has no evidence of secondary thrombocytopenia
- Does not have uncontrolled hypertension
- Has had no cardiovascular event (including but not limited to MI, unstable angina, PE, CVA, and/or NYHA Stage III or IV CHF) within the last 6 months
- Has no evidence of neutropenia or lymphocytopenia
- Prescribed by or in consultation with a hematologist/oncologist
- Tavalisse is not being used concomitantly with other chronic ITP therapy

Non-FDA-approved uses are NOT approved.

PA expires in 120 days.

Renewal criteria: Fostamatinib (Tavalisse) can be renewed for an additional year if all criteria are met:

- Has demonstrated a response to fostamatinib (Tavalisse) as defined by a sustained platelet count > 50 x 10^9/L or an increase in platelet count by ≥ 20 x 10^9/L above baseline. Sustained is defined by two separate tests (at least 2 or more weeks apart) meeting either or both of the aforementioned criteria

- Has no evidence of active or chronic infection

- Has no evidence of secondary thrombocytopenia

- If patient carries a diagnosis of hypertension, it is well controlled according to national guidelines (e.g., JNC 8)

- Has had no cardiovascular event (including but not limited to MI, unstable angina, PE, CVA, and/or NYHA Stage III or IV CHF) within the last 6 months

- Has no evidence of neutropenia or lymphocytopenia.

- Prescribed by or in consultation with a hematologist/oncologist

j) hydroxyurea (Siklos)

Manual PA criteria apply to all new users of Siklos older than 18 years of age.

Automated PA criteria: Siklos will be approved for patients ≤ 18 years of age.

Manual PA criteria: Siklos is approved if all criteria are met:

- Age ≥ 19 years

- The provider documents a patient-specific reason why the patient cannot use the preferred product (generic hydroxyurea or Droxia).

- Acceptable responses would include:

    - The patient has a diagnosis of sickle cell disease AND has swallowing difficulties

- Note that use of Siklos for malignancy (e.g., chronic myelocytic leukemia or other cancers) is not approved

Non-FDA-approved uses are NOT approved.

PA expires after 1 year.

Renewal criteria: Coverage will be approved indefinitely if all of the following apply:

- Patient continues to have swallowing difficulties that preclude the use of hydroxyurea 200 mg, 300 mg, 400 mg, or 500 mg capsules

- Patient has been monitored and has had at least two laboratory draws in the last year and has not developed hematologic toxicity (Toxic hematologic ranges: Neutrophils < 2,000/mm3; platelets < 80,000/mm3; hemoglobin < 4.5 g/dL; and reticulocytes < 80,000/mm3 if hemoglobin is < 9 g/dL)

- Patient has achieved a stable dose with no hematologic toxicity for 24 weeks

k) lofexidine (Lucemyra)

Manual PA criteria apply to all new users of Lucemyra.

Manual PA criteria: Lucemyra is approved if all criteria are met:

- Lucemyra is prescribed for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation

- Patient is ≥ 18 years old

- Lucemyra will not be prescribed for longer than 14 days

- The provider documents a patient-specific reason why the patient cannot use the preferred product, clonidine. Acceptable responses include that the patient has experienced orthostatic hypotension or severe bradycardia with previous clonidine use

Non-FDA-approved uses are NOT approved (e.g., blood pressure control, nicotine withdrawal, Tourette syndrome, or ADHD).

PA expires after 3 months.

Renewal criteria: Renewal of therapy will not be allowed

l) pegvaliase-pqpz (Palynziq)

Manual PA criteria apply to all new users of Palynziq.

Manual PA criteria: Palynziq is approved for initial therapy if all criteria are met:

- Patient is ≥ 18 years of age
- Patient has uncontrolled blood phenylalanine concentrations > 600 micromol/L on at least one existing treatment modality (e.g., restriction of dietary phenylalanine and protein intake, or prior treatment with Kuvan [sapropterin dihydrochloride tablets and powder for oral solution])
- Palynziq is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases)
- Provider acknowledges and has educated the patient on the risk of anaphylaxis
- Patient has a prescription for self-administered SQ epinephrine
- Patient is not using Palynziq concomitantly with Kuvan

Non-FDA-approved uses are NOT approved.

PA expires in 6 months.

Renewal criteria (maintenance/continuation therapy): Coverage will be approved for 1 year if:

- The patient's blood phenylalanine concentration is ≤ 600 micromol/L OR
- The patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting Palynziq therapy) AND
- Patient is not using Palynziq concomitantly with Kuvan

m) tolvaptan (Jynarque)

Manual PA criteria apply to all new and current users of Jynarque.

Manual PA criteria: Jynarque is approved if all criteria are met:

- Age ≥ 18
- Jynarque is prescribed by or in consultation with a nephrologist

- Provider acknowledges that Jynarque requires liver function monitoring with evaluation of transaminases and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter

- Patient has rapidly progressing autosomal dominant polycystic kidney disease (ADPKD, defined as reduced or declining renal function [i.e., glomerular filtration rate {GFR} less than or equal to 65 mL/min/1.73 m^2] and high total kidney volume [i.e., greater than or equal to 750ml])

- Patient does not have Stage 5 chronic kidney disease (CKD) [GFR < 15 mL/min/1.73 m^2]

- Patient is not receiving dialysis

- Patient is not currently taking Samsca (tolvaptan)

Non-FDA-approved uses are NOT approved.

PA does not expire.

4. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF and PA Implementation Plan

The P&T Committee recommended (group 1 and group 3: 14 for, 0 opposed, 0 abstained, 0 absent; and group 2: 13 for, 0 opposed, 0 abstained, 1 absent) an effective date upon the first Wednesday two weeks after signing of the minutes in all points of service.

Summary of Physician's Perspective:

We reviewed 16 new drugs at this meeting; with 11 recommended for UF status, and 5 recommended for non-formulary placement. For the drugs recommended for non-formulary status, several of them fall into classes that have already been reviewed by the P&T Committee, where there are cost effective alternative products already available in the class.

For this review, 13 drugs have PA recommended. Six of these drugs fall into classes that have already been reviewed and have existing PA requirements.

Several of the new drugs this time were evaluated for orphan diseases or unique indications that the P&T Committee had not previously reviewed. The PA requirements overall were to ensure that the drugs are being used in accordance with the product labeling.

Out of these 13 drugs with PAs, 11 will have the PA apply to new users only, so current users will be grandfathered. For two drugs (Tavalisse for ITP and Jynarque for autosomal polycystic kidney disease) the PA will apply to new and current users (or a "no grandfathering scenario").

The Committee was concerned that there are monitoring requirements for these two drugs due to safety issues, and wanted to ensure current patients are receiving the appropriate monitoring.

There were a couple of comments made at the meeting for some of the drugs recommended to have Prior Authorization:

- Aimovig (for migraine): This is the first drug in a new therapeutic class, and more products are in the pipeline. Due to the potential for high numbers of patients to be impacted if a PA were to be implemented several months after market introduction, the PA was placed administratively close after launch, after consultation with a specialist. The PA does require a trial of commonly used preventive products first, which is consistent with current migraine headache guidelines. Currently we have over 600 patients on this drug.

- Palynziq (for PKU): PA criteria were recommended here also due to safety concerns, specifically anaphylaxis. A REMS program from the FDA requires that the patient also receive an Epi Pen with the prescription. We have made arrangements to ensure the Epi Pen can be dispensed at the time Palynziq is being dispensed.

Summary of Panel Questions and Comments:

Mr. Hostettler inquired as to the number of patients currently utilizing these products.

Lt Col Khoury said that most of the products have 1-20 users but erenumab-aooe (Aimovig) has 600 users.

Mr. Hostettler asked about Osmolex ER. Is there any difference in side effects between the long acting and the immediate release? Are there any clinical differences between two products?

LCDR Hansen said that the data that was reviewed show no difference between two agents. Lt Col Khoury also stated for this product that there are no utilizers.

Mr. Hostettler asked, regarding the estradiol (Imvexxy), whether all of the other products that LCDR Hansen mentioned, are all these UF products.

Lt Col Khoury said that yes they were.

Regarding Implementation Criteria: Mr. Hostettler stated that the P&T Committee has managed to get all of these new approved drugs done with 2 weeks but the earlier discussion on HCV DAAs needed a 60-day implementation.

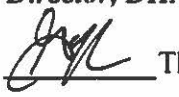
Lt Col Khoury stated that the drugs on the earlier topic required changes including forms that need to be modified, so it requires more time. This one has a new form and few, if any, patients.

There were no more questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, and UF and PA Implementation Plan for Newly Approved Drugs.

- **Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF Recommendation**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

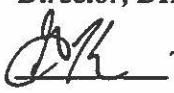
  Director, DHA:

   These comments were taken under consideration prior to my final decision

- **Newly Approved Drugs per CFR 199.21 (g)(5) – PA Criteria**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

   These comments were taken under consideration prior to my final decision

- **Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF and PA Implementation**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

   These comments were taken under consideration prior to my final decision

III. UTILIZATION MANAGEMENT

1. PA Criteria and Step Therapy

Updates to the step therapy and manual PA criteria for several drugs were recommended by the P&T Committee due to a variety of reasons, including expanded FDA indications and drug shortages. The updated manual PAs outlined below will apply to new users.

a) **Epinephrine Auto-Injectors: Auvi-Q Temporary Removal of Manual PA Criteria—** The Auvi-Q device includes audible voice instructions and has a needle that automatically retracts following injection. Manual PA criteria were previously recommended for all epinephrine auto-injectors, including Epi-Pen, generic epinephrine auto-injectors, and Auvi-Q, at the February 2017 P&T Committee meeting. The PA requirements for Epi-Pen were administratively removed on May 23, 2018, due to a national shortage. There have

been continued shortages of Epi-Pen, and intermittent availability of generic epinephrine auto-injectors.

Although Auvi-Q is significantly more expensive than Epi-Pen, the manual PA requirements for Auvi-Q will be temporarily lifted, but re-instated administratively when the supply of Epi-Pen and generic epinephrine auto-injectors has stabilized. The Committee acknowledged, however, that it is doubtful that the current Auvi-Q supply will support the volume required to replace Epi-Pen.

b) **Renin Angiotensin Antihypertensive Agents (RAAs): candesartan and candesartan/HCTZ Step-Therapy—**Step therapy in the RAAs class requires a trial of losartan, telmisartan, valsartan, or irbesartan, or their respective combinations with hydrochlorothiazide (HCTZ), prior to use of non-step-preferred angiotensin receptor blockers (ARBs). Two ARBs, candesartan and irbesartan, are approved for treating heart failure with reduced ejection fraction (HFrEF), in addition to hypertension. Candesartan and candesartan/HCTZ are currently designated as UF but non-step-preferred.

There is currently a national recall of valsartan, due to contamination with a carcinogen. There is no immediate risk to patients currently taking valsartan. However, availability of valsartan lots not affected by the recall are in limited supply, and it remains uncertain as to when the shortage will be resolved.

A group of MHS cardiologists has requested removing the step therapy requirement for candesartan, due to the valsartan recall. Cost-effective formulations of candesartan and candesartan/HCTZ are now available. Candesartan and candesartan/HCTZ will now be designated as step-preferred, with the step therapy criteria and medical necessity criteria for the remaining non-step-preferred RAAs updated accordingly.

c) **Oncological Agents for unresectable or metastatic melanoma: dabrafenib (Tafinlar), trametinib (Mekinist), and vemurafenib (Zelboraf) Manual PA criteria—**These drugs are approved for treating unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. They are exclusively used in unique pair combinations of a specific BRAF drug with a specific mitogen-activated extracellular signal regulated kinase (MEK) inhibitor. Due to the risk of enhanced toxicity if other combinations of BRAF with MEK inhibitors are administered together, the PA criteria were updated to prevent the use of concurrent therapies outside of the FDA-approved combination.

Criteria were also updated for dabrafenib (Tafinlar) and trametinib (Mekinist) to include the new FDA-approved indication for combination use for locally advanced or metastatic anaplastic thyroid cancer without satisfactory locoregional treatment options.

d) **Oncological Agents: Prostate II - enzalutamide (Xtandi)—**In August 2012, manual PA criteria were recommended for Xtandi. PA criteria were updated in February 2015 to remove the co-administration requirement of docetaxel. Xtandi is now FDA-approved for treatment of castration-resistant prostate cancer, and does not require the presence of metastatic disease. Additionally, the PA criteria were also updated to include new product

labeling that requires the patient receive concomitant therapy with a gonadotropin-releasing hormone (GnRH) analog, or have had bilateral orchiectomy.

e) **Targeted Immunomodulatory Biologics (TIBs): Tofacitinib (Xeljanz/Xeljanz XR)—** The TIBs were reviewed in August 2014, with step therapy requiring a trial of adalimumab (Humira) first. Xeljanz was originally approved for treating rheumatoid arthritis. In February 2018, PA criteria were updated to add the indication for active psoriatic arthritis in adults. The PA criteria were further expanded to include a new FDA-approved indication of ulcerative colitis.

2. Updated Manual PA Criteria

The P&T Committee recommended the following:

- (12 for, 0 opposed, 0 abstained, 2 absent) to temporarily remove the manual PA criteria for Auvi-Q, until adequate supply of the Epi-Pen auto-injector has been established.

- (14 for, 0 opposed, 0 abstained, 0 absent) updates to the manual PA criteria and step therapy for candesartan and candesartan/HCTZ.

- (13 for, 0 opposed, 0 abstained, 1 absent) updates to the manual PA criteria for Tafinlar, Mekinist, Zelboraf, Xeljanz/Xeljanz XR, and Xtandi.

3. Updated Manual PA Criteria and PA Renewal Criteria—PA Implementation Plan

The P&T Committee recommended the following implementation periods:

- (12 for, 0 opposed, 0 abstained, 2 absent) and (14 for, 0 opposed, 0 abstained, 0 absent) To administratively implement the removal of manual PA requirements for Auvi-Q and to designate candesartan and candesartan/HCTZ as step-preferred.

- (13 for, 0 opposed, 0 abstained, 1 absent) Updates to the current PAs for Tafinlar, Mekinist, Zelboraf, Xeljanz, Xeljanz XR, and Xtandi become effective on the first Wednesday two weeks after the signing of the minutes.

Summary of Physician's Perspective:

<u>Epi pen and Auvi Q: Removal of PA requirements</u>

The Committee does want to respond quickly in the event of a compelling national shortage. This is why the PA requirements for EPI PEN and the generic pen were administratively removed back in May. For Auvi Q, we actually implemented the recommendation to remove the PA on one week after the P&T mtg. We would like to comment that other commercial health plans, including Walgreens have also recently loosened their restrictions on Auvi Q, so

it is unlikely that Auvi Q stock will be able to meet the needs of all the patients who may not be able to obtain Epi-Pen.

Valsartan shortage and removal of candesartan step therapy

This is another example of where the Committee wanted to react quickly. There are several drugs that are first-line treatments for hypertension, including ACE inhibitors and other ARBs, besides valsartan. The overall risk of developing cancer with valsartan is low. The FDA estimates that there would be one additional cancer case over the lifetime of 8,000 patients taking the highest valsartan dose over four years.

However, because candesartan is the only other ARB with an additional indication for CHF, we implemented the change in step therapy one week after the August meeting. We do want to respond quickly when these types of issues come up.

Summary of Panel Questions and Comments:

Mr. Ostrowski asked, regarding the Epi-pen, when the P&T Committee makes the administrative change back after it has stabilized is there any effect on the beneficiary such as copay difference.

Lt Col Khoury said that once the shortage has been resolved, we want them to go back to the Epi-pen because of the cost effectiveness relative to the Auvi-Q. If someone is on the Epi-pen, there will be no effect as long as they're able to get the drug.

Mr. Ostrowski asked if the cost of the patient is the same.

Lt Col Khoury said that the Epi-pen is on the formulary but is not sure about Auvi-Q. He'll need to confirm that. The PA is what we're changing, not the copay. In order to get the Auvi-Q, you had to try and fail the Epi-pen first so we're removing that requirement. It didn't make sense to require the use of Epi-pen if it wasn't available.

Lt Col Khoury said that there is an alternate, based on what we're seeing supply-wise, but they also expect an issue with the Auvi-Q supply as well. They don't expect that all of the people having issues obtaining the Epi-pen are going to have their problems solved by going to Auvi-Q but we didn't want to have a restriction keeping them from getting it.

Mr. Hostettler appreciates that the P&T Committee took action and did so quickly. Is Auvi-Q is non-formulary.

Lt Col Khoury believes that it is NF but will need to verify that.

Mr. Hostettler said that leaves patients with no formulary product for an extremely important drug. Administratively, is there any way to ensure that is a formulary option available? There has been a shortage for a long time and it is getting worse.

Lt Col Khoury will take that back and verify before the close of the meeting. He then confirmed Auvi-Q is formulary.

Mr. Hostettler had a question on the valsartan issue as well. There are no plans to reverse decision once the valsartan issue is resolved, correct? The P&T Committee is not going to put candesartan back in?

Lt Col Khoury said that this was correct, there are no reversals planned.

There were no more questions or comments from the Panel. The Chair called for a vote on the Manual PA and PA Renewal Criteria and the Manual PA and PA Renewal Implementation Plan for Utilization Management of several drugs.

- **Updated Manual PA Criteria and PA Renewal Criteria – Auvi-Q**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

  _____ These comments were taken under consideration prior to my final decision

- **Updated Manual PA and PA Renewal Implementation Plan -**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

  Director, DHA:

  _____ These comments were taken under consideration prior to my final decision

Mr. Ostrowski concludes the meeting. He thanks the P&T Committee for their work and all those attending the meeting.

(Meeting Concludes)

Appendix A – Table of Implementation Status of UF Recommendations/Decisions Summary
Appendix B – Brief Listing of Acronyms Used in this Summary
Appendix C – Private Citizen Comments - US WorldMeds
Appendix D – Private Citizen Comments – Sidley Austin LLP on behalf of Mallinckrodt Pharmaceuticals

Appendix A

Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action	UF Medications	Nonformulary Medications	Implement Date	Notes and Unique Users Affected
Aug 2018	**Corticosteroids -Immune Modulators: Atopic Dermatitis**	UF Class Review	UF ▪ pimecrolimus (Elidel) ▪ dupilumab (Dupixent) injection ▪ tacrolimus (Protopic, generics) ▪	NF ▪ crisaborole (Eucrisa) ointment	2 weeks after signing of the minutes	▪ Manual PA criteria applies to all new users for dupilumab (Dupixent) ▪ Updates made to the Dupixent PA ▪ No changes recommended to the current Eucrisa PA criteria Unique Users Affected None
Aug 2018	**Hepatitis C Virus Direct-Acting Antivirals**	UF Class review Class previously reviewed in Feb 2017, May 2015, Nov 2012; New drug review in Nov 2017	UF ▪ sofosbuvir/velpatasvir (Epclusa) ▪ ledipasvir/sofosbuvir (Harvoni) ▪ glecaprevir/ pibrentasvir (Mavyret) ▪ paritaprevir/ritonavir/ ombitasvir (Technivie) ▪ paritaprevir/ritonavir/ ombitasvir/dasabuvir XR tablets (Viekira XR) ▪ dasabuvir tablets pak (Viekira Pak) ▪ sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	NF ▪ daclatasvir (Daklinza) ▪ simeprevir (Olysio) ▪ sofosbuvir (Sovaldi) ▪ grazoprevir/elbasvir (Zepatier)	60 days	▪ Manual PA required ▪ Previous requirement for step therapy with Harvoni removed ▪ PA criteria simplified for all the DAAs except Vosevi ▪ Vosevi separate PA form due to unique FDA indication Unique Users Affected Mail – 3 MTF – 3 Retail – 5 Total – 11

Table of Implementation Status of UF Recommendations/Decisions Summary

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Aug 2018	**Hepatitis C Virus Direct-Acting Antivirals**	UF Class review Class previously reviewed in Feb 2017, May 2015, Nov 2012; New drug review in Nov 2017	UF ▪ sofosbuvir/velpatasvir (Epclusa) ▪ ledipasvir/sofosbuvir (Harvoni) ▪ glecaprevir/ pibrentasvir (Mavyret) ▪ paritaprevir/ritonavir/ ombitasvir (Technivie) ▪ paritaprevir/ritonavir/ ombitasvir/dasabuvir XR tablets (Viekira XR) ▪ dasabuvir tablets pak (Viekira Pak) ▪ sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	NF ▪ daclatasvir (Daklinza) ▪ simeprevir (Olysio) ▪ sofosbuvir (Sovaldi) ▪ grazoprevir/elbasvir (Zepatier)	60 days	▪ Manual PA required ▪ Previous requirement for step therapy with Harvoni removed ▪ PA criteria simplified for all the DAAs except Vosevi ▪ Vosevi separate PA form due to unique FDA indication Unique Users Affected Mail – 3 MTF – 3 Retail – 5 Total – 11

Appendix B **07/12/2018 BAP Meeting**

Brief Listing of Acronyms Used in this Summary

Abbreviated terms are spelled out in full in this summary; when they are first used, the acronym is listed in parentheses immediately following the term. All of the terms commonly used as acronyms in the Panel discussions are listed below for easy reference. The term "Pan" in this summary refers to the "Uniform Formulary Beneficiary Panel," the group who's meeting in the subject of this report.

- AIDS – Acquired Immunodeficiency Syndrome
- ARI – Alpha Reductase Inhibitor
- BAP – Beneficiary Advisory Panel
- BIA – Budget Impact Analysis
- cAMP – Cyclic Adenosine Monophosphate
- CFR – Code of Federal Regulations
- CFTR – Cystic Fibrosis Transmembrane Conductance Regulator
- CMA – Cost Minimization Analysis
- COPD – Chronic Obstructive Pulmonary Disease
- CT – Cognitive Therapy
- CVOTs – Cardiovascular Outcome Trials
- CYP3A4 – Cytochrome P450 isoforms
- DoD – Department of Defense
- eGFR – Estimated Glomerular Filtration Rate
- EPI – Exocrine Pancreatic Insufficiency
- ER – Extended Release
- FDA – Food and Drug Administration
- G-Tube – Gastronomy-Tube
- GI-2 – Gastrointestinal-2
- GSA – Growth Stimulating Agents
- HCT- Hematrocrit
- HIV – Human Immunodeficiency Virus
- IR – Immediate Release
- JIA – Juvenile Idiopoathic Arthritis
- L – liter
- LDL – Low Density Lipoprotein
- Mg – Milligram
- MTF – Military Treatment Facility
- NDAA – National Defense Authorization Act
- NDC – National Drug Code
- NF – Non Formulary
- NSAIDs – Nonsteroidal Anti-Inflammatory Drugs
- ODE4 – Phosphodiesterase-4
- OIC – Opioid-Induced Constipation
- OTC – Over the Counter
- P&T – Pharmacy and Therapeutics Committee
- PA – Prior Authorization

- PAMORAs – Peripherally Acting Mu Opioid Receptor Antagonists
- PERT – Pancreatic Enzyme Replacement Therapy
- POS – Point of Sale
- rhGH – Recombinant Human Growth Hormone
- SGLT2s – Sodiun Glucose Co-Transporter
- ShoX – Short Stature Homeobox
- SIADH – Syndrome Inappropriate Antidiuretic Hormone
- SNRI – Serotonin Norepinephrine Reuptake Inhibitor
- SSRI – Selective Reuptake Inhibitor
- TIBs – Targeted Immunomodulatory Agents
- TRICARE – Healthcare Network
- UF -0 Uniform Formulary
- XR – Extended Release

US WORLDMEDS PUBLIC COMMENT FOR THE UNIFORM FORMULARY BENEFIT ADVISORY PANEL MEETING SEPTEMBER 27th, 2018

Re: LUCEMYRA® Department of Defense Pharmacy and Therapeutics Committee Preliminary Recommendation

Pursuant to 41 CFR 102–3.140 we seek to provide comment on the preliminary recommendation from the DoD P&T Committee for the Uniform Formulary Beneficiary Advisory Panel for Lucemyra. Specifically, the P&T Committee recommendations for Lucemyra are as follows:

lofexidine (Lucemyra)
Manual PA criteria apply to all new users of Lucemyra.
Manual PA criteria: Lucemyra is approved if all criteria are met:
• Lucemyra is prescribed for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation
• Patient is ≥ 18 years old
• Lucemyra will not be prescribed for longer than 14 days
• The provider documents a patient-specific reason why the patient cannot use the preferred product, clonidine. Acceptable responses include that the patient has experienced orthostatic hypotension or severe bradycardia with previous clonidine use
Non-FDA-approved uses are NOT approved (e.g., blood pressure control, nicotine withdrawal, Tourette syndrome, or ADHD).
PA expires after 3 months.
Renewal criteria: Renewal of therapy will not be allowed

US WorldMeds Comment:
Lucemyra is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. It is the first and only FDA-approved non-opioid medication for the mitigation of opioid withdrawal syndrome.

Especially in the context of our current opioid crisis, it is important that prescribing and formulary authorization criteria reflect clinical judgement and nuances specific to the disease state. We ask the Committee to reconsider PA criteria that have the potential to adversely affect treatment goals for providers and their patients who require acute opioid withdrawal management.

The current PA Criteria require that "*The provider documents a patient-specific reason why the patient cannot use the preferred product, clonidine. Acceptable responses include that the patient has experienced orthostatic hypotension or severe bradycardia with previous clonidine use*". This is clinically unacceptable for the following reasons:

1. Clonidine is not FDA-approved and lacks consistent, evidence-based and standardized clonidine dosing guidelines for opioid withdrawal management. We note that the Lucemyra PA includes specific criteria that "*Non-FDA uses are NOT approved*". We concur that when available, a FDA-approved drug supported by robust clinical efficacy and safety data should take precedence and priority.

2. A 'step-through' requirement for clonidine trial and/or failure places unwarranted burden on providers who are unfamiliar or unwilling to prescribe clonidine off-label. And unnecessary restriction on their patients who otherwise do not have access to the only FDA-approved, non-opioid treatment with proven, evidence-based, standardized dosing and administration instructions. This is especially true for providers, including primary care, who may be uncomfortable or unwilling to prescribe opioid-based treatments to manage withdrawal.

3. There are 4 historical blinded, head-to-head studies that compared clonidine with lofexidine (Lucemyra). All consistently showed similar efficacy and a superior safety profile for lofexidine. A recently published Cochrane Review also concluded no significant efficacy differences between treatment regimens and a better safety profile for lofexidine compared with clonidine. In the

context of opioid withdrawal management, safety and tolerability play a key role in patient retention and increase HCP confidence to engage and manage their patients through this critical treatment step. Note that these four studies are not included in the label.

[Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews 2016*, Issue 5. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub5.], [Carnwath T, Hardman J. Randomised double-blind comparison of lofexidine and clonidine in the outpatient treatment of opiate withdrawal. *Drug and Alcohol Dependence* 1998;50(3):251–4.], [Kahn A, Mumford JP, Rogers GA, Beckford H. Doubleblind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. *Drug and Alcohol Dependence* 1997;44(1):57–61.], [Lin S-K, Strang J, Su L-W, Tsai C-J, Hu W-H. Doubleblind randomised controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal. *Drug and Alcohol Dependence* 1997;48(2):127–33.], [Gerra G, Zaimovic A, Giusti F, Di Gennaro C, Zambelli U, Gardini S, Delsignore R. Lofexidine versus clonidine in rapid opiate detoxification. *J Subst Abuse Treat*. 2001 Jul;21(1):11-7.]

4. A healthcare provider and patient decision to 'tackle' opioid withdrawal is a critical time window that requires the best chance for success. These patients typically are highly sensitive to, and fearful of, opioid withdrawal symptoms. Early and effective withdrawal management is critical to keep patients engaged in withdrawal treatment. Off-label clonidine treatment requires early titration that increases the likelihood of early undertreatment and treatment failure. These are potentially devastating consequences if withdrawal could have been completed but was intentionally inadequate due to step-through restriction of a non-approved medication.

Lucemyra is not a treatment for opioid use disorder (or post-withdrawal addiction treatment). It is the only FDA-approved, non-opioid treatment for mitigation of opioid withdrawal symptoms. Opioid withdrawal symptoms are debilitating and perpetuate opioid use in the majority of chronic opioid users, including patients for whom the initial prescription was for pain.

In summary, we ask the Committee to give patients and their providers the best chance possible to successfully navigate opioid withdrawal.

This includes direct access to Lucemyra as Uniform Formulary and without requirement for step-through of a non-approved medication that lacks standardized, evidence-based dosing and administration for efficacy and safety.

Thank you for your additional consideration of our comments.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUCEMYRA safely and effectively. See full prescribing information for LUCEMYRA.

LUCEMYRA™ (lofexidine) tablets, for oral use
Initial U.S. Approval: 2018

---------- INDICATIONS AND USAGE ----------

LUCEMYRA is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- The usual LUCEMYRA dosage is three 0.18 mg tablets taken orally 4 times daily at 5- to 6-hour intervals. LUCEMYRA treatment may be continued for up to 14 days with dosing guided by symptoms. (2.1)
- Discontinue LUCEMYRA with a gradual dose reduction over 2 to 4 days. (2.1)
- Hepatic or Renal Impairment: Dosage adjustments are recommended based on degree of impairment. (2.2, 2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 0.18 mg. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Hypotension, Bradycardia, and Syncope: May cause a decrease in blood pressure, a decrease in pulse, and syncope. Monitor vital signs before dosing and advise patients on how to minimize the risk of these cardiovascular effects and manage symptoms, should they occur. Monitor symptoms related to bradycardia and orthostasis. When using in outpatients, ensure that patients are capable of self-monitoring signs and symptoms. Avoid use in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure, as well as in patients with marked bradycardia. (5.1)
- Risk of QT Prolongation: LUCEMYRA prolongs the QT interval. Avoid use in patients with congenital long QT syndrome. Monitor ECG in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, hepatic or renal impairment, or in patients taking other medicinal products that lead to QT prolongation. (5.2)
- Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs: LUCEMYRA potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. (5.3)
- Increased Risk of Opioid Overdose after Opioid Discontinuation: Patients who complete opioid discontinuation are at an increased risk of fatal overdose should they resume opioid use. Use in conjunction with a comprehensive management program for treatment of opioid use disorder and inform patients and caregivers of increased risk of overdose. (5.4)
- Risk of Discontinuation Symptoms: Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy, reduce dose gradually. (5.5)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥ 10% and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds at 1-833-LUCEMYRA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

- Methadone: Methadone and LUCEMYRA both prolong the QT interval. ECG monitoring is recommended when used concomitantly. (7.1)
- Oral Naltrexone: Concomitant use may reduce efficacy of oral naltrexone. (7.2)
- CYP2D6 Inhibitors: Concomitant use of paroxetine resulted in increased plasma levels of LUCEMYRA. Monitor for symptoms of orthostasis and bradycardia with concomitant use of a CYP2D6 inhibitor. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUCEMYRA is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The usual LUCEMYRA starting dosage is three 0.18 mg tablets taken orally 4 times daily during the period of peak withdrawal symptoms (generally the first 5 to 7 days following last use of opioid) with dosing guided by symptoms and side effects. There should be 5 to 6 hours between each dose. The total daily dosage of LUCEMYRA should not exceed 2.88 mg (16 tablets) and no single dose should exceed 0.72 mg (4 tablets).

LUCEMYRA treatment may be continued for up to 14 days with dosing guided by symptoms.

Discontinue LUCEMYRA with a gradual dose reduction over a 2- to 4-day period to mitigate LUCEMYRA withdrawal symptoms (e.g., reducing by 1 tablet per dose every 1 to 2 days) *[see Warnings & Precautions (5.5)]*. The LUCEMYRA dose should be reduced, held, or discontinued for individuals who demonstrate a greater sensitivity to LUCEMYRA side effects *[see Adverse Reactions (6.1), Warnings and Precautions (5.1)]*. Lower doses may be appropriate as opioid withdrawal symptoms wane.

LUCEMYRA can be administered in the presence or absence of food.

2.2 Dosage Recommendations for Patients with Hepatic Impairment

Recommended dosage adjustments based on the degree of hepatic impairment are shown in Table 1. *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

Table 1: Dosage Recommendations in Patients with Hepatic Impairment

	Mild Impairment	Moderate Impairment	Severe Impairment
Child-Pugh score	5-6	7-9	> 9
Recommended dose	3 tablets 4 times daily (2.16 mg per day)	2 tablets 4 times daily (1.44 mg per day)	1 tablet 4 times daily (0.72 mg per day)

2.3 Dosage Recommendations for Patients with Renal Impairment

Recommended dosage adjustments based on the degree of renal impairment are shown in Table 2. LUCEMYRA may be administered without regard to the timing of dialysis *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Table 2: Dosage Recommendations in Patients with Renal Impairment

	Moderate Impairment	Severe Impairment, End-Stage Renal Disease, or on Dialysis
Estimated GFR, mL/min/1.73 m^2	30-89.9	< 30
Recommended dose	2 tablets 4 times daily (1.44 mg per day)	1 tablet 4 times daily (0.72 mg per day)

3 DOSAGE FORMS AND STRENGTHS

LUCEMYRA is available as round, peach-colored, film-coated tablets, imprinted with “LFX” on one side and “18” on the other side. Each tablet contains 0.18 mg lofexidine (equivalent to 0.2 mg of lofexidine hydrochloride).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hypotension, Bradycardia, and Syncope

LUCEMYRA can cause a decrease in blood pressure, a decrease in pulse, and syncope *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*. Monitor vital signs before dosing. Monitor symptoms related to bradycardia and orthostasis.

Patients being given LUCEMYRA in an outpatient setting should be capable of and instructed on self-monitoring for hypotension, orthostasis, bradycardia, and associated symptoms. If clinically significant or symptomatic hypotension and/or bradycardia occur, the next dose of LUCEMYRA should be reduced in amount, delayed, or skipped.

Inform patients that LUCEMYRA may cause hypotension and that patients moving from a supine to an upright position may be at increased risk for hypotension and orthostatic effects. Instruct patients to stay hydrated, on how to recognize symptoms of low blood pressure, and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position). Instruct outpatients to withhold LUCEMYRA doses when experiencing symptoms of hypotension or bradycardia and to contact their healthcare provider for guidance on how to adjust dosing.

Avoid using LUCEMYRA in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, and in patients with marked bradycardia.

Avoid using LUCEMYRA in combination with medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension.

5.2 Risk of QT Prolongation

LUCEMYRA prolongs the QT interval.

Avoid using LUCEMYRA in patients with congenital long QT syndrome.

Monitor ECG in patients with congestive heart failure, bradyarrhythmias, hepatic impairment, renal impairment, or patients taking other medicinal products that lead to QT prolongation (e.g., methadone). In patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), correct these abnormalities first, and monitor ECG upon initiation of LUCEMYRA *[see Dosing and Administration (2.1), Adverse Reactions (6.1), Special Populations (8.6)(8.7), Clinical Pharmacology (12.2)]*.

5.3 Increased Risk of Central Nervous System Depression with Concomitant use of CNS Depressant Drugs

LUCEMYRA potentiates the CNS depressive effects of benzodiazepines and can also be expected to potentiate the CNS depressive effects of alcohol, barbiturates, and other sedating drugs. Advise patients to inform their healthcare provider of other medications they are taking, including alcohol.

Advise patients using LUCEMYRA in an outpatient setting that, until they learn how they respond to LUCEMYRA, they should be careful or avoid doing activities such as driving or operating heavy machinery.

5.4 Increased Risk of Opioid Overdose after Opioid Discontinuation

LUCEMYRA is not a treatment for opioid use disorder. Patients who complete opioid discontinuation are likely to have a reduced tolerance to opioids and are at increased risk of fatal overdose should they resume opioid use. Use LUCEMYRA in patients with opioid use disorder only in conjunction with a comprehensive management program for the treatment of opioid use disorder and inform patients and caregivers of this increased risk of overdose.

5.5 Risk of Discontinuation Symptoms

Stopping LUCEMYRA abruptly can cause a marked rise in blood pressure. Symptoms including diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain have also been observed with LUCEMYRA discontinuation. Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy with LUCEMYRA tablets, gradually reduce the dose *[see Dosing and Administration (2.1)]*.

Symptoms related to discontinuation can be managed by administration of the previous LUCEMYRA dose and subsequent taper.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Hypotension, Bradycardia, and Syncope *[see Warnings and Precautions (5.1)]*
- QT Prolongation *[see Warnings and Precautions (5.2)]*
- Central Nervous System Depression *[see Warnings and Precautions (5.3)]*
- Opioid Overdose *[see Warnings and Precautions (5.4)]*
- Discontinuation Symptoms *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to adverse reaction rates observed for another drug and may not reflect the rates observed in practice.

The safety of LUCEMYRA was supported by three randomized, double-blind, placebo-controlled clinical trials, an open-label study, and clinical pharmacology studies with concomitant administration of either methadone, buprenorphine, or naltrexone.

The three randomized, double-blind, placebo-controlled clinical trials enrolled 935 subjects dependent on short-acting opioids undergoing abrupt opioid withdrawal. Patients were monitored before each dose in an inpatient setting.

Table 3 presents the incidence, rounded to the nearest percent, of adverse events that occurred in at least 10% of subjects treated with LUCEMYRA and for which the incidence in patients treated with LUCEMYRA was greater than the incidence in subjects treated with placebo in a study that tested two doses of LUCEMYRA, 2.16 mg per day and 2.88 mg per day, and placebo. The overall safety profile in the combined dataset was similar.

Orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth were notably more common in subjects treated with LUCEMYRA than subjects treated with placebo.

Table 3: Adverse Reactions Reported by ≥10% of LUCEMYRA-Treated Patients and More Frequently than Placebo

Adverse Reaction	LUCEMYRA 2.16 mg[1] (%) N=229	LUCEMYRA 2.88 mg[1] (%) N=222	Placebo (%) N=151
Insomnia	51	55	48
Orthostatic Hypotension	29	42	5
Bradycardia	24	32	5
Hypotension	30	30	1
Dizziness	19	23	3
Somnolence	11	13	5
Sedation	13	12	5
Dry Mouth	10	11	0

[1] Assigned dose; mean average daily dose received was 79% of assigned dose due to dose-holds for out-of-range vital signs.

Other notable adverse reactions associated with the use of LUCEMYRA but reported in <10% of patients in the LUCEMYRA group included:

- Syncope: 0.9%, 1.4% and 0% for LUCEMYRA 2.16 mg/day and 2.88 mg/day and placebo, respectively
- Tinnitus: 0.9%, 3.2% and 0% for LUCEMYRA 2.16 mg/day and 2.88 mg/day and placebo, respectively

Blood pressure changes and adverse reactions after LUCEMYRA cessation

Elevations in blood pressure above normal values (≥ 140 mmHg systolic) and above a subject's pre-treatment baseline are associated with discontinuing LUCEMYRA, and peaked on the second day after discontinuation, as shown in Table 4. Blood pressure values were evaluated for 3 days following the last dose of a 5-day course of LUCEMYRA 2.88 mg/day.

Table 4: Blood Pressure Elevations after Stopping Treatment

	Abrupt LUCEMYRA Discontinuation 2.88 mg (N = 134)		Placebo (N = 129)	
	N at risk	n (%)	N at risk	n (%)
Systolic Blood Pressure on Day 2 after Discontinuation				
≥ 140 mmHg and ≥ 20 mmHg increase from baseline	58	23 (39.7)	37	6 (16.2)
≥ 170 mmHg and ≥ 20 mmHg increase from baseline	58	5 (8.6)	37	0

Blood pressure elevations of a similar magnitude and incidence were observed in a small number of patients (N=10) that had a one-day, 50% dose reduction prior to discontinuation.

After stopping treatment, subjects that were taking LUCEMYRA also had a higher incidence of diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain compared to subjects who were taking placebo.

Sex-specific adverse event findings

Four out of 101 females (4%) had serious cardiovascular adverse events compared to 3 out of 289 (1%) of males assigned to receive LUCEMYRA 2.88 mg per day.

Discontinuations and dose holds due to bradycardia and orthostatic hypotension, which are the most common adverse reactions associated with LUCEMYRA, occurred with a greater incidence in females assigned to receive the highest studied dose of LUCEMYRA, 2.88 mg per day as shown in Table 5.

Table 5: Discontinuations and Dose Holds for Bradycardia and Orthostatic Hypotension by LUCEMYRA Dose and Sex

	LUCEMYRA 2.16 mg	LUCEMYRA 2.88 mg
Male	22/162 (14%)	29/158 (18%)
Female	9/67 (13%)	20/64 (31%)

6.2 Postmarketing Experience

Lofexidine is marketed in other countries for relief of opioid withdrawal symptoms. The following events have been identified during postmarketing use of lofexidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Since lofexidine's initial market introduction in 1992, the most frequently reported postmarketing adverse event with lofexidine has been hypotension *[see Warnings and Precautions (5.1)]*. There has been one report of QT prolongation, bradycardia, torsades de pointes, and cardiac arrest with successful resuscitation in a patient that received lofexidine and three reports of clinically significant QT prolongation in subjects concurrently receiving methadone with lofexidine.

7 DRUG INTERACTIONS

7.1 Methadone

LUCEMYRA and methadone both prolong the QT interval. ECG monitoring is recommended in patients receiving methadone and LUCEMYRA *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

7.2 Oral Naltrexone

Coadministration of LUCEMYRA and oral naltrexone resulted in statistically significant differences in the steady-state pharmacokinetics of naltrexone. It is possible that oral naltrexone efficacy may be reduced if used concomitantly within 2 hours of LUCEMYRA. This interaction is not expected if naltrexone is administered by non-oral routes *[see Clinical Pharmacology (12.3)]*.

7.3 CNS Depressant Drugs

LUCEMYRA potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. Advise patients to inform their healthcare provider of other medications they are taking, including alcohol *[see Warnings and Precautions (5.3)]*.

7.4 CYP2D6 Inhibitor - Paroxetine

Coadministration of LUCEMYRA and paroxetine resulted in 28% increase in the extent of absorption of LUCEMYRA. Monitor for orthostatic hypotension and bradycardia when an inhibitor of CYP2D6 is used concomitantly with LUCEMYRA *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety of LUCEMYRA in pregnant women has not been established. In animal reproduction studies, oral administration of lofexidine during organogenesis to pregnant rats and rabbits caused a reduction in fetal weights, increases in fetal resorptions, and litter loss at exposures below that in humans. When oral lofexidine was administered from the beginning of organogenesis through lactation, increased stillbirths and litter loss were noted along with decreased viability and lactation indices. The offspring exhibited delays in sexual maturation, auditory startle, and surface righting. These effects occurred at exposures below that in humans *[see Animal Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

Increased incidence of resorptions, decreased number of implantations, and a concomitant reduction in the number of fetuses were observed when pregnant rabbits were orally administered lofexidine hydrochloride during organogenesis (from gestation day [GD] 7 to 19) at a daily dose of 5.0 mg/kg/day (approximately 0.08 times the maximum recommended human dose [MRHD] of 2.88 mg lofexidine base on an AUC basis). Maternal toxicity evidenced by increased mortality was noted at the highest tested dose of 15 mg/kg/day (approximately 0.4 times the MRHD on an AUC basis).

Decreased implantations per dam and decreased mean fetal weights were noted in a study in which pregnant rats were treated with oral lofexidine hydrochloride during organogenesis (from GD 7 to 16) at a daily dose of 3.0 mg/kg/day (approximately 0.9 times the MRHD on an AUC basis). This dose was associated with maternal toxicity (decreased body weight gain and mortality). No malformations or evidence of developmental toxicity were evident at 1.0 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis).

A dose-dependent increase in pup mortality was noted in all doses of lofexidine hydrochloride administered orally to pregnant rats from GD 6 through lactation at an exposure less than the human exposure based on AUC comparisons. Doses higher than 1.0 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis) resulted in incidences of total litter loss and maternal toxicity (piloerection and decreased body weight gain). The highest dose tested of 2.0 mg/kg/day (approximately 0.6 times the MRHD on an AUC basis), increased stillbirths as well as decreased viability and lactation indices were reported. Surviving offspring exhibited lower body weights, developmental delays, and increased delays in auditory startle at doses of 1.0 mg/kg/day or higher. Sexual maturation was delayed in male offspring (preputial separation) at 2.0 mg/kg/day and in female offspring (vaginal opening) at 1.0 mg/kg/day or higher.

8.2 Lactation

Risk Summary

There is no information regarding the presence of LUCEMYRA or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Caution should be exercised when LUCEMYRA is administered to a nursing woman.

The developmental and health benefits should be considered along with the mother's clinical need for LUCEMYRA and any other potential adverse effects on breastfed children from LUCEMYRA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

In animal studies that included some fertility endpoints, lofexidine decreased breeding rate and increased resorptions at exposures below human exposures. The impact of lofexidine on male fertility has not been adequately characterized in animal studies *[see Impairment of Fertility (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of LUCEMYRA have not been established in pediatric patients.

8.5 Geriatric Use

No studies have been performed to characterize the pharmacokinetics of LUCEMYRA or establish its safety and effectiveness in geriatric patients. Caution should be exercised when it is administered to patients over 65 years of age. Dosing adjustments similar to those recommended in patients with renal impairment should be considered *[see Dosage and Administration (2.3), Use in Specific Populations (8.7)]*.

8.6 Hepatic Impairment

Hepatic impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration than on AUC values following a single dose. Dosage adjustments are recommended based on the degree of hepatic impairment. *[see Dosage and Administration (2.2), Clinical Pharmacology (12.2)]*.

Clinically relevant QT prolongation may occur in subjects with hepatic impairment *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.2)]*.

8.7 Renal Impairment

Renal impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration than on AUC values following a single dose. Dosage adjustments are recommended based on the degree of renal impairment *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

Only a negligible fraction of the LUCEMYRA dose is removed during a typical dialysis session, so no additional dose needs to be administered after a dialysis session; LUCEMYRA may be administered without regard to the timing of dialysis *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

Clinically relevant QT prolongation may occur in subjects with renal impairment *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.2)]*.

8.8 CYP2D6 Poor Metabolizers

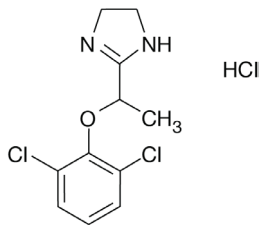
Although the pharmacokinetics of LUCEMYRA have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to LUCEMYRA would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Overdose with LUCEMYRA may manifest as hypotension, bradycardia, and sedation. In the event of acute overdose, perform gastric lavage where appropriate. Dialysis will not remove a substantial portion of the drug. Initiate general symptomatic and supportive measures in cases of overdosage.

11 DESCRIPTION

LUCEMYRA tablets contain lofexidine, a central alpha-2 adrenergic agonist, as the hydrochloride salt. Lofexidine hydrochloride is chemically designated as 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5 dihydro-1*H*- imidazole monohydrochloride with a molecular formula of $C_{11}H_{12}Cl_2N_2O$•HCl. Its molecular weight is 295.6 g/mole and its structural formula is:



Lofexidine hydrochloride is a white to off-white crystalline powder freely soluble in water, methanol, and ethanol. It is slightly soluble in chloroform and practically insoluble in n-hexane and benzene.

LUCEMYRA is available as round, convex-shaped, peach-colored, film-coated tablets for oral administration. Each tablet contains 0.18 lofexidine, equivalent to 0.2 mg of lofexidine hydrochloride, and the following inactive ingredients: 92.6 mg lactose, 12.3 mg citric acid, 1.1 mg povidone, 5.7 mg microcrystalline cellulose, 1.4 mg calcium stearate, 0.7 mg sodium lauryl sulphate, and Opadry OY S 9480 (contains indigo carmine and sunset yellow).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lofexidine is a central alpha-2 adrenergic agonist that binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and decreases sympathetic tone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Single LUCEMYRA doses of 1.44 to 1.8 mg produced maximum mean change from baseline in QTcF (ΔQTcF) of 14.4 msec (upper two-sided 90% CI: 22.3 msec) and 13.6 msec (17.4 msec) for 1.44 and 1.8 mg respectively in healthy normal volunteers.

In a Phase 3 placebo-controlled, dose response study in opioid dependent subjects, LUCEMYRA was associated with a maximum mean prolongation of the QTcF interval 7.3 (8.8) and 9.3 (10.9) msec at doses of 2.16 and 2.88 mg/day, respectively.

Patients with hepatic impairment

Administration of LUCEMYRA to subjects with hepatic impairment was associated with prolongation of the QTc interval, which was more pronounced in subjects with severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

Patients with renal impairment

Administration of LUCEMYRA to subjects with renal impairment was associated with prolongation of the QTc interval, which was more pronounced in subjects with severe renal impairment *[see Use in Specific Populations (8.7)]*

LUCEMYRA coadministered with methadone

LUCEMYRA (2.88 mg/day) coadministered with methadone in 18 methadone-maintained patients (80-120 mg/day) resulted in a maximum mean increase from methadone-alone baseline in QTcF of 9.1 (14.2) msec.

LUCEMYRA coadministered with buprenorphine

LUCEMYRA (2.88 mg/day) coadministered with buprenorphine in 21 buprenorphine-maintained patients (16-24 mg/day) resulted in a maximum mean QTcF increase in QTcF of 15 (5.6) msec compared to a buprenorphine-alone baseline.

In Vitro Binding

LUCEMYRA exhibits *in vitro* binding affinity and functional agonist activity with alpha-2A and alpha-2C adrenoreceptors at concentrations within clinical exposure plasma levels (K_i values of approximately 7.2 nM and 12 nM, and EC_{50} values of 4.9 nM and 0.9 nM, respectively).

12.3 Pharmacokinetics

Absorption

LUCEMYRA is well absorbed and achieves peak plasma concentration 3 to 5 hours after administration of a single dose.

LUCEMYRA shows approximately dose-proportional pharmacokinetics. Administration of LUCEMYRA with food does not alter its pharmacokinetics.

The absolute bioavailability of a single oral LUCEMYRA dose (0.36 mg in solution) compared with an intravenous infusion (0.2 mg infused for 200 minutes) was 72%. Mean LUCEMYRA C_{max} after the oral dose and intravenous infusion was 0.82 ng/mL (at median T_{max} of 3 hours) and 0.64 ng/mL (at median T_{max} of 4 hours), respectively. Mean estimates of overall systemic exposure (AUC_{inf}) were 14.9 ng•h/mL and 12.0 ng•h/mL, respectively.

Distribution

Mean LUCEMYRA apparent volume of distribution and volume of distribution values following the administration of an oral dose and an intravenous dose were 480.0 L and 297.9 L, respectively, which are appreciably greater than total body volume, suggesting extensive LUCEMYRA distribution into body tissue.

LUCEMYRA protein binding is approximately 55%.

LUCEMYRA is not preferentially taken up by blood cells. In a study comparing LUCEMYRA concentrations in plasma and whole blood at the time of peak LUCEMYRA concentrations in human volunteers, it was determined that red blood cells contain approximately 27% the LUCEMYRA concentration of the plasma.

Elimination

Metabolism

From absolute bioavailability results, approximately 30% of the administered LUCEMYRA dose is converted to inactive metabolites during the first pass effect associated with drug absorption from the gut.

LUCEMYRA and its major metabolites did not induce or inhibit any CYP450 isoforms, with the exception of a slight inhibition of CYP2D6 by LUCEMYRA, with an IC_{50} of 4551 nM (approximately 225 times the steady-state C_{max} for LUCEMYRA with 0.72 mg 4 times daily dosing). Any LUCEMYRA interaction with CYP2D6 substrates is not expected to be clinically significant.

LUCEMYRA is metabolized when incubated *in vitro* with human liver microsomes, the major contributor to the hepatic metabolism of LUCEMYRA is CYP2D6, with CYP1A2 and CYP2C19 also capable of metabolizing LUCEMYRA.

Excretion

The elimination half-life is approximately 12 hours and mean clearance is 17.6 L/h following an IV infusion.

LUCEMYRA has a terminal half-life of approximately 11 to 13 hours following the first dose. At steady-state, the terminal half-life is approximately 17 to 22 hours. Accumulation occurs up to 4 days with repeat dosing, following the recommended dosing regimen.

A mass balance study of LUCEMYRA showed nearly complete recovery of radiolabel in urine (93.5%) over 144 hours postdose, with an additional 0.92% recovered in the feces over 216 hours postdose. Thus, it appears that all, or nearly all, of the dose was absorbed, and that the primary route of elimination of the parent drug and its metabolites is via the kidney. Renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose.

Specific Populations

Hepatic Impairment

Hepatic impairment slows the elimination of LUCEMYRA, but exhibits less effect on the peak plasma concentration following a single dose. In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in mild, moderate, and severe hepatically impaired subjects to subjects with normal hepatic function (6 subjects in each hepatic function group), mean C_{max} values were similar for subjects with normal, mild, and moderate hepatic impairment as shown in Table 6.

Table 6: LUCEMYRA Pharmacokinetics in Subjects with Hepatic Impairment

	Normal	Mild Impairment	Moderate Impairment	Severe Impairment
Child-Pugh Class & Score	Normal Function	Class A 5-6	Class B 7-9	Class C 10-15
C_{max} % of normal	100	114	117	166
AUC_{last} % of normal	100	127	190	304
AUC_{∞} % of normal	100	117	185	260
$t_{1/2}$ % of normal	100	139	281	401

Renal Impairment

Renal impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration following a single dose. In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in 8 end-stage renal disease subjects on 3 times weekly hemodialysis to 8 subjects with normal renal function matched for sex, age, and body mass index, mean C_{max} values were similar for end-stage renal disease and normal renal function subjects, indicating no change in maximum LUCEMYRA exposure with renal impairment as shown in Table 7.

The impact of dialysis on the overall pharmacokinetics of LUCEMYRA during a typical 4-hour dialysis was minimal; the drop in LUCEMYRA plasma concentrations produced during the dialysis session was transient, with a rebound to nearly predialysis concentrations after re-equilibration within a few hours following completion of the dialysis cycle *[see Dosage and Administration (2.3), Use in Specific Populations (8.7)]*.

In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in 6 subjects each with normal renal function, mild renal impairment, and moderate renal impairment as well as 5 subjects with severe renal impairment but not requiring dialysis, there were similar increases in mean C_{max} values in subjects with mild and moderate renal impairment in comparison to subjects with normal renal function with additional increase in mean C_{max} values in subjects with severe renal impairment. Mean AUC_{last}, AUC_{∞}, and $t_{1/2}$ increased with severity of renal impairment as shown in Table 7.

Table 7: LUCEMYRA Pharmacokinetics in Subjects with Renal Impairment

	Normal	Mild Impairment	Moderate Impairment	Severe Impairment	ESRD or on dialysis
eGFR (mL/min/1.73 m^2)	≥ 90	60-89	30-59	15-29	< 15
C_{max} % of normal	100	124	117	154	104
AUC_{last} % of normal	100	157	187	272	181
AUC_{∞} % of normal	100	144	173	243	171
$t_{1/2}$ % of normal	100	111	145	157	137

Drug Interaction Studies

LUCEMYRA coadministered with methadone

In a double-blind placebo-controlled study of 23 patients maintained on a methadone dose of 80-120 mg/day and concomitantly administered LUCEMYRA up to 2.88 mg/day, LUCEMYRA did not alter the pharmacokinetics of methadone. LUCEMYRA concentrations may be slightly increased when coadministered with methadone; however, the increase at concentrations expected with recommended dosing is not clinically meaningful *[see Drug Interactions (7.1)]*.

LUCEMYRA coadministered with buprenorphine

In a double-blind placebo-controlled study of 30 subjects maintained on buprenorphine (16-24 mg/day) concomitantly administered LUCEMYRA up to 2.88 mg/day, no pharmacokinetic or pharmacodynamic interactions between LUCEMYRA and buprenorphine were seen.

LUCEMYRA coadministered with oral naltrexone

In an open-label, single-arm study of 24 healthy subjects, oral naltrexone (50 mg/day) did not significantly alter the single-dose pharmacokinetics of LUCEMYRA (0.36 mg). The alteration in steady-state pharmacokinetics of oral naltrexone was statistically significant in the presence of LUCEMYRA. The t_{max} was delayed for both naltrexone and 6ß-naltrexol (2-3 hours), and overall exposure was slightly reduced when naltrexone was administered with LUCEMYRA *[see Drug Interactions (7.2)]*.

LUCEMYRA coadministered with paroxetine

In an open-label, single-sequence study of 24 healthy subjects, the strong CYP2D6 inhibitor paroxetine (40 mg/day) increased LUCEMYRA (0.36 mg) C_{max} and AUC_{∞} by approximately 11% and 28%, respectively *[see Drug Interactions (7.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No adequate long-term animal studies have been completed to evaluate the carcinogenic potential of lofexidine.

Mutagenesis

Lofexidine tested positive in the *in vitro* mouse lymphoma assay. Lofexidine tested negative in the *in vitro* bacterial reverse mutation assay (Ames assay) and in the *in vivo* rat micronucleus assay.

Impairment of Fertility

In a female fertility study in rabbits, fertility was not adversely impacted by administration of lofexidine hydrochloride up to 6.4 mg/kg/day (approximately 0.1 times the MRHD of 2.88 mg on an AUC basis) when administered orally to female rabbits starting 2 weeks prior to mating and through gestation and lactation. However, decreased breeding rate and higher post-implantation loss was observed at this dose, which correlated with higher resorptions and reduced litter size. Maternal toxicity, which included increased mortality rate, reduced body weight gain, and moderate sedation was observed at 6.4 mg/kg/day. The NOAEL for female fertility was 6.4 mg/kg/day and the NOAEL for female-mediated developmental parameters was 0.4 mg/kg/day (approximately 0.005 times the MRHD on an AUC basis).

In a fertility study in rats, fertility was unaffected by administration of lofexidine up to 0.88 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis) via diet to male and female rats prior to mating and to the dams through gestation and lactation. No evidence of maternal toxicity was observed. However, no assessment of sperm or reproductive organs were performed in this study.

Reduced testes, epididymis, and seminiferous tubule weights, as well as delayed sexual maturation of males and females and decreases in the number of corpora lutea and implantations after mating, were noted in offspring of pregnant rats administered lofexidine hydrochloride orally from GD 6 through lactation at exposures less than the human exposure based on AUC comparisons.

14 CLINICAL STUDIES

Two randomized, double-blind, placebo-controlled trials supported the efficacy of LUCEMYRA.

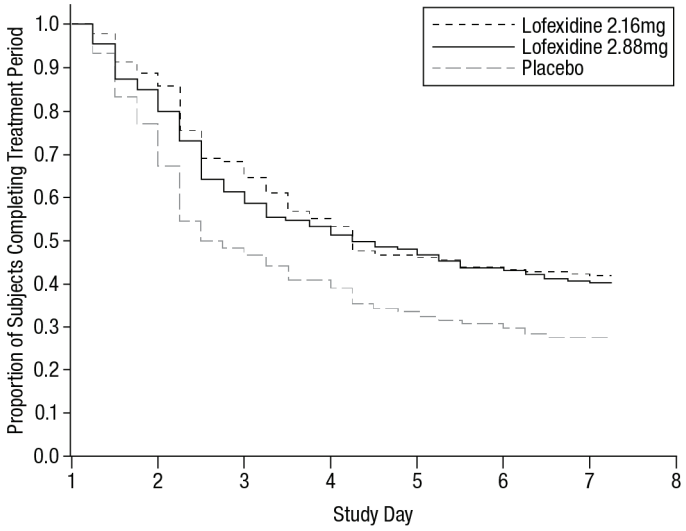
Study 1, NCT01863186

Study 1 was a 2-part efficacy, safety, and dose-response study conducted in the United States in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). The first part of the study was an inpatient, randomized, double-blind, placebo-controlled design consisting of 7 days of inpatient treatment (Days 1 – 7) with LUCEMYRA 2.16 mg total daily dose (0.54 mg 4 times daily) (n=229), LUCEMYRA 2.88 mg total daily dose (0.72 mg 4 times daily) (n=222), or matching placebo (n=151). Patients also had access to a variety of support medications for withdrawal symptoms (guaifenesin, antacids, dioctyl sodium sulfosuccinate, psyllium hydrocolloid suspension, bismuth sulfate, acetaminophen, and zolpidem). The second part of the study (Days 8 – 14) was an open-label design where all patients who successfully completed Days 1 – 7 were eligible to receive open-label treatment with variable dose LUCEMYRA treatment (as determined by the investigator, but not to exceed 2.88 mg total daily dose) for up to an additional 7 days (Days 8 – 14) in either an inpatient or outpatient setting as determined by the investigator and the patient. No patient received LUCEMYRA for more than 14 days.

The two endpoints to support efficacy were the mean Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) total score on Days 1 – 7 of treatment and the proportion of patients that completed 7 days of treatment. The SOWS-Gossop, a patient-reported outcome (PRO) instrument, evaluates the following opioid withdrawal symptoms: feeling sick, stomach cramps, muscle spasms/twitching, feeling of coldness, heart pounding, muscular tension, aches and pains, yawning, runny eyes and insomnia/problems sleeping. For each opioid withdrawal symptom, patients are asked to rate their symptom severity using four response options (none, mild, moderate, and severe). The SOWS-Gossop total score ranges from 0 to 30 where a higher score indicates a greater withdrawal symptom severity. The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on Days 1 – 7.

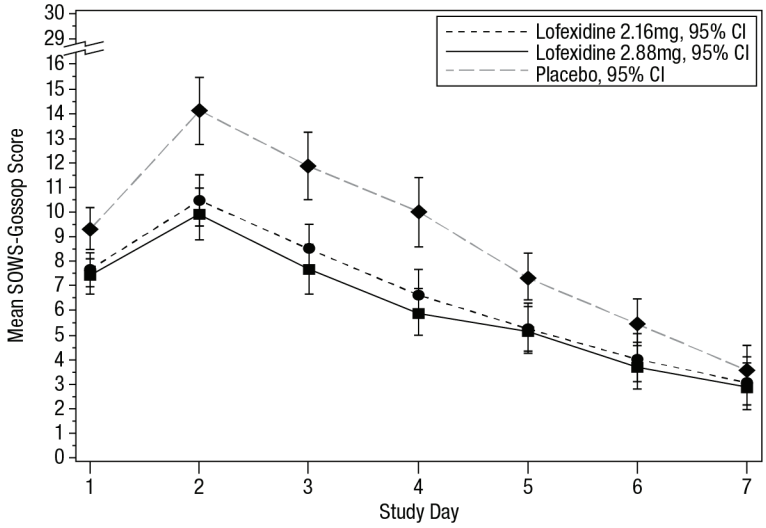
Of the randomized and treated patients, 28% of placebo patients, 41% of LUCEMYRA 2.16 mg and 40% of LUCEMYRA 2.88 mg patients completed 7 days of treatment. The difference in proportion in both LUCEMYRA groups was significant compared to placebo. See Figure 1. Patients in the placebo group were more likely to drop out of the study prematurely due to lack of efficacy than patients treated with LUCEMYRA.

Figure 1: Completion of treatment period for Study 1



The mean SOWS-Gossop scores for Days 1 – 7 were 8.8, 6.5, and 6.1 for placebo, LUCEMYRA 2.16 mg and LUCEMYRA 2.88 mg, respectively. Results are shown in Figure 2. The mean difference between LUCEMYRA 2.16 mg and placebo was -2.3 with a 95% CI of (-3.4, -1.2). The mean difference between LUCEMYRA 2.88 mg and placebo was -2.7 with a 95% CI of (-3.9, -1.6). They were both significant. Symptoms assessed on the SOWS-Gossop were recorded as absent or mild for almost all patients remaining to the end of the assessment period.

Figure 2: Mean SOWS-Gossop Scores for Days 1 – 7 in Study 1



Study 2, NCT00235729

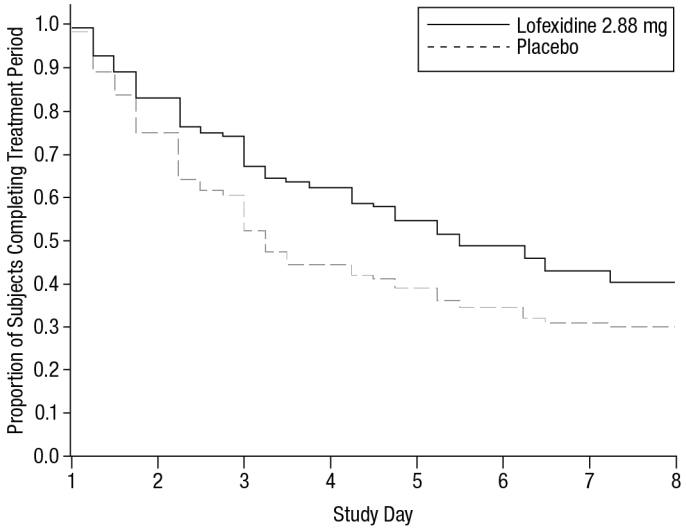
Study 2 was an inpatient, randomized, multicenter, double-blind, placebo-controlled study carried out in the United States in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). Patients were treated with LUCEMYRA tablets (2.88 mg/day [0.72 mg four times daily]) or matching placebo for 5 days (Days 1 – 5). Patients also had access to a variety of support medications for withdrawal symptoms (guaifenesin, antacids, dioctyl sodium sulfosuccinate, psyllium hydrocolloid suspension, bismuth sulfate, acetaminophen, and zolpidem). All patients then received placebo on Days 6 and 7 and were discharged on Day 8.

The two endpoints to support efficacy were the mean SOWS-Gossop total score on Days 1 – 5 of treatment and the proportion of patients that completed 5 days of treatment. The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on Days 1 – 5.

A total of 264 patients were randomized into the study. Of these, 134 patients were randomized to LUCEMYRA 2.88 mg/day and 130 patients to placebo.

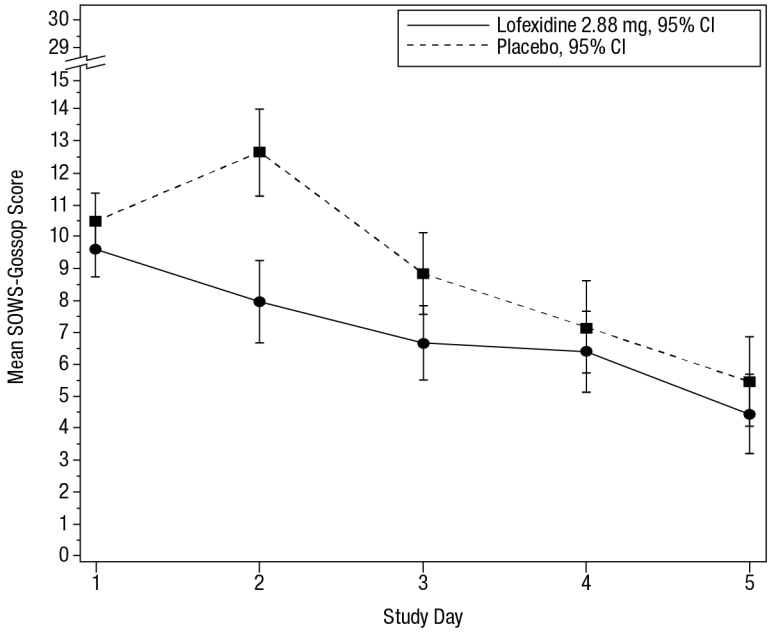
Of the randomized and treated patients, 33% of placebo patients and 49% of LUCEMYRA patients completed 5 days of treatment. The difference in proportion between the two groups was significant. See Figure 3. Patients in the placebo group were more likely to drop out of the study prematurely due to lack of efficacy than patients treated with LUCEMYRA.

Figure 3: Completion of treatment period in Study 2



The mean SOWS-Gossop scores for Days 1 – 5 were 8.9 and 7.0 for placebo and LUCEMYRA 2.88 mg, respectively. Results are shown in Figure 4. The mean difference was -1.9 with a 95% CI of (-3.2, -0.6) and was statistically significant.

Figure 4: Mean SOWS-Gossop Scores for Days 1 – 5 in Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Available as 0.18 mg round, convex-shaped, peach colored, film-coated tablets, imprinted with “LFX” on one side and “18” on the other side; approximately 7 mm in diameter.

Bottles of 36 tablets . . . . . NDC 27505-050-36

Bottles of 96 tablets . . . . . NDC 27505-050-96

Storage

Store in original container at controlled room temperature, 25°C (77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep LUCEMYRA away from excess heat and moisture both in the pharmacy and after dispensing. Do not remove desiccant packs from bottles until all tablets are used. Keep LUCEMYRA and all medicines out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

LUCEMYRA may mitigate, but not completely prevent, the symptoms associated with opioid withdrawal syndrome, which may include feeling sick, stomach cramps, muscle spasms or twitching, feeling of cold, heart pounding, muscular tension, aches and pains, yawning, runny eyes and sleep problems (insomnia). Patients should be advised that withdrawal will not be easy. Additional supportive measures should be clearly advised, as needed.

Hypotension and Bradycardia

Inform patients to be alert for any symptoms of low blood pressure or pulse (e.g., dizziness, lightheadedness, or feelings of faintness at rest or on abruptly standing). Advise patients on how to reduce the risk of serious consequences should hypotension occur (sit or lie down, carefully rise from a sitting or lying position).

Patients being given LUCEMYRA in an outpatient setting should be capable of and instructed on self-monitoring for hypotension, orthostasis and bradycardia and advised to withhold LUCEMYRA doses and contact their healthcare provider for instructions if they experience these signs or related symptoms *[see Warnings and Precautions (5.1)]*.

Advise patients to avoid becoming dehydrated or overheated, which may potentially increase the risks of hypotension and syncope *[see Warnings and Precautions (5.1)]*.

Concomitant Medications

Review with patients all concomitant medications being taken and request that they immediately inform their healthcare provider of any changes in concomitant medications, including any other medications that may be used to treat individual symptoms of withdrawal.

Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs

Inform patients of the increased risk of CNS depression with concomitant use of benzodiazepines, alcohol, barbiturates, or other sedating drugs *[see Warnings and Precautions (5.3)]*.

Advise patients using LUCEMYRA in an outpatient setting that, until they learn how they respond to LUCEMYRA, they should be careful or avoid doing activities such as driving or operating heavy machinery.

Sudden Discontinuation of LUCEMYRA

Inform patients not to discontinue LUCEMYRA without consulting their healthcare provider *[see Warnings and Precautions (5.5)]*.

Risk of Opioid Overdose After Discontinuation of Opioids

Advise patients that after a period of not using opioid drugs, they may be more sensitive to the effects of opioids and at greater risk of overdosing *[see Warnings and Precautions (5.4)]*.

US WorldMeds

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360-10020

PATIENT INFORMATION

LUCEMYRA™ (LEW-sem-EER-uh)
(lofexidine)
tablets

What is the most important information I should know about LUCEMYRA and discontinuing opioid drugs?

LUCEMYRA can cause serious side effects, including low blood pressure (hypotension), slow heart rate (bradycardia), and fainting.

If you get any of the following signs or symptoms, tell your healthcare provider right away:

- low blood pressure
- slow heartbeat
- dizziness
- lightheadedness
- feeling faint at rest or when standing up

If you take LUCEMYRA at home and have any of these signs and symptoms, do not take your next dose of LUCEMYRA until you have talked to your healthcare provider. You should avoid becoming dehydrated or overheated during treatment with LUCEMYRA, which may increase your risk of low blood pressure and fainting. You should also be careful not to stand up too suddenly from lying down or sitting.

When your treatment is complete you will need to stop taking LUCEMYRA gradually or your blood pressure could increase. For more information about side effects, see **"What are the possible side effects of LUCEMYRA?"**

Increased risk of opioid overdose. After a period of time of not using opioid drugs, you can become more sensitive to the effects of opioids if you start using opioids again. This may increase your risk of overdose and death.

What is LUCEMYRA?

LUCEMYRA is a non-opioid prescription medicine used in adults to help with the symptoms of opioid withdrawal that may happen when you stop taking an opioid suddenly.

LUCEMYRA will not completely prevent the symptoms of opioid withdrawal, which may include feeling sick, stomach cramps, muscle spasms or twitching, feeling of cold, heart pounding, muscular tension, aches and pains, yawning, runny eyes and sleep problems (insomnia).

LUCEMYRA is not a treatment for opioid use disorder. If you have been diagnosed with opioid use disorder (opioid addiction), your healthcare provider may prescribe LUCEMYRA as part of a complete treatment program for your opioid use disorder (opioid addiction).

It is not known if LUCEMYRA is safe and effective in children.

Before taking LUCEMYRA, tell your healthcare provider about all of your medical conditions, including if you:

- have low blood pressure
- have a slow heart rate
- have any heart problems, including history of heart attack or a condition called long QT syndrome
- have liver or kidney problems
- drink alcohol
- are pregnant or plan to become pregnant. It is not known if LUCEMYRA can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LUCEMYRA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with LUCEMYRA.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements, and any medications you may take for the individual symptoms of opioid withdrawal (such as pain relievers or medications for upset stomach).

Especially tell your healthcare provider if you take benzodiazepines, barbiturates, tranquilizers, or sleeping pills. Taking LUCEMYRA with these medicines can cause serious side effects. Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines.

How should I take LUCEMYRA?

- Take LUCEMYRA exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose if needed.
- Do not change your dose or stop taking LUCEMYRA without talking to your healthcare provider.
- Take LUCEMYRA with or without food.
- If you take too much LUCEMYRA, go to the nearest hospital emergency room right away.

LUCEMYRA™ (lofexidine) tablets

What should I avoid while taking LUCEMYRA?

Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how LUCEMYRA affects you.

What are the possible side effects of LUCEMYRA?

The most common side effects of LUCEMYRA include:

- low blood pressure or symptoms of low blood pressure such as lightheadedness
- slow heart rate
- dizziness
- sleepiness
- dry mouth

These are not all the possible side effects of LUCEMYRA.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to US WorldMeds at 1-833-LUCEMYRA.

How should I store LUCEMYRA?

- Store LUCEMYRA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep LUCEMYRA in its original container.
- Keep LUCEMYRA away from heat and moisture.
- LUCEMYRA bottles contain desiccant packs to help keep the tablets dry. Do not remove the desiccant packs until all the tablets are used.

Keep LUCEMYRA and all medicines out of the reach of children.

General information about the safe and effective use of LUCEMYRA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LUCEMYRA for a condition for which it was not prescribed. Do not give LUCEMYRA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about LUCEMYRA that is written for health professionals.

What are the ingredients of LUCEMYRA?

Active ingredient: lofexidine.

Inactive ingredients: lactose, citric acid, povidone, microcrystalline cellulose, calcium stearate, sodium lauryl sulphate, and Opadry OY S 9480 (contains indigo carmine and sunset yellow).

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US WorldMeds, LLC is the exclusive licensee and distributor of LUCEMYRA™ in the United States and Its territories.

For more information, go to www.LUCEMYRA.com or call 1-833-LUCEMYRA

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 05/2018

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AMERICA • ASIA PACIFIC • EUROPE

September 20, 2018

By Federal Express and Email

Beneficiary Advisory Panel
Designated Federal Officer
Colonel Paul J. Hoerner, USAF
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101
Email: dha.ncr.healthit.mbx.baprequests@mail.mil

Re: September 27, 2018 Beneficiary Advisory Panel Background Information (H.P. Acthar® Gel)

Dear Beneficiary Advisory Panel Members:

We write on behalf of Mallinckrodt Pharmaceuticals (Mallinckrodt) to provide the members of the Beneficiary Advisory Panel (BAP) with comments on the coverage restrictions proposed by the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee for H.P. Acthar® Gel (repository corticotropin injection) (Acthar), which will be discussed at the BAP meeting currently scheduled for September 27, 2018. In summary, Mallinckrodt vigorously opposes the proposed coverage restrictions, which are not evidence-based and threaten grievous harm to vulnerable TRICARE beneficiaries.

The comments discussed below should seem familiar to BAP members. The same flawed coverage restrictions for Acthar were rejected by the BAP in April 2018. The P&T Committee seeks a "mulligan" and is re-presenting the same proposals. By doing so, the P&T Committee hopes to obtain a more favorable outcome than the rejection that it received from the BAP less than six months ago. The BAP should once again reject the P&T Committee's flawed proposals. No new data or information has been produced, and the P&T Committee's background materials are misleading at best.

BACKGROUND

Acthar is the only drug in the class known as adrenocorticotropic hormones (ACTH) that is approved by the U.S. Food and Drug Administration (FDA) for therapeutic use in the United States. Acthar is widely known as the standard of care (and the preferred first-line treatment) for West Syndrome, also known as infantile spasms (IS), a rare but potentially fatal neurologic condition affecting young children. Another key indication is the treatment of acute exacerbations

of multiple sclerosis (MS), where Acthar is often prescribed to patients who are intolerant of, or do not respond to, other medications. In addition, Acthar is an important later-line treatment for a broad array of conditions, such as proteinuria in nephrotic syndrome; dermatomyositis / polymyositis; rheumatoid arthritis; systemic lupus erythematosus; ophthalmic disease; and symptomatic sarcoidosis.

The present dispute dates to the P&T Committee's first consideration of Acthar in 2013. At that time, the P&T Committee adopted limited prior authorization (PA) criteria regarding the use of Acthar to treat IS.[1] However, the P&T Committee determined that certain other indications (including exacerbations of MS and nephrotic syndrome) would be covered on appeal only, while other indications would be excluded from coverage altogether. "Appeal only" coverage, however, is inconsistent with Defense Health Agency (DHA) regulations. It also led to widespread confusion among TRICARE providers and patients, who were not informed that "appeal only" coverage existed for MS, nephrotic syndrome, or other uses. In fact, TRICARE's prime vendor falsely described the coverage rules applicable to Acthar in denial notices, which undermined the affected beneficiaries' appeal rights.

For these and other reasons, Mallinckrodt engaged with DHA to seek a clear and more appropriate coverage policy for Acthar. On or about November 6, 2017, the agency told Mallinckrodt that its concerns would be addressed by the P&T Committee in its February 2018 meeting.

That did not occur. Instead, the P&T Committee proposed additional coverage restrictions. First, the P&T Committee proposed to impose a new PA criteria regarding IS that would require all pediatric patients to first try and fail "off-label" steroid treatment before being prescribed Acthar, the recognized first line therapy for IS.[2] Second, the P&T Committee proposed to require that patients try and fail treatment with steroids prior to each individual exacerbation of MS. Finally, the P&T Committee proposed to deny all coverage for all remaining uses—including conditions, like nephrotic syndrome, that had been covered as a result of appeals by beneficiaries.

These proposals were firmly opposed by stakeholders. Multiple groups and healthcare providers wrote to DHA to voice their opposition—including the Child Neurology Foundation, Multiple Sclerosis Association of America, Nephcure Kidney International, the National Kidney Foundation, and leading pediatric neurologists from the University of Tennessee Health Science

[1] The 2013 PA criteria for IS were that the patient was less than 24 months old, that the IS diagnosis had been confirmed, and that the patient has not previously been treated with Acthar. These criteria are consistent with the model criteria that Acthar urges all payors to adopt.

[2] Go C.Y. et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society – Neurology, 2012;78:1974-1980.

Center, the Children's Hospital of Orange County, and the Children's Hospital of Pittsburg. These materials are provided for consideration by the BAP as Exhibit A to these comments.

Importantly, the BAP rejected these proposals. The P&T Committee presented its recommendations to the BAP on April 5, 2018. During that presentation, BAP members asked probing questions regarding the recommendation to eliminate coverage for uses currently covered on appeal. The BAP members quite correctly pointed out that the P&T Committee failed to support its position to eliminate coverage for those uses. On the contrary, BAP members noted that the P&T Committee had effectively conceded that clinicians and patients needed access to Acthar as an alternative where prior treatments had been ineffective. The BAP ultimately voted 3-1 to not concur in the P&T Committee's flawed recommendations.

Despite the BAP's rejection and broad stakeholder opposition, the DHA Director adopted the P&T Committee's recommendations, without change, on April 24, 2018. After that decision, Mallinckrodt again raised the procedural and substantive defects in the new coverage restrictions and was informed, on July 10, 2018, that the P&T Committee would be conducting another review of Acthar at its meeting on August 8-9, 2018. The P&T Committee now seeks to present the same, rejected proposals to the BAP on September 27, 2018.

DISCUSSION

It is disappointing that the P&T Committee has reiterated the same flawed proposals. We fear that it reflects that the P&T Committee is wedded to a result and is searching for a justification. Such a "result first" approach is a disservice to military families and the antithesis of the reasoned decision-making required of all federal agencies. We have included our prior presentation to the BAP as Exhibit B to these comments. The BAP should reject the current proposals for largely the same reasons it rejected the prior iteration. In brief summary:

- Infantile Spasms. The prior authorization criteria for the IS indication should not include a requirement that patients first receive a 2-week course of high-dose prednisone/prednisolone. It is clearly inappropriate to prefer an unapproved use of steroids over Acthar, which is the accepted standard of care.

  First, a two-week course of steroids threatens grievous harm to vulnerable patients by delaying the onset of treatment with Acthar. Infantile Spasms is a rare but catastrophic syndrome characterized by both spasms and hypsarrhythmic EEG patterns. Delayed treatment that exposes infants to even a few weeks of hypsarrhythmia can cause increased impairment.[3] Thus, the approach proposed by the P&T Committee threatens unnecessary, permanent disability.

[3] Mackay MT, et al. Neurology. 2004;62(10):1668-1681; Goh S, et al. Neurology. 2005;65(2):235-238.

Second, Acthar's status as the standard of care for infantile spasms is well established. That status was recognized by the FDA in 2010. It is supported by the joint clinical guidelines of the American Academy of Neurology and the Child Neurology Society, which not only endorse Acthar as a first line therapy, but also conclude that there is insufficient evidence to recommend preferential use of steroids.[4] Similarly, a 2010 meeting of knowledge leader concluded that a high-dose regimen of Acthar "continues to be the clinical standard of treatment of infantile spasms in the United States and several other countries."[5]

Third, robust clinical evidence supports the use of Acthar as the first-line treatment. Thus, a study published in 2016 by the National Infantile Spasms Consortium found that ACTH appeared to be a more effective treatment for Infantile Spasms than other standard therapies.[6] Similarly, a randomized trial published in 1996, which found that a 2-week course of high-dose ACTH (86.6% efficacy) was superior to 2 weeks of what would now be considered low-dose prednisone (28.6%) for treatment of infantile spasms as assessed by both clinical and EEG criteria.[7]

- Exacerbations of MS. The prior authorization criteria for the MS indication should not require treatment failure with steroids for each individual exacerbation. It is plainly inappropriate to require a failed treatment for each individual exacerbation as it occurs. Forcing patients to endure multiple, repeated treatment failures would be an entirely unreasonable barrier to access to an established second line therapy.

  Repeated steroid treatments also pose quality of life problems for patients. During the time it takes for a steroid trial to fail, patients can experience a range of harms, from difficulty walking to optic neuritis and cognitive delays. A steroidal treatment also typically requires the patient to visit a clinic every day to receive the infusion, as opposed to Acthar, which can be administered by the patient in the home. For a patient in an exacerbation, with limited or no mobility, that is a very real and very serious barrier to treatment and recovery.

- Other Conditions. TRICARE should not deny coverage for other uses of Acthar, including nephrotic syndrome, that previously have been covered on appeal. A policy

[4] Go C.Y. et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society – Neurology, 2012;78:1974-1980.

[5] Stafstrom CE et al. Treatment of IS insights from clinical & basic science perspectives - J Child Neurol 2011 26(11) 1411-1421.

[6] Knupp K.G. et al. Response to Treatment in a Prospective National Infantile Spasms Cohort – Ann Neurol 2016;79:475-484.

[7] Barram TZ et al. High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study – Pediatrics 1996;97(3):375-379.

> of no coverage under any circumstances, no matter how severe the patient need and no matter how extensively other therapies have been tried and failed, is plainly arbitrary and capricious.
>
> In addition, the P&T Committee failed to explain in any manner how new evidence justified the departure from its prior coverage policies, which did cover these uses in appropriate circumstances. While we have many concerns about providing coverage only on appeal, that policy did enable at least some patients to receive coverage. For instance, between January 2014 and March 2018, at least 113 naïve patients received coverage for Acthar for protein-wasting nephropathies. The P&T Committee's recommendation will severely harm these patients, as well as similarly-situated patients in the future.

We do not believe that the P&T Committee has offered a meaningful rebuttal to any of the above points. Indeed, in several respects, the P&T Committee's second review of Acthar has served only to exacerbate the errors and highlight the flaws in its proposals.

1. <u>Procedural Irregularities Prevented Stakeholder Participation</u>.

The simple fact that the P&T Committee chose to review Acthar for a second time in six months is highly unusual. But the way the second review was implemented violated DHA policies and procedures and prevented public participation.

Typically, the public receives months of advance notice to prepare and submit information to the P&T Committee. Here, the documentation related to the August 2018 meeting was posted to the internet on May 1, 2018; the industry teleconference was scheduled for May 14, 2018; sponsor presentations were to occur in May and June; and cost proposals were due on June 22, 2018. All of those dates had passed by the time Mallinckrodt was informed that Acthar would be re-reviewed. Other stakeholders received no notice whatsoever. As of this writing, the DHA website ***still*** fails to reveal that the ACTH or Acthar was discussed at the August meeting in direct violation of by Health Affairs Policy 04-032, which requires advance public notice of the P&T Committee's agenda via the website.[8] This violation is particularly troubling given the significant number of stakeholders who objected to the February 2018 proposals regarding Acthar.

2. The P&T Committee still has not responded to stakeholder opposition or <u>Mallinckrodt's proposal</u>.

To our knowledge, the P&T has not acknowledged, much less responded to, any of the stakeholder correspondence collected in Exhibit A to these comments. Nor is there any indication that the P&T Committee considered Mallinckrodt's prior submissions, which included model

[8] https://www.health.mil/About-MHS/OASDHA/Defense-Health-Agency/Operations/Pharmacy-Division/DoD-Pharmacy-and-Therapeutics-Committee.

coverage policies that include step edits that could be used to develop clinically appropriate prior authorization criteria for ***each*** relevant indication.

3. The P&T Committee still has not addressed the relevant clinical evidence and practice guidelines.

Mallinckrodt has repeatedly directed the P&T Committee to the relevant clinical practice guidelines and published studies regarding Acthar (see, e.g., footnotes 2-7 above). At no point has the P&T Committee addressed those materials, despite repeated claims of having conducted a "comprehensive review" of the relevant evidence.

4. The P&T Committee continues to prefer "off-label" use of steroids in violation of DHA regulations.

As before, the P&T Committee continues to recommend that all patients with IS first receive off-label treatment with steroids prior to being prescribed Acthar, which is FDA-approved for that use. As we have previously explained to the agency, DHA regulations hold that off-label uses may only be ***covered*** (let alone ***preferred***) when there has been a "demonstration[] from medical literature, national organizations, or technology assessment bodies that the off-label use of the drug or device is safe, effective, and in accordance with nationally accepted standards of practice in the medical community." 32 C.F.R. § 199.4 (emphasis added). Section 9.1 of Chapter 8 of the TRICARE Policy Manual contains the same requirement.

We are aware of no evidence that could support a "demonstration" that an unapproved use of oral steroids as a first-line treatment for infantile spasms is "in accordance with nationally accepted standards of practice." The P&T Committee's background materials do not attempt to make the demonstration required by the regulation or the corresponding manual provision. Instead, the P&T Committee suggests that it is appropriate to prefer off-label use of steroids for infantile spasms because the P&T Committee previously proposed, in 2017, to prefer off-label use of steroids for another rare disease affecting vulnerable children, namely, Duchene's muscular dystrophy. The fact that the P&T Committee could only identify ***one*** prior coverage policy that favors an unapproved treatment over an FDA-approved product indicates that such proposals are contrary to 32 C.F.R. § 199.4.

5. The P&T Committee still refuses to identify many of the materials on which it purports to rely.

The P&T Committee continues to make unsupported claims. For example, the P&T Committee claims to have received "additional information … from providers and the FDA as it relates to the clinical effectiveness and safety of [Acthar]." But the P&T Committee does not disclose who supposedly provided this alleged information, what information allegedly was provided, or what it purported to show about the safety or efficacy of Acthar. Similarly, the P&T Committee claims that it reviewed "[f]undamentals of inflammation," without identifying the materials reviewed or explaining how they are supposed to show that it is appropriate to require

TRICARE beneficiaries living with MS to repeat a failed steroid treatment potentially ten or more times over the course of their lives.

By far the most egregious example, however, involves unfounded allegations regarding safety. The P&T Committee writes that "[n]ew data … cause[d] the Committee to have more safety concerns than previously concluded." Yet the P&T Committee did not disclose the purported "new data" at issue, did not identify the source, and did not even specify the nature of the supposed safety concerns. These vague and unfounded references to safety are inappropriate and irresponsible. If the P&T Committee has ***actual*** safety concerns regarding Acthar, it must disclose what they are (and the data supporting them) so that Mallinckrodt and other stakeholders can evaluate and respond to them. Significantly, FDA has approved Acthar as safe and effective for all of the uses at issue here.

6. <u>The P&T Committee's materials reflect an effort to mislead.</u>

In the few instances in which the P&T Committee discloses the information on which it purports to rely, the P&T Committee misstates its content. In other places, the P&T Committee makes assertions that are misleading.

- First, the P&T Committee claims claims that "9 health care plans" do not cover Acthar "for any indication," but does not identify the plans in question. We believe the reference to "9 health care plans" may be referring to certain self-insured employers that do not cover Acthar. Even if there are such plans—and the information provided is insufficient to evaluate that point—it is well known that these types of self-insurance plans do not and cannot offer the same quality of care as national plans.[9] There is no showing that these plans operate under the statutory and regulatory mandates that apply to the TRICARE program, and it would be plainly inappropriate to reduce TRICARE benefits for active-duty service members and their families to the level of benefits provided by self-insured employers.

- Second, the P&T Committee asserts that the Intermountain Health System in Utah requires "a trial of oral corticosteroids prior to using [Acthar] for infantile spasms." We believe that assertion to be false. The public PA form used by Intermountain for commercial and Medicaid patients is specific to infantile spasms and it ***does not*** require

[9] See Kaiser Family Foundation, Employer Health Benefits, 2017 Summary of Findings, available at http://files.kff.org/attachment/Summary-of-Findings-Employer-Health-Benefits-2017 (stating "Despite continuing economic improvement, with lower rates of unemployment, and the ACA employer mandate, there are no signs that the longterm declines in the offer and coverage rates are reversing.")

a prior trial of steroids. That form is attached to these comments as Exhibit C for consideration by the BAP.[10]

- Third, the P&T Committee similarly contends that UCLA and Johns Hopkins also require a failed steroid trial before administering Acthar to patients with IS. Mallinckrodt has not been able to confirm the P&T Committee's assertion regarding Johns Hopkins, which appears to be based on non-public and undisclosed information. However, Mallinckrodt queried UCLA regarding its coverage policy and was told that—contrary to the P&T Committee's claim—UCLA does not impose the restriction asserted.

- Fourth, the P&T Committee asserts that steroids "better facilitate[]" urgent treatment of infantile spasms. This assertion is not supported by any citation. And for good reason: There is absolutely no support in the literature for the implicit claim that steroids are a superior (i.e., more effective) treatment for IS.

  The P&T Committee relatedly asserts that treatment with Acthar can be delayed because the distribution system for Acthar allegedly is "administratively burdensome." Again, the P&T Committee offers no support or explanation for the claim of burden. Mallinckrodt believes that Acthar is readily available for use in TRICARE facilities or distribution to TRICARE families and that it is TRICARE's policies that have imposed burdens on patients and providers.

- Fifth, the P&T Committee claims that its review "reaffirmed" that steroids should be "a frontline treatment ***alongside*** [Acthar] and vigabatrin." But that is not an accurate description of what the P&T Committee proposes to do. Acthar and steroids stood "alongside" each other as frontline treatments for IS under the prior coverage policy that was adopted in 2013. Since February 2018, the P&T Committee has been determined to place steroids ***in front of***, not alongside, Acthar in the armamentarium. That change is both critical and the genesis of this dispute.

Finally, we note that the above statements—each disturbing in its own right—build upon false assertions in the P&T Committee's prior recommendations in February 2018. At that time, the P&T Committee recommended against coverage of important uses of Acthar, including nephrotic syndrome, based on the factually incorrect premise that Acthar was only approved "in 1952, prior to the higher standards demonstrating clinical effectiveness." In truth, Acthar was approved ***for***

[10] In contrast, an Intermountain PA form for Medicare beneficiaries does inquire regarding prior trials with steroids. *See* Exhibit D. Medicare is plainly irrelevant—there is virtually no set of facts pursuant to which the Medicare program would ever be the responsible payor for an infant diagnosed with IS. Moreover, the Intermountain form for Medicare makes clear that the prior authorization questions being asked apply to a broad array of indications other than IS, as one would expect for an adult beneficiary population.

efficacy in the 1970s, *see* 42 Fed. Reg. 11891 (Mar. 1, 1977), and again in 2010 when FDA comprehensively reexamined and modernized the drug's labeling.

* * *

Thank you for your time. We greatly appreciate your review and consideration of these comments.

Best regards,

William A. Sarraille
Sean C. Griffin
SIDLEY AUSTIN LLP

EXHIBIT A

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Child Neurology FOUNDATION
Creating a Community of Support

201 Chicago Avenue, Suite 200
Minneapolis, MN 55415
612.928.6325

Vice Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101

May 1, 2018

Dear Vice Admiral Raquel C. Bono,

Thank you for the opportunity to comment on Tricare's proposed policy changes to health care benefits. The Child Neurology Foundation (CNF) serves as a collaborative center for patient education and support for the children and families living with the over 300 neurologic conditions. We are governed by board-certified child neurologists, allied health professionals, and parents. We utilize this multi-stakeholder expertise to guide our advocacy efforts.

Since 2016, CNF has convened the Infantile Spasms Action Network (ISAN); which is a collaborative advocacy model in which 25 national and international entities are actively engaged (www.childneurologyfoundation.org/infantilespasms). ISAN's goal is to increase awareness for the necessity for prompt and accurate diagnosis for infantile spasms (IS) and urgent and appropriate treatment for every child diagnosed with IS. As you may know, IS is associated with significantly elevated risk of developmental impairment, lifelong intractable epilepsy, autism, and death. To be clear, delays in diagnosis and treatment pose a grave threat to children with IS. Even short delays—as brief as 7 days—in receiving effective treatment have been associated with substantial and enduring intellectual harm. For further information, please note the recent position statement on "Immediate Access to Accepted Treatments for Infantile Spasms" by the American Epilepsy Society (www.aesnet.org/about_aes/position_statements/position_infantile_spasms) .

Whereas treatment protocols for IS vary among health care providers, there is tremendous consensus around:

1) A physician's right to treat infantile spasms as he/she deems appropriate
2) The critical need for the treating provider to have access to the appropriate treatment immediately

The proposed Tricare policy changes conflict with this established consensus and provide systematic opportunity for further delay in children receiving appropriate treatment for IS.

Therefore, our request is that you do not approve the proposed policy changes to Tricare's coverage as it relates to infantile spasms treatment.

Child Neurology FOUNDATION
Creating a Community of Support

201 Chicago Avenue, Suite 200
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612.928.6325

Feel free to reach out to us if we may provide you with further information.

Respectfully,

Ann Tilton, MD
President, CNF

Amy Brin Miller, MSN, MA, PCNS-BC
Executive Director, CNF

cc: Shaun Hussain, MD – CNF Chair of Content Review Committee
Scott Pomeroy, MD, PhD – CNF Secretary
William H. Trescher, MD – CNF Past President
Mary Zupanc, MD – CNF Board of Director

UT Le Bonheur
Pediatric Specialists

April 10, 2018

Vice-Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Blvd, Suite #5101
Falls Church, VA 22042-5101

RE: Tricare and the Treatment of Infantile Spasms

Dear Vice-Admiral Bono,

I am writing to you regarding your recent decision that Tricare has made recommending high-dose prednisolone therapy for two weeks as initial treatment for infantile spasms. I was one of the lead authors in the United States that was part of a special report (The Infantile Spasms Working Group) that reviewed the diagnosis, evaluation and treatment of infantile spasms. (I have enclosed a copy of this document for you).

As you can see, when this document was published in 2010, there were only two FDA approved treatments for Infantile Spasms in the United States, ACTH gel, and vigabatrin. Since that time, no other products have received FDA approval as initial treatment, and none have demonstrated superiority. As such, it caused me concern when your group recommended high-dose prednisolone as initial therapy. Since our study was published, other studies have also confirmed the superior efficacy of ACTH gel over the high dose prednisolone. Additionally, the studies have shown the delay in treatment of ongoing infantile spasms has negative developmental consequences for the infant that cannot be recovered from.

I would hope that you would consider these items and consider revision of your policy. I would be happy to discuss this with you at any time, and a phone call can be coordinated through my office if needed. Please do not hesitate to contact me if I can answer any questions.

Sincerely,

James W. Wheless, M.D., FAAP, FACP, FAAN, FAES
Professor and Chief of Pediatric Neurology
Le Bonheur Chair in Pediatric Neurology
University of Tennessee Health Science Center
Director, Le Bonheur Comprehensive Epilepsy Program & Neuroscience Institute
Le Bonheur Children's Hospital
Memphis, TN

enclosure

JWW/mwa

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Division of Neurology

Mary L. Zupanc, M.D., Division Chief
Amanda Fernandez, M.D. • Anjalee Galion, M.D. • Habib Ismail, M.D. • Sharon Kim, M.D.
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Daniel Shrey, M.D. • Maija Steenari, M.D. • Sharief Taraman, M.D. • Minodora Totoiu, M.D., PhD
Anne Tournay, M.D. • Lily Tran, M.D.
Aliza Riba, CPNP

April 12, 2018

Vice-Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
770 Arlington Blvd., Suite #5101
Falls Church, VA 22042-5101

RE: Tricare and the Treatment of Infantile Spasms

Dear Vice-Admiral Bono,

I am writing to you regarding your recent decision that Tricare has made recommending high-dose prednisolone therapy for two weeks as initial treatment for infantile spasms. Please see the attached article entitled "Infantile Spams: A US Consensus Report". Although I was not one of the lead authors for this particular article, I have authored multiple articles on infantile spasms, have participated in clinical studies using ACTH, and am recognized as a national expert on infantile spasms and its treatment.

As you can see, when this document was published in 2010, there were only two FDA approved treatments for Infantile Spasms in the United States, ACTH gel, and vigabatrin. Since that time, no other products have received FDA approval as initial treatment and none have demonstrated superiority. As such, I am very concerned that your group has recommended high-dose prednisolone as initial therapy. Since this study was published, other studies have also confirmed the superior efficacy of ACTH gel over the high dose prednisolone. Additionally, the studies have shown the delay in treatment of ongoing infantile spasms has negative developmental consequences for the infant that cannot be recovered from.

I hope that you will consider these items and consider revision of your policy. I would be happy to discuss this with you at any time, and a phone call can be coordinated through my office if needed. Please do not hesitate to contact me if I can answer any questions.

Sincerely,

Mary L. Zupanc MD

Mary L. Zupanc, MD, FAAP, FAAN
Professor and Chief of Neurology
Director of the Pediatric Epilepsy Program
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Children's Hospital of Pittsburgh | of UPMC

Yoshimi Sogawa, MD

Associate Professor of Pediatrics
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April 13, 2018

Vice-Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Blvd, Suite #5101
Falls Church, VA 22042-5101

RE: Tricare and the Treatment of Infantile Spasms

Dear Vice-Admiral Bono,

I am writing to you regarding your recent decision that Tricare has made recommending high-dose prednisolone therapy for two weeks as initial treatment for infantile spasms. I would like to point out that the most recent practice guideline (2012) published by the American Academy of Neurology clearly stated that " the evidence is insufficient to recommend the use of prednisolone as being as effective as ACTH (Level U)" In more detail, the response rate to prednisolone was 50-70%, which is much lower than 87% from high-dose ACTH. The reason for insufficient evidence is not due to the small difference in efficacy but to lack of sufficient number of patients on these studies to reach statistical significance.

In the United States, ACTH gel and vigabatrin are the FDA approved initial treatment for infantile spasms, and no other agents (including prednisolone) have demonstrated superiority. I am concerned that Tricare is recommending non-FDA approved agent as initial therapy for infantile spasms, which has devastating long-term neurological outcome if seizures are not controlled quickly.

I would hope that you would consider revision of your policy. I would be happy to discuss this with you at any time. Please feel free to contact me if I could answer any questions.

Sincerely,

Yoshimi Sogawa, MD

MULTIPLE SCLEROSIS
ASSOCIATION OF AMERICA
800-532-7667
856-488-4500
FAX: 856-661-9797
EMAIL: msaa@msassociation.org

Vice Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101

May 1, 2018

Dear Vice Admiral Bono:

The Multiple Sclerosis Association of America is a national 501(c)(3) patient advocacy organization that serves the more than 400,000 US residents diagnosed with multiple sclerosis. Founded 49 years ago, MSAA has established an excellent record of reasoned, fair and balanced public positions on various MS issues focusing on the needs of the patient. As a leading resource for the entire MS community, improving lives through vital services and support, we are strong advocates for patient access to all needed and appropriate treatments.

Our organization is extremely troubled by the Department of Defense Pharmacy and Therapeutic Committee's April recommendations for new manual prior authorization criteria for Adrenocorticotropic Hormones (ACTH), also known as HP Acthar Gel, in Tricare beneficiaries. According to this new criterion, patients with multiple sclerosis who are experiencing a disease relapse would be required to utilize IV/PO corticosteroids and fail each time an exacerbation has been determined by their treating physician before approval of ACTH is granted.

This is a worrying decision, as ACTH is typically used in MS patients who have displayed intolerance for corticosteroids, have struggled with the numerous side-effects present in the same, have found them ineffective in treating disease relapses, and may simply be unable to take medication through their veins. These barriers to treatment in the use of steroids make prescription of ACTH a vital option for exacerbations that have an immense impact on an individual's quality of life.

Signs of a disease relapse or "MS Attack" may include, but are not limited to: loss of or blurry vision, spasticity in various extremities, speech changes, leg/foot weakness, balance and walking difficulty, bowel and bladder issues, and extreme pain. These exacerbations, if left untreated, can lead to a deterioration of not only quality of life, but also increase the likelihood of long-term disability, and carry the risk of hospitalization and potential rehabilitative periods.

While it is common for an MS patient to face step-therapy requirements for ACTH during their initial relapse period, it is highly unusual for the individual in question to face the same requirement in each instance of recurrent disease activity. **MSAA urges for the betterment of all Tricare beneficiaries living with MS, that the Pharmacy and Therapeutics Committee reconsider this recommendation and instead amend it to allow for prescription of ACTH in perpetuity after the first corticosteroid failure has been determined.**

I would be happy to provide further insight in to our concerns about the negative impact that this might have on MS patients' long-term health outcomes. I can be reached at (800) 532-7667, x160 or kpinion@mymsaa.org. Thank you in advance for your attention to this matter.

Respectfully,

Kyle Pinion
Senior Director of Education, Healthcare Relations & Advocacy

NEPHCURE
Kidney International

April 30, 2018

Via Electronic Delivery
Vice Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101
Chief of Staff: Col Daniel E. Lee, USAF, MSC
Daniel.e.Lee8.mil@mail.mil
Re: Recommended Coverage Policy for H.P. Acthar® Gel

Dear Vice Admiral Bono:

On behalf of NephCure Kidney International, we would like to share concerns regarding the recent recommendations of the Department of Defense's Pharmacy & Therapeutics Committee regarding coverage for Acthar Gel. As the only organization committed exclusively to support research seeking the cause of the diseases that cause Nephrotic Syndrome, we believe these patients should have access to all available treatment options in all appropriate circumstances. NephCure is driven by a panel of respected medical experts and a dedicated band of patients and families.

Every patient's nephrotic syndrome journey is unique. This disease often involves a complex set of symptoms that varies significantly by patient. Because of the disease's complexities, patients' responses to the available therapies also varies. Therefore, it is critical that patients have access to the full range of treatment options, so that the appropriate medication for that patient is available to meet his or her needs. No patient should be denied any therapy appropriately prescribed by their physician without any consideration of their unique needs.

We understand that the P&T Committee's recommendations include serious restrictions to existing Acthar coverage criteria by, in part, determining that the use of Acthar for nephrotic syndromes is "unsupported" and not approved. It is not clear why the P&T Committee made this recommendation, especially given that veterans with nephrotic syndromes currently have access to Acthar through an appeal process. We are deeply concerned that the recommendations, if approved, may harm the patients we serve.

We understand that you will either approve or reject the P&T Committee's recommendations. We ask that you reject the recommendation to protect patients of this nephrotic syndrome and ensure that they have appropriate access to all treatment options.

We appreciate your consideration of these comments. If you have any questions about these comments or if we can be of any assistance, please let us know.

Sincerely,

Joshua M. Tarnoff
Chief Executive Officer

National Kidney Foundation™

30 E. 33rd Street
New York, NY 10016

Tel 212.889.2210
Fax 212.689.9261
www.kidney.org

May 2, 2018

Vice Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042

Subject: Coverage for Nephrotic Syndrome Therapies

Dear Vice Admiral Bono,

The National Kidney Foundation (NKF) is America's largest and oldest health organization dedicated to the awareness, prevention, and treatment of kidney disease for hundreds of thousands of healthcare professionals, millions of patients and their families, and tens of millions of people at risk. In addition, NKF has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD), since 1997 through the NKF Kidney Disease Outcomes Quality Initiative (NKF KDOQI). NKF has divisions and affiliates delivering education, programs, and services in all 50 states, to provide patients and professionals with the best available information and to help them make informed and appropriate treatment choices

It has come to our attention that you are considering reducing the coverage options available to patients suffering from nephrotic syndrome (NS) whose health benefits are covered by Tri Care, by eliminating NS as an approved indication for Acthar gel, repository corticotropin injection. NS is a serious disorder that can lead to chronic disability and to expensive renal replacement therapy. NS is a complex condition, caused by a variety of glomerular disorders that affect both adults and children. Fortunately, there are pharmaceutical interventions that can result in partial or complete remissions, thereby slowing progression and reducing the incidence of ESRD, as well as other adverse outcomes.

The first line treatment for primary NS is often corticosteroids, with other immunosuppressive agents added depending on the pathologic diagnosis. These agents may fail or cause significant adverse events. NKF believes that clinical outcomes for our patients are optimal when they have

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access to all FDA-approved therapies that their physicians prescribe. In order for this to be true the therapies need to be covered by insurance, even if in some cases step therapy approaches or other utilization review techniques are required prior to authorization

The NKF therefore respectfully requests that you cover all therapeutic agents, including Acthar, when prescribed for the treatment of steroid-resistant NS.

Sincerely,

Kerry Willis, PhD
Chief Scientific Officer

CC David W. Bobb, RPH, JD, Chief, Pharmacy Operations Division
CAPT Edward Norton, U.S. Navy, BAP Designated Federal Officer (DFO)
Bryan Wheeler, Deputy General Counsel

EXHIBIT B

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Mallinckrodt Pharmaceuticals
Comments on DoD P&T Committee Proposal

I. Introduction

- My name is Sean Griffin, and I am an attorney with the law firm Sidley Austin LLP.
- I am here today on behalf of Mallinckrodt Pharmaceuticals.
- Mallinckrodt has asked me to address a mix of clinical and legal concerns regarding the P&T Committee's recent recommendations regarding the class of drugs known as Adrenocorticotropic Hormones or ACTH.
- Mallinckrodt manufacturers Acthar Gel, which is the only ACTH product currently approved for therapeutic use in the United States.
- Acthar Gel is widely recognized as a medically necessary product and has the distinction of being FDA approved for 19 different indications.
- We have not had much time to review the Committee's recommendations, so my comments today are necessarily at a high-level.
- Mallinckrodt is concerned, however, that certain of the PA criteria recommended for the Infantile Spasm (IS) and Multiple Sclerosis (MS) indications are inappropriate and will harm patients by delaying access to an important and effective therapy.
- Mallinckrodt also is concerned about the omission of any prior authorization criteria for the other FDA-approved indications. That omission appears to be based on a false premise—namely, that those indications have not been evaluated or approved by FDA for effectiveness. That is false. Each of the current labeled uses was approved for effectiveness in 1977 and again in 2010.
- These clinical and factual issues also raise serious legal issues. Under the Administrative Procedures Act (or APA), agency decisions must be evidence-based and supported by a reasoned explanation.[1] Those requirements take on special force when, as now, an agency proposes to substantially revise a policy that has been in place for several years.[2] At a minimum, the Committee should have acknowledged that it was changing the coverage policy for IS and other uses, explained why the change is justified based on specific, reliable evidence, and addressed the legitimate reliance that patients, providers,

[1] *Motor Vehicle Mfrs. Assn. of United States, Inc. v. State Farm Mut. Automobile Ins. Co.*, 463 U.S. 29, 43 (1983) ("[T]he agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'").

[2] *FCC v. Fox Television Stations, Inc.*, 129 S. Ct. 1800, 1811 (2009) (An agency must "provide a more detailed justification … when, for example, its new policy rests upon factual findings that contradict those which underlay its prior policy.").

and Mallinckrodt have placed on the prior policies.[3] The Committee appears not to have followed these important APA requirements.

- In light of these concerns, we request that the Panel modify the Committee's recommendations in three ways.
    - First, we believe that the PA criteria for the IS indication should not include a requirement that patients first receive a 2-week course of high-dose prednisone/prednisolone. This will harm patients and is inconsistent with nationally-accepted clinical practice guidelines.
    - Second, we believe that the PA criteria for the MS indication should be edited to remove the words "for the present exacerbation." It is plainly inappropriate to require a failed steroid treatment for each individual exacerbation as it occurs. Forcing patients to endure multiple, repeated treatment failures would be an entirely unreasonable barrier to access to an established second line therapy.
    - Finally, we believe that the Panel should strike the Committee's language describing other FDA-approved uses of Acthar Gel as "unsupported" or "unproven" and adopt appropriate PA criteria for at least those uses that previously have been covered "on appeal." The Committee failed to explain in any manner how new evidence justified the departure from its prior coverage policies, which did cover these uses in appropriate circumstances. A policy of no coverage under any circumstances, no matter how severe the patient need and no matter how extensively other therapies have been tried and failed, is plainly arbitrary and capricious.
- I will now address our three concerns in greater detail.

II. Infantile Spasms

- We have several concerns regarding the Committee's proposal that patients be required to receive 2 weeks of steroids before receiving Acthar Gel. First and foremost, we are concerned that a two-week course of steroids will harm patients by delaying the onset of treatment with Acthar Gel.
    - Infantile Spasms is a rare but catastrophic syndrome that typically onsets within the first year of life and is characterized by both spasms and hypsarrhythmic EEG patterns.
    - The condition very frequently results in neurological delay or impairment.

[3] *Perez v. Mortgage Bankers Ass'n*, 135 S. Ct. 1199, 1209 (2015) ("It would be arbitrary and capricious to ignore" "serious reliance interests that must be taken into account."); *accord Smiley v. Citibank (South Dakota), N.A.*, 517 U.S. 735, 742 (1996).

  - Delayed treatment that exposes infants to three or more weeks of hypsarrhythmia has been shown to cause increased impairment.[4]

  - We are concerned that a two-week delay before commencing treatment with Acthar Gel could result in unnecessary, permanent disability.

- Our concerns are underscored by the fact that neither prednisone nor prednisolone has been approved by FDA for the treatment of IS.

  - We think it is plainly inappropriate to rely on unapproved uses of these steroids as a first-line treatment for such a serious and time-sensitive condition.

  - Indeed, we are not aware of any government payor or major commercial payor that currently requires patients suffering from Infantile Spasms to receive steroid treatment prior to receiving Acthar Gel.

- To the contrary, Acthar Gel is widely recognized as the standard of care for IS.

- Mallinckrodt previously submitted a comprehensive set of articles and studies related to the use of Acthar Gel as a treatment for IS. We would particularly like to draw the Panel's attention to:

  - The current evidence-based clinical guidelines from the American Academy of Neurology / Child Neurology Society, which not only endorse Acthar Gel as a first line therapy but also conclude that there is insufficient evidence to recommend the use of prednisolone or other therapies.[5]

  - A 2010 meeting of knowledge leaders, which concluded that a high-dose regimen of Acthar Gel "continues to be the clinical standard of treatment of infantile spasms in the United States and several other countries."[6]

  - A study published in 2016 by the National Infantile Spasms Consortium, which found that ACTH appeared to be a more effective treatment for Infantile Spasms than other standard therapies.[7]

  - A randomized trial published in 1996, which found that a 2-week course of high-dose ACTH (86.6% efficacy) was superior to 2 weeks of what would now be

[4] Mackay MT, et al. Neurology. 2004;62(10):1668-1681; Goh S, et al. Neurology. 2005;65(2):235-238.

[5] Go C.Y. et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society – Neurology, 2012;78:1974-1980.

[6] Stafstrom CE et al. Treatment of IS insights from clinical & basic science perspectives - J Child Neurol 2011 26(11) 1411-1421.

[7] Knupp K.G. et al. Response to Treatment in a Prospective National Infantile Spasms Cohort – Ann Neurol 2016;79:475-484.

considered low-dose prednisone (28.6%) for treatment of infantile spasms as assessed by both clinical and EEG criteria.[8]

- We believe that the Committee's recommendation would not survive judicial review under the APA.
    - The Committee's recommendation does not appear to be evidence based. Although there are oblique statements regarding a review of the evidence, the Committee does not cite any particular source that supports its position.
    - The Committee also appears to have ignored the materials I've mentioned, none of which are acknowledged in the decision, and all of which contradict the recommendation.
    - The Committee's recommendation does not acknowledge that the 2 weeks of steroids requirement is a substantial change in policy. The PA criteria that have been in place since 2013 do not require prior steroid treatment. No new evidence is presented, and we are not aware of new evidence that would be sufficient to outweigh or contradict the settled view that Acthar Gel is the standard of care for this condition.
    - Last, the Committee did not consider the reliance interests of patients, providers, and Mallinckrodt surrounding the prior policy.
    - Each of these issues is independently a basis to conclude that the Committee's recommendation is arbitrary and capricious under the APA.
- Accordingly, we ask the Panel to remove the PA criteria that all patients with IS first try a 2 week course of steroids.

III. Multiple Sclerosis

- With respect to the MS indication, we agree that prior authorization is appropriate and that patients should try and fail treatment with steroids prior to receiving Acthar Gel for MS exacerbations.
- Our objection is only to the requirement that patients must have failed steroid treatment in connection with "the present exacerbation," which seems plainly unreasonable.
    - MS patients often experience multiple exacerbations or relapses, with many experiencing more than one exacerbation a year.
    - If steroids failed in a prior exacerbation, there should be no reason to force the patient to repeat the failed therapy again.

[8] Barram TZ et al. High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study – Pediatrics 1996;97(3):375-379.

- If the Committee's recommendation is adopted, veterans theoretically could be forced to try steroid treatments 5, 6, 7 or more times beyond the first failure, with each exacerbation forcing a new trial and failure.

- We cannot believe that was the Committee's intent.

- Repeated steroid treatments also pose quality of life problems for MS patients:

  - During an exacerbation without appropriate treatment, patients can experience a range of harms, from difficulty walking to optic neuritis, a painful vision issue, and cognitive delays.

  - A steroidal treatment also typically requires the patient to visit a clinic every day to receive the infusion, as opposed to Acthar Gel, which can be administered by the patient in the home. For a patient in an exacerbation, with limited or no mobility, that is a very real and very serious barrier to care.

- Accordingly, we ask the Committee to remove the requirement that steroids must be used first in the "present exacerbation."

IV. All Other Uses

- For all remaining indications of Acthar Gel, the P&T Committee recommends that all other uses "are unsupported and excluded from TRICARE coverage."

- We have several concerns about this recommendation.

- First, the recommendation is based on a plain misunderstanding of the facts and the law.

  - The Committee document (at page 13) asserts that all indications other than IS and MS have not been approved by FDA for clinical effectiveness because the drug was originally approved prior to the 1962 Amendments to the FDCA.

  - That is false.

  - ACTH was considered through the Drug Efficacy Study Implementation Program. Through that program, Acthar Gel was reviewed and approved as effective in 1977 for a large number of indications and in 1978 for MS.

  - FDA then re-reviewed the drug in 2010 as part of a supplemental NDA filing, and reaffirmed 19 approved indications. Each of those indications have been approved by FDA for both safety and effectiveness.

  - The APA does not permit an agency to base a decision on a false premise.

- Second, the recommendation is a break from existing coverage policy.
    - Previously, the program provided coverage for indications like lupus and protein-wasting nephropathies on "appeal only."
    - While we have many concerns about the legality of "appeal only" coverage, that policy did enable at least some patients to receive coverage.
    - For instance, between January 2014 and March 2018, at least 113 naïve patients received coverage for Acthar Gel for protein-wasting nephropathies on appeal.
    - By statute, this means that the Department has recognized that these uses were medically necessary in those particular cases.[9]
- Thus, the Committee articulated a change of position, but without any explanation, such as new evidence that could support the decision to cut off coverage for uses that were previously covered. The change therefore is subject to challenge under the APA.
- Finally, we are very concerned that the recommendation does not address the legal concerns that we have raised over the past several months.
    - Previously, we raised a serious of concerns in which some patients who had been prescribed Acthar Gel for these uses were not given initial determinations that they are entitled to receive under applicable law.
    - They were instead given appeal rights, but were falsely told by DoD's contractor that the appeal would necessarily fail. Not only did this result in delay, it strongly disincented patients from pursuing their appeal rights.
    - We were told that the P&T Committee review would address these serious issues, but the current recommendation makes the problem worse.
    - There is no mechanism to correct for past patients to receive the initial coverage determination that they were deprived. Nor is there a process to correct the false statements made to patients regarding their appeals.
    - And, for future patients, there is no indications that they will even receive appeal rights, let alone an initial determination.
- Accordingly, we believe the Panel should establish PA criteria for the uses previously covered on appeal.
- Thank you for your time. The company will be following up with an additional letter and we can address the questions in that letter.

[9] TRICARE's coverage is limited to services and supplies that "are medically or psychologically necessary for the diagnosis or treatment of a covered illness . . . or injury . . . ." 32 CFR 199.4(g)(1).

EXHIBIT C

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PRIOR AUTHORIZATION FORM
Acthar - Commercial/Medicaid

Unless otherwise indicated below, authorization quantities are limited to the manufacturer recommended dosage

selecthealth

P.O. Box 30192
Salt Lake City, UT 84130-0192
SELECTHEALTH.ORG

Phone: 801-442-4912 or 800-442-3129	**Fax back to: 801-442-3006**
Patient Information	
Patient's Name:	Patient's Date of Birth:
Patient's ID:	Patient's Phone #:
Diagnosis Code(s):	
Requesting Provider Information	
Name:	Phone #:
NPI/DEA:	Fax #:
Address:	Supervising Physician (if requesting provider bills under a different provider)
	Name:
	NPI/DEA:
Servicing Provider Information (if different than requesting provider)	
Name of provider or facility:	Phone number:
NPI/DEA:	Address:

Drug Name and Strength:	Directions / SIG:

Q1. Is the prescribing physician a neurologist?
☐ Yes ☐ No

Q2. Has the patient been diagnosed with infantile spasms as confirmed by EEG?
☐ Yes ☐ No

Q3. Is the patient less than 24 months old?
☐ Yes ☐ No

Q4. Please supply infant's body surface area (BSA):

Q5. Additional Comments:

This form is intended for SelectHealth members only. All requests for preauthorization should be sent via fax to 1-801-442-3006. Missing, inaccurate, or incomplete information may cause a delay or denial of authorization.

Prescriber Signature

Date

EXHIBIT D

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PRIOR AUTHORIZATION FORM
Acthar - Medicare

Unless otherwise indicated below, authorization quantities are limited to the manufacturer recommended dosage

selecthealth ADVANTAGE
P.O. Box 30196
Salt Lake City, UT 84130-0196
SELECTHEALTHADVANTAGE.ORG

Phone: 801-442-9988 or 855-442-9988	**Fax back to: 801-442-0413**
Patient Information	
Patient's Name:	Patient's Date of Birth:
Patient's ID:	Patient's Phone #:
Diagnosis Code(s):	
Requesting Provider Information	
Name:	Phone #:
NPI/DEA:	Fax #:
Address:	Supervising Physician (if requesting provider bills under a different provider)
	Name:
	NPI/DEA:
Servicing Provider Information (if different than requesting provider)	
Name of provider or facility:	Phone number:
NPI/DEA:	Address:

Drug Name and Strength:	Directions / SIG:
☐ Urgent Request (24 hours)	☐ Standard Request (72 hours)

Q1. What is Acthar being prescribed to treat?

- ☐ Infantile Spasms
- ☐ Multiple Sclerosis
- ☐ Nephrotic Syndrome
- ☐ Systemic Lupus Erythematosus (Rheumatic disorder)
- ☐ Rheumatoid Arthritis (Rheumatic disorder)
- ☐ Psoriatic Arthritis (Rheumatic disorder)
- ☐ Ankylosing Spondylitis (Rheumatic disorder)
- ☐ Severe Erythema Multiforme (Dermatalogic disorder)
- ☐ Stevens-Johnson Syndrome (Dermatalogic disorder)
- ☐ Systemic Dermatomyositis
- ☐ Symptomatic Sarcoidosis
- ☐ Serum Sickness
- ☐ Other

Q2. If other, does the patient have keratitis; iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis; or anterior segment inflammation? ☐ Yes ☐ No
Q3. If no, please provide the diagnosis and rationale for request:
Q4. For Infantile Spasms, is the prescribing physician a neurologist? ☐ Yes ☐ No
Q5. Has the patient been diagnosed with infantile spasms as confirmed by electroencephalogram (EEG)? ☐ Yes ☐ No
Q6. Is the patient less than 24 months old? ☐ Yes ☐ No
Q7. Has the patient failed treatment with prednisone, prednisolone, hydrocortisone, or dexamethasone? ☐ Yes ☐ No
Q8. Has the patient failed treatment with vigabatrin and/or cosyntropin? ☐ Yes ☐ No
Q9. For Exacerbations of Multiple Sclerosis, is the prescribing physician a neurologist? ☐ Yes ☐ No
Q10. Has the patient failed at least two courses of treatment with Solu-Medrol for two separate multiple sclerosis exacerbations? ☐ Yes ☐ No
Q11. For Nephrotic Syndrome, is the prescribing physician a nephrologist? ☐ Yes ☐ No
Q12. Has the patient failed therapy with at least two corticosteroids? ☐ Yes ☐ No
Q13. Has the patient failed therapy with either cyclophosphamide or cyclosporine? ☐ Yes ☐ No
Q14. For Rheumatic Disorders, Is the prescribing physician a rheumatologist? ☐ Yes ☐ No
Q15. Has the patient failed therapy with oral corticosteroids? ☐ Yes ☐ No
Q16. Has the patient failed therapy with an oral disease-modifying antirheumatic drug (DMARD)? ☐ Yes ☐ No
Q17. For Dermatologic Disorders, is the prescribing physician a dermatologist? ☐ Yes ☐ No
Q18. Has the patient failed therapy with methylprednisolone? ☐ Yes ☐ No
Q19. Additional Comments:

This form is intended for SelectHealth members only. All requests for preauthorization should be sent via fax to 1-801-442-3006. Missing, inaccurate, or incomplete information may cause a delay or denial of authorization.

Prescriber Signature

Date

Uniform Formulary Beneficiary Advisory Panel (BAP)

Meeting Summary
September 27, 2018
Washington, D.C.

Present Panel Members

- Mr. Jon Ostrowski, Non Commissioned Officers Association, Chairperson
- Mr. Richard Bertin, Commissioned Officer Association (COA) of the United States Public Health Service, Inc.
- Mr. Charles Hostettler, AMSUS
- Ms. Sarika Joshi, HeathNet Federal Services
- Mr. John Du Teil, US Army Warrant Officers Association

Absent Panel Members

- Mr. Suzanne Walker, Military Officers Association of America

This meeting was held at Naval Heritage Center Theater, 701 Pennsylvania Ave., N.W., Washington D.C., and Col Paul Hoerner called the meeting to order at 9:05 a.m.

Agenda

The Agenda for the meeting of the Panel is as follows:

- Welcome and Opening Remarks
- Public Citizen Comments
- Therapeutic Class Reviews

1. Drug Class Reviews

    a) Corticosteroids-Immune Modulators: Atopic Dermatitis Subclass
    b) Hepatitis C Virus (HCV) Direct-Acting Antivirals (DAAs) Subclass
    c) Corticosteroids-Immune Modulators: Adrenocorticotropic Hormones (ACTH)

2. Newly Approved Drugs per 32 CFR 199.21(g)(5)

    a) abiraterone acetate micronized (Yonsa) – Oral Oncologic Agent for Prostate Cancer
    b) amantadine extended release tablets (Osmolex ER) – Parkinson's Agent
    c) avatrombopag (Doptelet) – Hematological Agent: Platelets for Thrombocytopenia in Chronic Liver Disease
    d) baricitinib (Olumiant) – Targeted Immunomodulatory Biologic (TIB) for Rheumatoid Arthritis

e) binimetinib (Mektovi) – Oral Oncologic Agent for Metastatic Melanoma
f) encorafenib (Braftovi) – Oral Oncologic Agent for Metastatic Melanoma
g) epoetin-alfa-epbx (Retacrit) injection – Hematological Agent: Red Blood Cell Stimulant for Erythropoiesis
h) erenumab-aooe (Aimovig) injection– Migraine Agent (calcitonin gene-related peptide [CGRP]) for Migraine Headache Prophylaxis
i) estradiol (Imvexxy) vaginal insert – Miscellaneous Gynecological Agent for Dyspareunia
j) fostamatinib (Tavalisse) – Hematological Agent: Platelets for Chronic Immune Thrombocytopenia
k) hydroxyurea (Siklos) tablets – Hematological Agent: Sickle Cell Anemia Agent for Sickle Cell Anemia in Pediatrics
l) levonorgestrel/ethinyl estradiol/ferrous (Balcoltra) – Oral Combined Contraceptive Agent
m) lofexidine (Lucemyra) – Alpha 2 Antagonist for Mitigation of Symptoms of Opioid Withdrawal
n) oxycodone IR (Roxybond) – Narcotic Analgesic Abuse Deterrent Formulation for Pain
o) pegvaliase-pqpz (Palynziq) injection – Miscellaneous Metabolic Agent for Phenylketonuria
p) tolvaptan (Jynarque) – Miscellaneous Nephrology Agent for Rapidly Progressing Autosomal Dominant Polycystic Kidney Disease (ADPKD)

3. Utilization Management Issues

a) Prior Authorization Criteria—Updated Criteria

- Epinephrine Auto-Injectors: Auvi-Q Temporary Removal of Manual PA
- Renin Angiotensin Antihypertensive Agents (RAAs): candesartan and candesartan/HCTZ Step Therapy
- Oncological Agents for unresectable or metastatic melanoma: Dabrafenib (Tafinlar), Trametinib (Mekinist), and vemurafenib (Zelboraf)
- Oncological Agents: Prostate II - enzalutamide (Xtandi)
- TIBs: Tofacitinib (Xeljanz/Xeljanz XR)

4. Panel Discussions

The UF BAP will have the opportunity to ask questions to each of the presenters. Upon completion of the presentation and any questions, the Panel will discuss the recommendations and vote to accept or reject them. The Panel will provide comments on their vote as directed by the Panel Chairman.

Opening Remarks

Col Paul Hoerner introduced himself as the Designated Federal Officer (DFO) for the Uniform Formulary (UF) Beneficiary Advisory Panel (BAP). The Panel has convened to comment on the recommendations of the DoD Pharmacy and Therapeutics (P&T) Committee meeting, which occurred on August 8-9, 2018.

Col Hoerner indicated Title 10, United States, (U.S.C.) section 1074g, subsection b requires the Secretary of Defense to establish a DoD Uniform Formulary (UF) of the pharmaceutical agent and established the P&T committee to review the formulary on a periodic basis to make additional recommendations regarding the formulary as the committee determines necessary and appropriate.

In addition, 10 U.S.C. Section 1074g, subsection c, also requires the Secretary to establish a UF Beneficiary Advisory Panel (BAP) to review and comment on the development of the Uniform Formulary. The Panel includes members that represent non-governmental organizations and associations that represent the views and interests of a large number of eligible covered beneficiaries. The Director of the Defense Health Agency (DHA) must consider the Panel comments before establishing the UF or implementing changes to the UF.

The Panel's meetings are conducted in accordance of the Federal Advisory Committee Act (FACA).

The duties of the Uniform Formulary Beneficiary Advisory Panel include the following:

- To review and comment on the recommendations of the P&T Committee concerning the establishment of the UF and subsequently recommending changes. The Director of the DHA must review comments regarding recommended formulary status, pre-authorizations and the effective dates for changing drugs from "formulary" to "non-formulary" status before making a final decision.

- To hold quarterly meetings in an open forum. The Panel may not hold meetings except at the call or with the advance approval of the DFO and in consultation with the chairperson of the Panel.

- To prepare minutes of the proceedings and prepared comments of the Secretary or his designee regarding the Uniform Formulary or changes to the Formulary. The minutes will be available on the website, and comments will be prepared for the Director of DHA. As guidance to the Panel regarding this meeting, Col Hoerner said the role of the BAP is to comment on the UF recommendations made by the P&T Committee at their last meeting. While the department appreciates that the BAP maybe interested in the drug class they selected for review, drugs recommended for the basic core formula (BCF) or specific pricing data, these items do not fall under the purview of the BAP.

- The P&T Committee met for approximately 15 hours conducting this review of the drug class recommendation presented today. Since this meeting is considerably shorter, the Panel will not receive the same extensive information as presented to the P&T Committee members.

However, the BAP will receive an abbreviated version of each presentation and its discussion. The materials provided to the Panel are available on the TRICARE website. Detailed minutes of this meeting are being prepared. The BAP minutes, the DoD P&T Committee minutes, and the Director's decisions will be available on the TRICARE website in approximately four to six weeks.

The DFO provided ground rules for conducting the meeting:

- All discussions take place in an open public forum. There is to be no committee discussion outside the room, during breaks, or at lunch.

- Audience participation is limited to private citizens who signed up to address the Panel.

- Members of the Formulary Management Branch and P&T Committee are available to answer questions related to the BAP's deliberations. Should a misstatement be made, these individuals may interrupt to ensure the minutes accurately reflect relevant facts, regulations, or policy.

Col Hoerner introduced the individual Panel members (see list above) and noted housekeeping considerations.

Private citizen comments from US WorldMeds and Sidley Austin LLP on behalf of Mallinckrodt Pharmaceuticals were forwarded to the Panel for review and consideration. SEE APPENDIX C and D.

Chairman's Opening Remarks

Mr. Ostrowski welcomes audience, welcomes Panel members, welcomes LT COL Khoury for presenting today’s Panel meeting notes, and thanks Ms. Armstead for preparation for this Panel.

DRUG CLASS REVIEW PRESENTATION

(POD Script - LT COL KHOURY)

GOOD MORNING. I am Lieutenant Colonel Ronald Khoury, Chief of the Formulary Management Branch of the DHA Pharmacy Operations Division. Joining me is doctor and retired Army Colonel John Kugler, the Chairman of the Pharmacy and Therapeutics Committee, who will provide the physician perspective and comments on the recommendations made by the P&T Committee. Also joining us from the Formulary Management Branch today is LCDR Todd Hansen, the Navy physician at the Formulary Management Branch. I would also like to recognize Mr. Bryan Wheeler, Assistant General Counsel.

The DoD Formulary Management Branch supports the DoD P&T Committee by conducting the relative clinical effectiveness analyses and relative cost effectiveness analyses of the drugs and drug classes under review and consideration by the DoD P&T Committee for the Uniform Formulary (relative meaning in comparison to the other agents defined in the same class).

We are here to present an overview of the analyses presented to the P&T Committee. 32 Code of Federal Regulations (CFR) establishes procedures for inclusion of pharmaceutical agents on the Uniform Formulary based upon both relative clinical effectiveness and relative cost effectiveness.

The goal of this presentation is not to provide you with the same in-depth analyses presented to the DoD P&T Committee but a summary of the processes and analyses presented to the DoD P&T Committee. These include:

- A brief overview of the relative clinical effectiveness analyses considered by the DoD P&T Committee. All reviews include but are not limited to the sources of information listed in 32 CFR 199.21 (e)(1) and (g)(5). Also note that nonformulary medications are generally restricted to the mail order program according to amended section 199.21, revised paragraphs (h)(3)(i) and (ii), effective August 26, 2015.

- A brief general overview of the relative cost effectiveness analyses. This overview will be general in nature since we are unable to disclose the actual costs used in the economic models. This overview will include the factors used to evaluate the costs of the agents in relation to the safety, effectiveness, and clinical outcomes.

- The DoD P&T Committee's Uniform Formulary recommendation is based upon the Committee's collective professional judgment when considering the analyses from both the relative clinical and relative cost effectiveness evaluations.

  The Committee reviewed the following:

  1. The P&T Committee reviewed two Uniform Formulary Drug Classes:

  a) the Atopic Dermatitis Subclass and

b) the Hepatitis C Virus Direct Acting Antivirals (HCV DAAs) Subclass.

The Committee also re-evaluated the clinical conclusion from the February 2018 DoD P&T Committee meeting for the Corticosteroids-Immune Modulators: Adrenocorticotropic Hormones (ACTH) subclass.

A summary table of the UF drug class recommendations and the numbers of affected utilizers is found on page 26 of the background document.

2. The P&T Committee also evaluated 16 newly approved drugs per 32 CFR 199.21 (g)(5), which are currently in pending status and available under terms comparable to nonformulary drugs.

and

3. We also discussed prior authorizations (PAs) for **9** drugs in **5** drug classes.

a) Epinephrine Auto-Injectors (Miscellaneous Respiratory Agents)
b) Renin Angiotensin Antihypertensive Agents (RAAs)
c) Oncological Agents for unresectable or metastatic melanoma
d) Oncological Agents for prostate cancer
e) Targeted Immunomodulatory Biologics

The DoD P&T Committee will make a recommendation as to the effective date of the agents being changed from the Uniform Formulary tier to Nonformulary tier. Based on 32 CFR 199.21, such change will not be longer than 180 days from the final decision date but may be less.

UNIFORM FORMULARY DRUG CLASS REVIEWS

I. UF CLASS REVIEWS

A. CORTICOSTEROIDS-IMMUNE MODULATORS: ATOPIC DERMATITIS

(LT COL KHOURY)

1. Corticosteroids-Immune Modulators: Atopic Dermatitis—Relative Clinical Effectiveness Analysis and Conclusion

Background—The P&T Committee evaluated the relative clinical effectiveness of the atopic dermatitis subclass, which has not been previously reviewed for formulary placement. The products in the subclass include tacrolimus 0.03% and 0.01% ointment (Protopic, generics), pimecrolimus 1% cream (Elidel), crisaborole 2% ointment (Eucrisa), and dupilumab injection (Dupixent). Other drugs used for treating atopic dermatitis, such as topical corticosteroids and systemic immunomodulatory agents were not included in this review.

The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 0 absent) the following:

Professional Treatment Guidelines for Atopic Dermatitis

- The American Academy of Dermatology (AAD) 2014 guidelines recommend topical emollients as the basis for atopic dermatitis therapy. When additional intervention is required, topical corticosteroids are considered first-line therapies for mild to severe atopic dermatitis, while topical calcineurin inhibitors (pimecrolimus and tacrolimus) are considered second-line after topical corticosteroids.

- Concerns regarding adverse effects with topical corticosteroids include adrenal suppression, striae, and skin atrophy. Evidence from large systematic reviews show that mild to moderate potency corticosteroids pose little to no risk to patients when used appropriately. However, “steroid phobia” can affect patient compliance.

- For severe to uncontrolled atopic dermatitis, systemic therapies are options and include cyclosporine, azathioprine, mycophenolate, and methotrexate.

- The AAD 2017 consensus statement regarding the utilization of systemic therapy in patients with moderate to severe atopic dermatitis recommended use of topical treatments and phototherapy, prior to systemic therapy. Overall, no one therapy was preferred over the others, and individual patient factors should guide treatment selection.

- Crisaborole and dupilumab are not yet mentioned in the AAD guidelines.

Topical Calcineurin Inhibitors (TCIs): pimecrolimus and tacrolimus

- Pimecrolimus (Elidel) is FDA-approved for treating mild to moderate atopic dermatitis, while tacrolimus (Protopic) is approved for moderate to severe atopic dermatitis. Both drugs are approved for use in children as young as two years of age.

- A 2016 AAD meta-analysis concluded that the TCIs and topical corticosteroids show similar rates of improvement of dermatitis and treatment success, but TCIs are associated with a higher incidence of adverse events including skin burning and pruritus on application.

- A 2007 Cochrane review reported moderate- to high-potency corticosteroids and tacrolimus 0.1% were more effective than pimecrolimus. Similar results were reported in a 2015 Cochrane review that concluded tacrolimus 0.1% was more effective than low-potency corticosteroids, pimecrolimus 1%, and tacrolimus 0.03%.

- The product labeling for TCIs contains a black box warning for rare case reports of malignancy. A study published in JAMA Dermatology (2015) evaluated rates of cancer in over 7,400 pediatric pimecrolimus users. The authors concluded it was unlikely that pimecrolimus was associated with an increased risk of malignancy. No skin-related cancers were reported.

Topical Phosphodiesterase (PDE)-4 inhibitor: crisaborole (Eucrisa)

- Crisaborole (Eucrisa) is a non-steroidal phosphodiesterase (PDE)-4 inhibitor indicated for patients as young as 2 years of age with mild to moderate atopic dermatitis. In the two controlled trials used for FDA approval, crisaborole treatment resulted in statistically significant improvement in atopic dermatitis signs and symptoms, compared to placebo vehicle. Although the results were statistically significant, the drugs provided only modest clinical benefit. There are no trials available comparing crisaborole with topical corticosteroids or the TCIs.

- The 2017 Institute for Clinical and Economic Review (ICER) review of crisaborole noted that there is not an agreed-upon definition of "mild-to-moderate" or "moderate-to-severe" atopic dermatitis. ICER also concluded that for patients with mild to moderate atopic dermatitis, there is inadequate evidence on both the relative efficacy and safety of crisaborole compared to other treatment options.

- Common side effects for crisaborole include burning and itching on application.

- Overall, despite the novel mechanism of action, crisaborole has no compelling advantages over the current formulary drugs used for atopic dermatitis.

Systemic therapy: dupilumab injection (Dupixent)

- Dupilumab is an interleukin-4/interleukin-13 antagonist monoclonal antibody indicated for moderate to severe atopic dermatitis that is not adequately controlled with topical prescription therapies. The 2017 ICER review concluded there was high certainty that dupilumab provides at least a small net health benefit relative to treatment with emollients, with or without continued failed topical treatments. Additionally, there was moderate certainty that the net health benefit of dupilumab is comparable or better than that provided by cyclosporine.

- Limitations to dupilumab include the lack of comparative trials with standard systemic treatments, the lack of long-term safety data, and the fact that it is only approved for use in adults. Pediatric trials are ongoing.

- The most common side effects for dupilumab are injection-site reactions and conjunctivitis.

- Dupilumab has fewer known side effects and monitoring requirements compared to azathioprine, cyclosporine, methotrexate, and mycophenolate.

2. Atopic Dermatitis—Relative Cost-Effectiveness Analysis and Conclusion

Cost-minimization analysis (CMA) and budget impact analysis (BIA) were performed to evaluate the atopic dermatitis agents.

The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA results showed that generic tacrolimus was the most cost-effective atopic dermatitis drug, followed by pimecrolimus (Elidel), branded tacrolimus (Protopic), crisaborole ointment (Eucrisa), and dupilumab injection (Dupixent).

- BIA was performed to evaluate the potential impact of designating selected agents as formulary or NF on the UF. BIA results found that designating pimecrolimus (Elidel), tacrolimus, and dupilumab (Dupixent) as formulary, with crisaborole (Eucrisa) as NF demonstrated significant cost avoidance for the Military Health System (MHS).

3. Atopic Dermatitis—UF Recommendation

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) the following, based on clinical and cost effectiveness:

- UF
  - pimecrolimus (Elidel)
  - dupilumab (Dupixent)
  - tacrolimus (Protopic, generics)

- NF
  - crisaborole (Eucrisa)

4. Atopic Dermatitis—Manual Prior Authorization (PA) Criteria

Manual PA criteria for both crisaborole ointment and dupilumab injection were recommended at the May 2017 P&T Committee meeting.

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) updating the current PA criteria for dupilumab (Dupixent), to require a trial of phototherapy, if feasible, in all new users, due to the AAD 2017 consensus statement on systemic therapies. The Committee also recommended maintaining the current manual PA criteria for crisaborole (Eucrisa), which requires a two-week trial of at least two formulary medium to high potency topical corticosteroids or a TCI first.

a. Eucrisa

No changes from the November 2017 meeting

Manual PA criteria apply to all new users of Eucrisa.

Manual PA criteria: Coverage is approved if all of the following criteria are met:

- Patient has mild to moderate atopic dermatitis
- Prescribed by a dermatologist, allergist, or immunologist
- Patient has a contraindication to, intolerability to, or failed treatment with a two-week trial of at least one medium to high potency topical corticosteroid

AND

- Patient has a contraindication to, intolerability to, or failed treatment with a two-week trial of a second agent including
  - An additional medium - high potency topical corticosteroid OR
  - Topical calcineurin inhibitor (i.e., tacrolimus, Elidel)

Non-FDA-approved uses are NOT approved.

PA does not expire.

b. Dupixent

August 2018 updates are in BOLD.

Manual PA criteria apply to all new users of Dupixent.

Manual PA criteria: Coverage will be approved for initial therapy for 6 months if all criteria are met:

- Patient has moderate to severe or uncontrolled atopic dermatitis
- Patient must be 18 years of age or older
- Prescribed by a dermatologist, allergist, or immunologist
- Patient has a contraindication to, intolerability to, or failed treatment with at least ONE high potency/class 1 topical corticosteroid
- Patient has a contraindication to, intolerability to, or failed treatment with at least ONE systemic immunosuppressant
- **Patient has a contraindication to, intolerability to, inability to access treatment, or failed treatment with Narrowband UVB phototherapy**

Non-FDA-approved uses are NOT approved.

PA expires after 6 months.

Renewal PA criteria: coverage will be approved indefinitely for continuation of therapy if:

- The patient has had a positive response to therapy, e.g., an Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1)

5. Atopic Dermatitis—UF and PA Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) an effective date upon the first Wednesday two weeks after the signing of the minutes in all points of service.

6. Physician's Perspective

Although this is the first formulary review for the class, both Eucrisa and Dupixent were previously reviewed as new drugs in 2017. There are no formulary changes recommended, so patients will be paying the same co-pay.

Eucrisa is currently non-formulary. A survey of Military Health System (MHS) providers felt Eucrisa is marginally effective, and it is appropriate to have a prior authorization (PA) requiring a trial of topical corticosteroids and TCIs (topical calcineurin inhibitors). This requirement is in the current PA.

MHS providers felt Dupixent was effective for severe cases, and acknowledged that a PA requiring a trial of other immunosuppressives would be appropriate. The PA was updated to also include the trial of phototherapy.

7. Panel Questions and Comments

Mr. Hostettler requested the total cost of this therapeutic category to the Department of Defense or Military Health System.

Lt Col Khoury said that total cost was approximately 25-30 million. He later amended that to 25.5 million.

Mr. Hostettler inquired about the reasoning for the 2-week implementation period.

Lt Col Khoury said there were no changes. Those drugs on UF stayed on the UF and NF drugs are staying NF so there are no real changes to patients. The PA criteria only affects new users.

There were no more questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, and UF and PA Implementation Plan for Atopic Dermatitis.

- **Atopic Dermatitis—UF Recommendation**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

- **Atopic Dermatitis—Manual PA Criteria**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

- **Atopic Dermatitis— UF and PA Implementation Plan**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

B. HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS (DAAS)

(LT COL KHOURY)

1. Hepatitis C Virus (HCV) Direct-Acting Antivirals (DAAs)—Relative Clinical Effectiveness Analysis and Conclusion

Background—The HCV DAAs subclass has previously been reviewed for formulary placement three times, most recently in February 2017. Two products, glecaprevir/pibrentasvir (Mavyret) and sofosbuvir/velpatasvir/voxilaprevir (Vosevi), were reviewed as new drugs at the November 2017 P&T Committee meeting. Since the last

review, simplification of HCV treatment has occurred, including introduction of additional regimens lasting only 8 weeks, FDA approval of additional single-tablet regimens, and the availability of additional pangenotypic therapies.

The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 0 absent) the following:

- There were no major changes to the clinical effectiveness conclusion from the February 2017 meeting.

- The first-line HCV DAAs are Epclusa, Harvoni, and Mavyret.

- Advantages of Harvoni include approval for treatment courses as short as 8 weeks in treatment-naïve patients with HCV genotype (GT) 1, availability as a single tablet dosed once daily, and approval for use in patients with decompensated cirrhosis. Patients with GT 4, 5, and 6 require 12-week treatment courses. Harvoni should remain designated as UF, due to existing high utilization in DoD, provider familiarity, and the fact that the majority of MHS patients with HCV have GT 1.

- Advantages of Epclusa include that it was the first pangenotypic HCV DAA marketed, it is dosed as a single tablet once daily, and it has an improved resistance profile. It remains an option of HCV therapy for treatment-naïve patients, but requires a 12-week course of therapy. It can be used in patients with decompensated cirrhosis.

- Mavyret was the third pangenotypic HCV DAA to receive FDA approval. It provides an 8-week course of therapy in treatment-naïve patients and treatment-experienced patients who do not have cirrhosis. Mavyret can also be used in patients with moderate to severe renal disease, including those on dialysis. It is dosed as three tablets once daily, and must be given with food.

- Vosevi was the second pangenotypic HCV DAA approved. It is reserved for use in treatment-experienced patients, and fills a unique niche for this population. It is dosed as a single tablet once daily for 12 weeks in most patients. It is not indicated for patients with moderate to severe renal dysfunction, including those with end-stage renal disease (ESRD).

- Daklinza, Olysio, Sovaldi, and Zepatier are no longer the standard of care for HCV, due to their longer treatment courses, limited genotype coverage, unfavorable tolerability and toxicity profiles, and/or higher pill burden.

- In the absence of head-to-head trials with all the DAAs, HCV treatment is based on individual patient characteristics, such as the HCV genotype and subtype, treatment history, stage of hepatic fibrosis, presence or absence of resistance-associated variants, comorbidities, concomitant medications, and cost.

2. HCV DAAs—Relative Cost-Effectiveness Analysis and Conclusion

CMA and BIA were performed to evaluate the HCV DAA agents. The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA results showed that glecaprevir/pibrentasvir (Mavyret), sofosbuvir/velpatasvir (Epclusa), and ledipasvir/sofosbuvir (Harvoni) were the most cost-effective HCV DAAs, followed by grazoprevir/elbasvir (Zepatier), paritaprevir/ritonavir/ombitasvir (Technivie), paritaprevir/ritonavir/ombitasvir/dasabuvir (Viekira Pak and Viekira XR), sofosbuvir/velpatasvir/voxilaprevir (Vosevi), daclatasvir (Daklinza), and sofosbuvir (Sovaldi).

- BIA was performed to evaluate the potential impact of designating selected agents as formulary or NF on the UF. BIA results showed that designating Mavyret, Epclusa, Harvoni, Technivie, Viekira, Viekira XR, and Vosevi as formulary, and Daklinza, Olysio, Sovaldi, and Zepatier as NF demonstrated the largest cost avoidance for the MHS.

3. HCV DAAs—UF Recommendation

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) the following, based on clinical and cost effectiveness:

- UF
  - sofosbuvir/velpatasvir (Epclusa)
  - ledipasvir/sofosbuvir (Harvoni)
  - glecaprevir/pibrentasvir (Mavyret)
  - paritaprevir/ritonavir/ombitasvir (Technivie)
  - paritaprevir/ritonavir/ombitasvir/dasabuvir tablets pak (Viekira Pak)
  - paritaprevir/ritonavir/ombitasvir/dasabuvir XR tablets (Viekira XR)
  - sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

- NF
  - daclatasvir (Daklinza)
  - simeprevir (Olysio)
  - sofosbuvir (Sovaldi)
  - grazoprevir/elbasvir (Zepatier)

- Note that as part of this recommendation, the current requirement for a trial of Harvoni prior to another HCV DAA ("step therapy") has been removed. Additionally, no HCV DAA products were recommended for Extended Core Formulary (ECF) addition. For the HCV drug class, ribavirin 200 mg capsules and peginterferon alfa-2a (Pegasys) were designated ECF in November 2012.

4. HCV DAAs—Manual PA Criteria

Manual PA criteria is currently required for all the HCV DAAs, including the use of Harvoni as the step-preferred product. The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) revising the manual PA criteria for new users of Daklinza, Epclusa, Harvoni, Mavyret, Olysio, Sovaldi, Technivie, Viekira XR, Viekira Pak, and Zepatier, to remove the Harvoni step therapy requirement, and simplify the PA criteria by having these drugs on the same PA form.

Additionally, the P&T Committee recommended maintaining separate PA criteria for Vosevi, since it is reserved for treatment-experienced patients. Minor updates to the Vosevi PA criteria were also recommended for new users, including removal of the Harvoni step. Coverage for any HCV DAA is only allowed for the FDA-approved indications or as outlined in the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD/IDSA) HCV guidelines (www.HCVguidelines.org).

a) Daklinza, Epclusa, Harvoni, Mavyret, Olysio, Sovaldi, Technivie, Viekira XR, Viekira Pak, and Zepatier

Changes from the August 2018 meeting will replace current PA criteria in place for the HCV DAAs. Note that the Harvoni step therapy requirement has been removed.

Manual PA criteria apply to all new users of Daklinza, Epclusa, Harvoni, Mavyret, Olysio, Sovaldi, Technivie, Viekira Pak, Viekira XR, and Zepatier.

Manual PA criteria: The HCV DAA is approved if all of the following criteria are met:

- ≥ 18 years of age
- Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious disease physician, or a liver transplant physician
- Patient has laboratory evidence of hepatitis C virus infection
- The HCV genotype is documented (Check box – GT1a, GT1b, GT2, GT3, GT4, GT5, GT6)

Coverage for the HCV DAA is only allowed for the FDA-approved indications or as outlined in the AASLD/IDSA HCV guidelines.

PA expires in 1 year.

b) Vosevi

Changes from the November 2017 meeting are in strikethrough; August 2018 updates are in BOLD and strikethrough.

Manual PA criteria apply to all new users of Vosevi.

Manual PA criteria: Vosevi is approved if all the following criteria are met:

- ≥ 18 years of age and diagnosed with chronic hepatitis C virus (HCV)
- Prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician
- Laboratory evidence of chronic hepatitis C
- The HCV genotype is documented. (Check box – GT1a, GT1b, GT2, GT3, GT4, GT5, GT6)
- The patient does not have estimated glomerular filtration rate (eGFR) ≤ 30 mL/min or end-stage renal disease (ESRD) requiring hemodialysis
- The patient will not be receiving concomitant therapy with other hepatitis C drugs or rifampin
- The treatment course will not exceed the maximum duration of treatment of 12 weeks
- **Patient has one of the following:**
  - **Patient has HCV GT 1, 2, 3, 4, 5, or 6 and was previously treated with an HCV regimen containing an NS5A inhibitor (for example, daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, or velpatasvir).**

    OR

  - **Patient has HCV GT 1a or 3 and has previously been treated with an HCV regimen containing sofosbuvir with or without an NS5A inhibitor (for example, daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, or velpatasvir).**

- ~~Patient cannot use Harvoni (due to HCV GT2 or GT3) other agents (due to decompensation, etc.)~~

  ~~AND~~

- ~~Previously treated with an NS5A inhibitor OR~~

- ~~HCV GT-1a or-3 and treated with sofosbuvir without an NS5A inhibitor~~

Coverage for the HCV DAA is only allowed for the FDA-approved indications or as outlined in the AASLD/IDSA HCV guidelines.

PA expires after 1 year; complete original PA form for renewal of therapy.

5. HCV DAAs—UF and PA Implementation Plan

The P&T Committee recommended (14 for, 0 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 60-day implementation period in all points of service, and 2) DHA send letters to beneficiaries who are affected by the UF decision.

6. Physician's Perspective

This is the fourth time we've reviewed the class, because the treatment guidelines and therapies have been updated frequently. Now that there are single tablet regimens available that target all the HCV genotypes, we are not expecting any major advances in therapy going forward.

The four products recommended for non-formulary placement will be subject to the copay increase. The Committee felt that these drugs should be non-formulary since they are outdated drugs. However, there are fewer than 15 patients on these drugs currently, and it is likely that the patients will have completed their course of therapy by the time the implementation date occurs, which will be in January 2019.

Also, after the meeting we became aware that the manufacturer has voluntarily discontinued production of Technivie and Viekira, however we don't have any patients on these drugs right now.

Since these drugs first came on the market, there has been several improvements in therapy. The drugs that are most commonly used are all on the uniform formulary. Removing the step therapy for Harvoni ensures that the newer therapies can be used in the appropriate patients.

This is an excellent example of competition bringing improved agents to market, with better outcomes for patients, reduced toxicities, all the while seeing reduced overall costs amongst those agents.

7. Panel Questions and Comments

Mr. Hostettler wanted to understand how the P&T Committee's decision affects the implementation timeframe. Most current users would have completed therapy before the changes are in place. There is also an impact to new patients who may start treatment before the 60-day implementation. He asks if it feasible to put the PA in place "now" for new patients and delay the implementation for current users. This would allow current users to complete their therapy.

Lt Col Khoury believes it will be hard to avoid impacts to patients because it is a phased process. As the information states in the handouts, there are 11 patients on the NF designated agents. There will be no impact to current patients because they will have completed their course of treatment prior to the implementation period. Although he does not believe it is feasible to implement the PA immediately for new patients and delay the implementation for current patients, without an impact to current or new patients at some point, he will take the suggestion back for further review. The problem predicting when a new patient begins therapy and figuring out how to implement your recommendation.

Mr. Hostettler suggested implementing the new PA as soon as the Director, DHA signs the minutes. Then, new patients would not be required to pay the increase in co-pay for the 3rd Tier drugs. Current patient would complete his or her treatment within the 60 days with no negative impact or interruption to treatment.

Lt Col Khoury asked if Mr. Hostettler was suggesting a faster implementation.

Mr. Hostettler replied yes for the actual PA. As previously stated, he is concerned it will affect the treatment of current users. If a faster implementation is problematic, grandfather current users and allow them to complete their therapy.

Lt Col Khoury stated there are significant changes with the PA as well as limitations that will take time to coordinate with our stakeholder.

There were no more questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, and UF and PA Implementation Plan for HCV DAAs.

- **HCV DAAs —UF Recommendation**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

- **HCV DAAs —Manual PA Criteria**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

- **HCV DAAs— UF and PA Implementation Plan**

  Concur: 4 Non-Concur: 1 Abstain: 0 Absent: 1

Additional Panel Questions and Comments

There was additional discussion regarding this drug class.

Mr. Hostettler repeats his suggestion of delaying implementation of the PA for current users to ensure that their therapy is complete and putting the PA in place earlier for new patients to avoid any impact. Conversely, pursue the 60-day implementation but grandfather any patients who start therapy during the 60-days and allow them to complete their therapy under the old PA.

Lt Col Khoury wants to ensure he understands the question. He asked if Mr. Hostettler is recommending DoD grandfather the co-pay for new and current users.

Mr. Hostettler replied yes.

Lt Col Khoury stated historically we do not grandfather the co-pay when there is a change. The historical precedence is when the status changes the co-pay changes as well. However, I will take your recommendation back for further discussion.

C. CORTICOSTEROIDS-IMMUNE MODULATORS: ADRENOCORTICOTROPIC HORMONES (ACTH)

(LCDR HANSEN)

1. Corticosteroids-Immune Modulators: Adrenocorticotropic Hormones (ACTH)—Relative Clinical Effectiveness Analysis and Conclusion

Background—The P&T Committee previously evaluated the ACTH subclass at the February 2018 meeting. The ACTH subclass is comprised solely of injectable corticotropin (H.P. Acthar Gel). The Committee designated H.P. Acthar with UF status, with manual PA allowing use exclusively for infantile spasms or exacerbation of multiple sclerosis (MS) and only after failure of or intolerance to a course of corticosteroids.

At this meeting, the P&T Committee reviewed additional information received from providers and the FDA as it relates to the clinical effectiveness and safety of H.P. Acthar. There was no change to the cost effectiveness conclusion, Uniform Formulary recommendation, or PA criteria from the February 2018 P&T Committee meeting.

A comprehensive review of the evidence for H.P. Acthar Gel's efficacy for infantile spasms, multiple sclerosis exacerbation, other uses, and safety and tolerability across all

indications and usages was performed for the February 2018 P&T Committee meeting. That comprehensive body of evidence guided the P&T's decision-making in that meeting.

The P&T Committee concluded (14 for, 0 opposed, 0 abstained, 0 absent) the following:

- Infantile Spasms
    - New information was presented that reaffirms and strengthens the clinical conclusions reached by the P&T Committee at the February 2018 meeting, including the following:
        - Patients with infantile spasms require urgent treatment that is better facilitated by oral corticosteroids, which are widely available, rather than the administratively burdensome H.P. Acthar Gel, due to the limited distribution requirements by the manufacturer.
        - High-dose oral corticosteroids were reaffirmed as a frontline treatment alongside H.P. Acthar Gel and vigabatrin (Sabril).
- MS Exacerbation
    - Fundamentals of inflammation were reviewed, reaffirming the appropriateness of the requirement that patients try and fail the safer and more effective corticosteroid treatment option prior to approval of H.P. Acthar Gel for each multiple sclerosis exacerbation.
- Other Uses
    - There was no new data to support changing the original recommendation that uses other than infantile spasms and MS exacerbation be excluded from TRICARE coverage.[1]
- Safety
    - No new information was presented that helped allay the concerns of the Committee regarding the safety profile of H.P. Acthar Gel. New data, however, did cause the Committee to have more safety concerns than previously concluded.
- Other Factors
    - A review of coverage of H.P. Acthar Gel by several commercial health care plans performed for the February 2018 P&T Committee meeting found significant limitations or outright exclusions of H.P. Acthar Gel.

[1] As with any drug, an appeal is available for an eligible covered beneficiary or network or uniformed provider on behalf of the beneficiary to establish clinical justification for the use of a pharmaceutical agent that is not on the Uniform Formulary. See 10 U.S.C. § 1074g.

- For the August 2018 meeting, the P&T Committee reviewed an update to several national health care plans and health systems' coverage policies. Of the 50 pharmacy benefit managers (PBMs) reviewed in the update, 9 health care plans did not cover H.P. Acthar Gel for any indication for their respective beneficiaries.

- Several prominent health care plans and health systems require a trial of oral corticosteroids prior to using H.P. Acthar Gel for infantile spasms. These include Intermountain Health System in Utah and leading Academic Centers of Excellence in Pediatric Neurology, such as Johns Hopkins and UCLA.

- The P&T Committee reviewed prior decisions in other drug classes where the recommendation was to require a trial of a drug lacking FDA approval for a particular diagnosis prior to use of a drug that carries FDA approval for that particular diagnosis. One example is that patients with Duchenne's Muscular Dystrophy are required to try or have intolerance to prednisone prior to using deflazacort (Emflaza) [February 2017 DoD P&T Committee Meeting].

- Overall, the Committee evaluated the additional information presented and agreed that no new evidence was presented that would change the clinical conclusions reached by the P&T Committee at the February 2018 meeting. In fact, additional information for treatment of infantile spasms further confirmed the appropriateness of a trial of corticosteroids and the importance of early treatment, before using H.P. Acthar Gel. Additional safety concerns for H.P. Acthar Gel were raised by the new information. No changes to the existing manual PA criteria for H.P. Acthar Gel were recommended.

2. Physician's Perspective

The Committee did another review of the clinical data with Acthar. There were no changes to the cost conclusion, UF recommendation, or PA criteria. The PA criteria for Acthar cover both infantile spasms and MS exacerbation, but do require a trial of steroids first.

3. Panel Questions and Comments

Mr. Hostettler thanked the P&T Committee for going back and re-reviewing the information to confirm their recommendation.

There were no more questions or comments from the Panel. The Chair called for a vote for the Corticosteriods-Immune Modulators: Adrenocorticotropic Hormones (ACTH) to maintain current UF Status and PA Criteria.

- **ACTH—Maintain Current UF Status and PA Criteria**

Concur: 5	Non-Concur: 0	Abstain: 0	Absent: 1

II. NEWLY APPROVED DRUGS PER 32 CFR 199.21(G)(5)

(LCDR HANSEN)

1. Newly Approved Drugs per 32 CFR 199.21(g)(5)—Relative Clinical Effectiveness and Relative Cost-Effectiveness Conclusions

The P&T Committee agreed (group 1 and 3: 14 for, 0 opposed, 0 abstained, 0 absent; group 2: 13 for, 0 opposed, 0 abstained, 1 absent) with the relative clinical and cost-effectiveness analyses presented for the newly approved drugs reviewed according to 32 CFR 199.21(g)(5).

2. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF Recommendation

The P&T Committee recommended (group 1 and group 3: 14 for, 0 opposed, 0 abstained, 0 absent and group 2: 13 for, 0 opposed, 0 abstained, 1 absent) the following:

- UF:
  - abiraterone acetate micronized (Yonsa) – Oral Oncologic Agent for Prostate Cancer
  - avatrombopag (Doptelet) – Hematological Agent: Platelets for Thrombocytopenia in Chronic Liver Disease
  - baricitinib (Olumiant) – Targeted Immunomodulatory Biologic (TIB) for Rheumatoid Arthritis
  - binimetinib (Mektovi) – Oral Oncologic Agent for Metastatic Melanoma
  - encorafenib (Braftovi) – Oral Oncologic Agent for Metastatic Melanoma
  - epoetin-alfa-epbx (Retacrit) injection – Hematological Agent: Red Blood Cell Stimulant for Erythropoiesis
  - erenumab-aooe (Aimovig) injection – Migraine Agent (calcitonin gene-related peptide [CGRP]) for Migraine Headache Prophylaxis
  - fostamatinib (Tavalisse) – Hematological Agent: Platelets for Chronic Immune Thrombocytopenia
  - hydroxyurea (Siklos) tablets – Hematological Agent: Sickle Cell Anemia Agent for Sickle Cell Anemia in Pediatrics
  - pegvaliase-pqpz (Palynziq) injection – Miscellaneous Metabolic Agent for Phenylketonuria
  - tolvaptan (Jynarque) – Miscellaneous Nephrology Agent for Rapidly Progressing Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- NF:
  - amantadine extended release tablets (Osmolex ER) – Parkinson's Agent
  - estradiol (Imvexxy) vaginal insert – Miscellaneous Gynecological Agent for Dyspareunia
  - levonorgestrel/ethinyl estradiol/ferrous (Balcoltra) – Oral Combined Contraceptive Agent
  - lofexidine (Lucemyra) – Alpha 2 Antagonist for Mitigation of Symptoms of Opioid Withdrawal

- oxycodone IR (Roxybond) – Narcotic Analgesic Abuse Deterrent Formulation for Pain

3. Newly Approved Drugs per 32 CFR 199.21(g)(5)—PA Criteria

The P&T Committee recommended (group 1 and group 3: 14 for, 0 opposed, 0 abstained, 0 absent and group 2: 13 for, 0 opposed, 0 abstained, 1 absent) the following:

- Applying manual PA criteria to new users of Yonsa, Osmolex ER, Doptelet, Olumiant, Imvexxy, Mektovi, Braftovi, Lucemyra, Aimovig, Siklos, and Palynziq.

- Applying manual PA criteria to new and current users of Tavalisse and Jynarque.

Full PA Criteria for the Newly Approved Drugs per 32 CFR 199.21(g)(5)

a) abiraterone acetate micronized (Yonsa)

Manual PA criteria apply to all new users of Yonsa.

Manual PA criteria: Yonsa is approved if all criteria are met:

- Provider is aware that Yonsa may have different dosing and food effects than other abiraterone acetate products, due to the risks of medication errors and overdose

- Patient has documented diagnosis of metastatic castration-resistant prostate cancer (mCRPC)

- Patient must receive concomitant therapy with methylprednisolone

- The patient is concomitantly receiving a gonadotropin-releasing hormone (GnRH) analog or has had bilateral orchiectomy

Non-FDA-approved uses are NOT approved, with exception for treatment in patients with metastatic high-risk castration-sensitive prostate cancer (mHRCSPC).

PA does not expire.

b) amantadine extended release tablets (Osmolex ER)

Manual PA criteria apply to all new users of Osmolex ER.

Manual PA criteria: Osmolex ER is approved if all criteria are met:

- Patient is aged 18 years and older

- Patient has a diagnosis of either Parkinson's disease or drug-induced extrapyramidal symptoms

- Patient has had therapeutic failure of a trial of amantadine 300 mg per day given in divided doses using immediate release tablets.

Non-FDA-approved uses are NOT approved.

PA does not expire.

c) avatrombopag (Doptelet)

Manual PA criteria apply to all new users of Doptelet.

Manual PA criteria: Avatrombopag (Doptelet) is approved if all criteria are met:

- Age ≥ 18
- Patient is diagnosed with liver disease that has caused severe thrombocytopenia (platelet count less than 50 x 10^9/L)
- Patient is scheduled to undergo a procedure with a moderate to high bleeding risk within 10-13 days after starting avatrombopag
- Patient has no evidence of current thrombosis
- The drug is prescribed by or in consultation with a gastroenterologist

Non-FDA-approved uses are NOT approved.

PA expires in 60 days.

d) baricitinib (Olumiant)

Manual PA criteria apply to all new users of Olumiant.

Manual PA criteria: Baricitinib (Olumiant) is approved if all criteria are met:

- Provider acknowledges that Humira is the preferred TIB to treat rheumatoid arthritis
- Provider acknowledges that if a JAK inhibitor is desired, Xeljanz/Xeljanz XR is an alternative to baricitinib (Olumiant) without the black box warning risk of thrombosis
- Age ≥ 18
- Has diagnosis of moderate to severe active rheumatoid arthritis

- Has a contraindication, inadequate response, or had an adverse reaction to adalimumab (Humira)
- Has a contraindication, inadequate response, or had an adverse reaction to methotrexate
- Has no history of thromboembolic disease
- Is not receiving other potent immunosuppressants (e.g., azathioprine or cyclosporine)
- May not be used concomitantly with other TIB agents except for Otezla
- Must be prescribed by or in consultation with a rheumatologist

Non-FDA-approved uses are NOT approved.

PA does not expire.

e) binimetinib (Mektovi)

Manual PA criteria apply to all new users of Mektovi.

Manual PA criteria: Mektovi is approved if all criteria are met:

- Age ≥ 18 years
- Has unresectable or metastatic melanoma
- Has confirmed BRAF V600E or BRAF V600K mutation by an FDA-approved test
- Mektovi is being taken in combination with Braftovi
- Patient is not on concurrent dabrafenib (Tafinlar), trametinib (Mekinist), vemurafenib (Zelboraf), nor cobimetinib (Cotellic)
- Prescribed by or in consultation with an oncologist

Non-FDA-approved uses are NOT approved.

PA does not expire.

f) encorafenib (Braftovi)

Manual PA criteria apply to all new users of Braftovi.

Manual PA criteria: Braftovi is approved if all criteria are met:

- Age ≥ 18 years
- Has unresectable or metastatic melanoma
- Has confirmed BRAF V600E or BRAF V600K mutation by an FDA-approved test
- Braftovi is being taken in combination with Mektovi
- Patient is not on concurrent dabrafenib (Tafinlar), trametinib (Mekinist), vemurafenib (Zelboraf), nor cobimetinib (Cotellic)
- Prescribed by or in consultation with an oncologist

Non-FDA-approved uses are NOT approved.

PA does not expire.

g) erenumab-aooe (Aimovig) injection

Manual PA criteria apply to all new users of Aimovig.

Manual PA criteria: Aimovig is approved if all criteria are met:

- Patient ≥ 18 years old and not pregnant
- Must be prescribed by or in consultation with a neurologist
- Patient has a migraine diagnosis with at least 8 migraine days per month for 3 months
- Patient has a contraindication to, intolerability to, or has failed a 2-month trial of at least ONE drug from TWO of the following migraine prophylactic drug classes:
    - Prophylactic antiepileptic medications: valproate, divalproic acid, topiramate
    - Prophylactic beta-blocker medications: metoprolol, propranolol, atenolol, nadolol

- Prophylactic antidepressants: amitriptyline, venlafaxine

Non-FDA-approved uses are NOT approved.

PA expires after 6 months.

Renewal criteria: coverage will be approved indefinitely for continuation of therapy if:

- The patient has shown improvement in migraine prevention (e.g., reduced migraine headache days, reduced migraine frequency, reduced use of acute abortive migraine medication)

h) estradiol (Imvexxy) vaginal insert

Manual PA criteria apply to all new users of Imvexxy.

Manual PA criteria: Imvexxy is approved for 1 year if all criteria are met:

- Patient is a postmenopausal woman with a diagnosis of moderate to severe dyspareunia due to vulvar and vaginal atrophy
- Patient has tried and failed or has a contraindication to a low dose vaginal estrogen preparation (e.g., Premarin vaginal cream, Estrace vaginal cream, Estring, Vagifem)
- Patient does not have any of the following:
  - Undiagnosed abnormal genital bleeding
  - Pregnant or breastfeeding
  - History of breast cancer or currently has breast cancer
  - History of thromboembolic disease or currently has thromboembolism

Non-FDA-approved uses are NOT approved.

PA expires in 1 year.

Renewal criteria: Coverage is approved for an additional year if:

- Patient has an improvement in dyspareunia symptom severity

i) fostamatinib (Tavalisse)

Manual PA criteria apply to all new and current users Tavalisse.

Manual PA criteria: Fostamatinib (Tavalisse) is approved if all criteria are met:

- Age ≥ 18
- Has diagnosis of chronic primary idiopathic thrombocytopenic purpura (ITP) whose disease has been refractory to at least one previous therapy (including IVIG, thrombopoietin(s), corticosteroids, and/or splenectomy)
- Has laboratory evidence of thrombocytopenia with average [platelet] count less than 30 x 10^9/L over three discrete tests
- Has no evidence of active or chronic infection
- Has no evidence of secondary thrombocytopenia
- Does not have uncontrolled hypertension
- Has had no cardiovascular event (including but not limited to MI, unstable angina, PE, CVA, and/or NYHA Stage III or IV CHF) within the last 6 months
- Has no evidence of neutropenia or lymphocytopenia
- Prescribed by or in consultation with a hematologist/oncologist
- Tavalisse is not being used concomitantly with other chronic ITP therapy

Non-FDA-approved uses are NOT approved.

PA expires in 120 days.

Renewal criteria: Fostamatinib (Tavalisse) can be renewed for an additional year if all criteria are met:

- Has demonstrated a response to fostamatinib (Tavalisse) as defined by a sustained platelet count > 50 x 10^9/L or an increase in platelet count by ≥ 20 x 10^9/L above baseline. Sustained is defined by two separate tests (at least 2 or more weeks apart) meeting either or both of the aforementioned criteria
- Has no evidence of active or chronic infection
- Has no evidence of secondary thrombocytopenia

- If patient carries a diagnosis of hypertension, it is well controlled according to national guidelines (e.g., JNC 8)

- Has had no cardiovascular event (including but not limited to MI, unstable angina, PE, CVA, and/or NYHA Stage III or IV CHF) within the last 6 months

- Has no evidence of neutropenia or lymphocytopenia.

- Prescribed by or in consultation with a hematologist/oncologist

j) hydroxyurea (Siklos)

Manual PA criteria apply to all new users of Siklos older than 18 years of age.

Automated PA criteria: Siklos will be approved for patients ≤ 18 years of age.

Manual PA criteria: Siklos is approved if all criteria are met:

- Age ≥ 19 years

- The provider documents a patient-specific reason why the patient cannot use the preferred product (generic hydroxyurea or Droxia).

- Acceptable responses would include:

    - The patient has a diagnosis of sickle cell disease AND has swallowing difficulties

- Note that use of Siklos for malignancy (e.g., chronic myelocytic leukemia or other cancers) is not approved

Non-FDA-approved uses are NOT approved.

PA expires after 1 year.

Renewal criteria: Coverage will be approved indefinitely if all of the following apply:

- Patient continues to have swallowing difficulties that preclude the use of hydroxyurea 200 mg, 300 mg, 400 mg, or 500 mg capsules

- Patient has been monitored and has had at least two laboratory draws in the last year and has not developed hematologic toxicity (Toxic hematologic ranges: Neutrophils < 2,000/mm3; platelets < 80,000/mm3; hemoglobin < 4.5 g/dL; and reticulocytes < 80,000/mm3 if hemoglobin is < 9 g/dL)

- Patient has achieved a stable dose with no hematologic toxicity for 24 weeks

k) lofexidine (Lucemyra)

Manual PA criteria apply to all new users of Lucemyra.

Manual PA criteria: Lucemyra is approved if all criteria are met:

- Lucemyra is prescribed for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation
- Patient is ≥ 18 years old
- Lucemyra will not be prescribed for longer than 14 days
- The provider documents a patient-specific reason why the patient cannot use the preferred product, clonidine. Acceptable responses include that the patient has experienced orthostatic hypotension or severe bradycardia with previous clonidine use

Non-FDA-approved uses are NOT approved (e.g., blood pressure control, nicotine withdrawal, Tourette syndrome, or ADHD).

PA expires after 3 months.

Renewal criteria: Renewal of therapy will not be allowed

l) pegvaliase-pqpz (Palynziq)

Manual PA criteria apply to all new users of Palynziq.

Manual PA criteria: Palynziq is approved for initial therapy if all criteria are met:

- Patient is ≥ 18 years of age
- Patient has uncontrolled blood phenylalanine concentrations > 600 micromol/L on at least one existing treatment modality (e.g., restriction of dietary phenylalanine and protein intake, or prior treatment with Kuvan [sapropterin dihydrochloride tablets and powder for oral solution])
- Palynziq is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases)
- Provider acknowledges and has educated the patient on the risk of anaphylaxis
- Patient has a prescription for self-administered SQ epinephrine

- Patient is not using Palynziq concomitantly with Kuvan

Non-FDA-approved uses are NOT approved.

PA expires in 6 months.

Renewal criteria (maintenance/continuation therapy): Coverage will be approved for 1 year if:

- The patient's blood phenylalanine concentration is ≤ 600 micromol/L OR
- The patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting Palynziq therapy) AND
- Patient is not using Palynziq concomitantly with Kuvan

m) tolvaptan (Jynarque)

Manual PA criteria apply to all new and current users of Jynarque.

Manual PA criteria: Jynarque is approved if all criteria are met:

- Age ≥ 18
- Jynarque is prescribed by or in consultation with a nephrologist
- Provider acknowledges that Jynarque requires liver function monitoring with evaluation of transaminases and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter
- Patient has rapidly progressing autosomal dominant polycystic kidney disease (ADPKD, defined as reduced or declining renal function [i.e., glomerular filtration rate {GFR} less than or equal to 65 mL/min/1.73 m^2] and high total kidney volume [i.e., greater than or equal to 750ml])
- Patient does not have Stage 5 chronic kidney disease (CKD) [GFR < 15 mL/min/1.73 m^2]
- Patient is not receiving dialysis
- Patient is not currently taking Samsca (tolvaptan)

Non-FDA-approved uses are NOT approved.

PA does not expire.

4. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF and PA Implementation Plan

The P&T Committee recommended (group 1 and group 3: 14 for, 0 opposed, 0 abstained, 0 absent; and group 2: 13 for, 0 opposed, 0 abstained, 1 absent) an effective date upon the first Wednesday two weeks after signing of the minutes in all points of service.

5. Physician's Perspective

We reviewed 16 new drugs at this meeting; with 11 recommended for UF status, and 5 recommended for non-formulary placement. For the drugs recommended for non-formulary status, several of them fall into classes that have already been reviewed by the P&T Committee, where there are cost effective alternative products already available in the class.

For this review, 13 drugs have PA recommended. Six of these drugs fall into classes that have already been reviewed and have existing PA requirements.

Several of the new drugs this time were evaluated for orphan diseases or unique indications that the P&T Committee had not previously reviewed. The PA requirements overall were to ensure that the drugs are being used in accordance with the product labeling.

Out of these 13 drugs with PAs, 11 will have the PA apply to new users only, so current users will be grandfathered. For two drugs (Tavalisse for ITP and Jynarque for autosomal polycystic kidney disease) the PA will apply to new and current users (or a "no grandfathering scenario"). The Committee was concerned that there are monitoring requirements for these two drugs due to safety issues, and wanted to ensure current patients are receiving the appropriate monitoring.

There were a couple of comments made at the meeting for some of the drugs recommended to have Prior Authorization:

- Aimovig (for migraine): This is the first drug in a new therapeutic class, and more products are in the pipeline. Due to the potential for high numbers of patients to be impacted if a PA were to be implemented several months after market introduction, the PA was placed administratively close after launch, after consultation with a specialist. The PA does require a trial of commonly used preventive products first, which is consistent with current migraine headache guidelines. Currently we have over 600 patients on this drug.

- Palynziq (for PKU): PA criteria were recommended here also due to safety concerns, specifically anaphylaxis. A REMS program from the FDA requires that the patient also receive an Epi Pen with the prescription. We have made arrangements to ensure the Epi Pen can be dispensed at the time Palynziq is being dispensed.

6. Panel Comments and Questions

Mr. Hostettler inquired as to the number of patients currently utilizing these products.

Lt Col Khoury said that most of the products have 1-20 users but erenumab-aooe (Aimovig) has 600 users.

Mr. Hostettler asked about Osmolex ER. Is there any difference in side effects between the long acting and the immediate release? Are there any clinical differences between two products?

LCDR Hansen said that the data that was reviewed show no difference between two agents. Lt Col Khoury also stated for this product that there are no utilizers.

Mr. Hostettler asked, regarding the estradiol (Imvexxy), whether all of the other products that LCDR Hansen mentioned, are all these UF products.

Lt Col Khoury said that yes they were.

Regarding Implementation Criteria: Mr. Hostettler stated that the P&T Committee has managed to get all of these new approved drugs done with 2 weeks but the earlier discussion on HCV DAAs needed a 60-day implementation.

Lt Col Khoury stated that the drugs on the earlier topic required changes including forms that need to be modified, so it requires more time. This one has a new form and few, if any, patients.

There were no more questions or comments from the Panel. The Chair called for a vote on the UF Recommendation, Manual PA Criteria, and UF and PA Implementation Plan for Newly Approved Drugs.

- **Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF Recommendation**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

- **Newly Approved Drugs per CFR 199.21 (g)(5) – PA Criteria**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

- **Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF and PA Implementation**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

III. UTILIZATION MANAGEMENT

(LT COL KHOURY)

1. PA Criteria and Step Therapy

Updates to the step therapy and manual PA criteria for several drugs were recommended by the P&T Committee due to a variety of reasons, including expanded FDA indications and drug shortages. The updated manual PAs outlined below will apply to new users.

a) Epinephrine Auto-Injectors: Auvi-Q Temporary Removal of Manual PA Criteria— The Auvi-Q device includes audible voice instructions and has a needle that automatically retracts following injection. Manual PA criteria were previously recommended for all epinephrine auto-injectors, including Epi-Pen, generic epinephrine auto-injectors, and Auvi-Q, at the February 2017 P&T Committee meeting. The PA requirements for Epi-Pen were administratively removed on May 23, 2018, due to a national shortage. There have been continued shortages of Epi-Pen, and intermittent availability of generic epinephrine auto-injectors.

Although Auvi-Q is significantly more expensive than Epi-Pen, the manual PA requirements for Auvi-Q will be temporarily lifted, but re-instated administratively when the supply of Epi-Pen and generic epinephrine auto-injectors has stabilized. The Committee acknowledged, however, that it is doubtful that the current Auvi-Q supply will support the volume required to replace Epi-Pen.

b) Renin Angiotensin Antihypertensive Agents (RAAs): candesartan and candesartan/HCTZ Step-Therapy—Step therapy in the RAAs class requires a trial of losartan, telmisartan, valsartan, or irbesartan, or their respective combinations with hydrochlorothiazide (HCTZ), prior to use of non-step-preferred angiotensin receptor blockers (ARBs). Two ARBs, candesartan and irbesartan, are approved for treating heart failure with reduced ejection fraction (HFrEF), in addition to hypertension. Candesartan and candesartan/HCTZ are currently designated as UF but non-step-preferred.

There is currently a national recall of valsartan, due to contamination with a carcinogen. There is no immediate risk to patients currently taking valsartan. However, availability of valsartan lots not affected by the recall are in limited supply, and it remains uncertain as to when the shortage will be resolved.

A group of MHS cardiologists has requested removing the step therapy requirement for candesartan, due to the valsartan recall. Cost-effective formulations of candesartan and candesartan/HCTZ are now available. Candesartan and candesartan/HCTZ will now be designated as step-preferred, with the step therapy criteria and medical necessity criteria for the remaining non-step-preferred RAAs updated accordingly.

c) **Oncological Agents for unresectable or metastatic melanoma: dabrafenib (Tafinlar), trametinib (Mekinist), and vemurafenib (Zelboraf) Manual PA criteria—**These drugs are approved for treating unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. They are exclusively used in unique pair combinations of a specific BRAF drug with a specific mitogen-activated extracellular signal regulated kinase (MEK) inhibitor. Due to the risk of enhanced toxicity if other combinations of BRAF with MEK inhibitors are administered together, the PA criteria were updated to prevent the use of concurrent therapies outside of the FDA-approved combination.

   Criteria were also updated for dabrafenib (Tafinlar) and trametinib (Mekinist) to include the new FDA-approved indication for combination use for locally advanced or metastatic anaplastic thyroid cancer without satisfactory locoregional treatment options.

d) **Oncological Agents: Prostate II - enzalutamide (Xtandi)—**In August 2012, manual PA criteria were recommended for Xtandi. PA criteria were updated in February 2015 to remove the co-administration requirement of docetaxel. Xtandi is now FDA-approved for treatment of castration-resistant prostate cancer, and does not require the presence of metastatic disease. Additionally, the PA criteria were also updated to include new product labeling that requires the patient receive concomitant therapy with a gonadotropin-releasing hormone (GnRH) analog, or have had bilateral orchiectomy.

e) **Targeted Immunomodulatory Biologics (TIBs): Tofacitinib (Xeljanz/Xeljanz XR)—** The TIBs were reviewed in August 2014, with step therapy requiring a trial of adalimumab (Humira) first. Xeljanz was originally approved for treating rheumatoid arthritis. In February 2018, PA criteria were updated to add the indication for active psoriatic arthritis in adults. The PA criteria were further expanded to include a new FDA-approved indication of ulcerative colitis.

2. Updated Manual PA Criteria

The P&T Committee recommended the following:

- (12 for, 0 opposed, 0 abstained, 2 absent) to temporarily remove the manual PA criteria for Auvi-Q, until adequate supply of the Epi-Pen auto-injector has been established.

- (14 for, 0 opposed, 0 abstained, 0 absent) updates to the manual PA criteria and step therapy for candesartan and candesartan/HCTZ.

- (13 for, 0 opposed, 0 abstained, 1 absent) updates to the manual PA criteria for Tafinlar, Mekinist, Zelboraf, Xeljanz/Xeljanz XR, and Xtandi.

3. Updated Manual PA Criteria and PA Renewal Criteria—PA Implementation Plan

The P&T Committee recommended the following implementation periods:

- (12 for, 0 opposed, 0 abstained, 2 absent) and (14 for, 0 opposed, 0 abstained, 0 absent) To administratively implement the removal of manual PA requirements for Auvi-Q and to designate candesartan and candesartan/HCTZ as step-preferred.

- (13 for, 0 opposed, 0 abstained, 1 absent) Updates to the current PAs for Tafinlar, Mekinist, Zelboraf, Xeljanz, Xeljanz XR, and Xtandi become effective on the first Wednesday two weeks after the signing of the minutes.

4. Physician's Perspective

Epi pen and Auvi Q: Removal of PA requirements

The Committee does want to respond quickly in the event of a compelling national shortage. This is why the PA requirements for EPI PEN and the generic pen were administratively removed back in May. For Auvi Q, we actually implemented the recommendation to remove the PA on one week after the P&T mtg. We would like to comment that other commercial health plans, including Walgreens have also recently loosened their restrictions on Auvi Q, so it is unlikely that Auvi Q stock will be able to meet the needs of all the patients who may not be able to obtain Epi-Pen.

Valsartan shortage and removal of candesartan step therapy

This is another example of where the Committee wanted to react quickly. There are several drugs that are first-line treatments for hypertension, including ACE inhibitors and other ARBs, besides valsartan. The overall risk of developing cancer with valsartan is low. The FDA estimates that there would be one additional cancer case over the lifetime of 8,000 patients taking the highest valsartan dose over four years.

However, because candesartan is the only other ARB with an additional indication for CHF, we implemented the change in step therapy one week after the August meeting. We do want to respond quickly when these types of issues come up.

5. Panel Questions and Comments

Mr. Ostrowski asked, regarding the Epi-pen, when the P&T Committee makes the administrative change back after it has stabilized is there any effect on the beneficiary such as copay difference.

Lt Col Khoury said that once the shortage has been resolved, we want them to go back to the Epi-pen because of the cost effectiveness relative to the Auvi-Q. If someone is on the Epi-pen, there will be no effect as long as they're able to get the drug.

Mr. Ostrowski asked if the cost of the patient is the same.

Lt Col Khoury said that the Epi-pen is on the formulary but is not sure about Auvi-Q. He'll need to confirm that. The PA is what we're changing, not the copay. In order to get the Auvi-Q, you had to try and fail the Epi-pen first so we're removing that requirement. It didn't make sense to require the use of Epi-pen if it wasn't available.

Lt Col Khoury said that there is an alternate, based on what we're seeing supply-wise, but they also expect an issue with the Auvi-Q supply as well. They don't expect that all of the people having issues obtaining the Epi-pen are going to have their problems solved by going to Auvi-Q but we didn't want to have a restriction keeping them from getting it.

Mr. Hostettler appreciates that the P&T Committee took action and did so quickly. Is Auvi-Q is non-formulary.

Lt Col Khoury believes that it is NF but will need to verify that.

Mr. Hostettler said that leaves patients with no formulary product for an extremely important drug. Administratively, is there any way to ensure that is a formulary option available? There has been a shortage for a long time and it is getting worse.

Lt Col Khoury will take that back and verify before the close of the meeting. He then confirmed Auvi-Q is formulary.

Mr. Hostettler had a question on the valsartan issue as well. There are no plans to reverse decision once the valsartan issue is resolved, correct? The P&T Committee is not going to put candesartan back in?

Lt Col Khoury said that this was correct, there are no reversals planned.

There were no more questions or comments from the Panel. The Chair called for a vote on the Manual PA and PA Renewal Criteria and the Manual PA and PA Renewal Implementation Plan for Utilization Management of several drugs.

- **Updated Manual PA Criteria and PA Renewal Criteria – Auvi-Q**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

- **Updated Manual PA and PA Renewal Implementation Plan -**

  Concur: 5 Non-Concur: 0 Abstain: 0 Absent: 1

Mr. Ostrowski concludes the meeting. He thanks the P&T Committee for their work and all those attending the meeting.

(Meeting Concludes)

Appendix A – Table of Implementation Status of UF Recommendations/Decisions Summary
Appendix B – Brief Listing of Acronyms Used in this Summary
Appendix C – Private Citizen Comments - US WorldMeds
Appendix D – Private Citizen Comments – Sidley Austin LLP on behalf of Mallinckrodt Pharmaceuticals

Mr. Jon Ostrowski
UF BAP Chairperson

Table of Implementation Status of UF Recommendations/Decisions Summary

Date	DoD PEC Drug Class	Type of Action	UF Medications	Nonformulary Medications	Implement Date	Notes and Unique Users Affected
Aug 2018	**Corticosteroids -Immune Modulators: Atopic Dermatitis**	UF Class Review	UF ▪ pimecrolimus (Elidel) ▪ dupilumab (Dupixent) injection ▪ tacrolimus (Protopic, generics) ▪	NF ▪ crisaborole (Eucrisa) ointment	2 weeks after signing of the minutes	▪ Manual PA criteria applies to all new users for dupilumab (Dupixent) ▪ Updates made to the Dupixent PA ▪ No changes recommended to the current Eucrisa PA criteria Unique Users Affected None
Aug 2018	**Hepatitis C Virus Direct-Acting Antivirals**	UF Class review Class previously reviewed in Feb 2017, May 2015, Nov 2012; New drug review in Nov 2017	UF ▪ sofosbuvir/velpatasvir (Epclusa) ▪ ledipasvir/sofosbuvir (Harvoni) ▪ glecaprevir/ pibrentasvir (Mavyret) ▪ paritaprevir/ritonavir/ ombitasvir (Technivie) ▪ paritaprevir/ritonavir/ ombitasvir/dasabuvir XR tablets (Viekira XR) ▪ dasabuvir tablets pak (Viekira Pak) ▪ sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	NF ▪ daclatasvir (Daklinza) ▪ simeprevir (Olysio) ▪ sofosbuvir (Sovaldi) ▪ grazoprevir/elbasvir (Zepatier)	60 days	▪ Manual PA required ▪ Previous requirement for step therapy with Harvoni removed ▪ PA criteria simplified for all the DAAs except Vosevi ▪ Vosevi separate PA form due to unique FDA indication Unique Users Affected Mail – 3 MTF – 3 Retail – 5 Total – 11

Appendix B **07/12/2018 BAP Meeting**

Brief Listing of Acronyms Used in this Summary

Abbreviated terms are spelled out in full in this summary; when they are first used, the acronym is listed in parentheses immediately following the term. All of the terms commonly used as acronyms in the Panel discussions are listed below for easy reference. The term "Pan" in this summary refers to the "Uniform Formulary Beneficiary Panel," the group who's meeting in the subject of this report.

- AIDS – Acquired Immunodeficiency Syndrome
- ARI – Alpha Reductase Inhibitor
- BAP – Beneficiary Advisory Panel
- BIA – Budget Impact Analysis
- cAMP – Cyclic Adenosine Monophosphate
- CFR – Code of Federal Regulations
- CFTR – Cystic Fibrosis Transmembrane Conductance Regulator
- CMA – Cost Minimization Analysis
- COPD – Chronic Obstructive Pulmonary Disease
- CT – Cognitive Therapy
- CVOTs – Cardiovascular Outcome Trials
- CYP3A4 – Cytochrome P450 isoforms
- DoD – Department of Defense
- eGFR – Estimated Glomerular Filtration Rate
- EPI – Exocrine Pancreatic Insufficiency
- ER – Extended Release
- FDA – Food and Drug Administration
- G-Tube – Gastronomy-Tube
- GI-2 – Gastrointestinal-2
- GSA – Growth Stimulating Agents
- HCT- Hematrocrit
- HIV – Human Immunodeficiency Virus
- IR – Immediate Release
- JIA – Juvenile Idiopoathic Arthritis
- L – liter
- LDL – Low Density Lipoprotein
- Mg – Milligram
- MTF – Military Treatment Facility
- NDAA – National Defense Authorization Act
- NDC – National Drug Code
- NF – Non Formulary
- NSAIDs – Nonsteroidal Anti-Inflammatory Drugs
- ODE4 – Phosphodiesterase-4
- OIC – Opioid-Induced Constipation
- OTC – Over the Counter
- P&T – Pharmacy and Therapeutics Committee
- PA – Prior Authorization

- PAMORAs – Peripherally Acting Mu Opioid Receptor Antagonists
- PERT – Pancreatic Enzyme Replacement Therapy
- POS – Point of Sale
- rhGH – Recombinant Human Growth Hormone
- SGLT2s – Sodiun Glucose Co-Transporter
- ShoX – Short Stature Homeobox
- SIADH – Syndrome Inappropriate Antidiuretic Hormone
- SNRI – Serotonin Norepinephrine Reuptake Inhibitor
- SSRI – Selective Reuptake Inhibitor
- TIBs – Targeted Immunomodulatory Agents
- TRICARE – Healthcare Network
- UF -0 Uniform Formulary
- XR – Extended Release

US WORLDMEDS PUBLIC COMMENT FOR THE UNIFORM FORMULARY BENEFIT ADVISORY PANEL MEETING SEPTEMBER 27th, 2018

Re: LUCEMYRA® Department of Defense Pharmacy and Therapeutics Committee Preliminary Recommendation

Pursuant to 41 CFR 102–3.140 we seek to provide comment on the preliminary recommendation from the DoD P&T Committee for the Uniform Formulary Beneficiary Advisory Panel for Lucemyra. Specifically, the P&T Committee recommendations for Lucemyra are as follows:

lofexidine (Lucemyra)
Manual PA criteria apply to all new users of Lucemyra.
Manual PA criteria: Lucemyra is approved if all criteria are met:
• Lucemyra is prescribed for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation
• Patient is ≥ 18 years old
• Lucemyra will not be prescribed for longer than 14 days
• The provider documents a patient-specific reason why the patient cannot use the preferred product, clonidine. Acceptable responses include that the patient has experienced orthostatic hypotension or severe bradycardia with previous clonidine use
Non-FDA-approved uses are NOT approved (e.g., blood pressure control, nicotine withdrawal, Tourette syndrome, or ADHD).
PA expires after 3 months.
Renewal criteria: Renewal of therapy will not be allowed

US WorldMeds Comment:
Lucemyra is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. It is the first and only FDA-approved non-opioid medication for the mitigation of opioid withdrawal syndrome.

Especially in the context of our current opioid crisis, it is important that prescribing and formulary authorization criteria reflect clinical judgement and nuances specific to the disease state. We ask the Committee to reconsider PA criteria that have the potential to adversely affect treatment goals for providers and their patients who require acute opioid withdrawal management.

The current PA Criteria require that "*The provider documents a patient-specific reason why the patient cannot use the preferred product, clonidine. Acceptable responses include that the patient has experienced orthostatic hypotension or severe bradycardia with previous clonidine use*". This is clinically unacceptable for the following reasons:

1. Clonidine is not FDA-approved and lacks consistent, evidence-based and standardized clonidine dosing guidelines for opioid withdrawal management. We note that the Lucemyra PA includes specific criteria that "*Non-FDA uses are NOT approved*". We concur that when available, a FDA-approved drug supported by robust clinical efficacy and safety data should take precedence and priority.

2. A 'step-through' requirement for clonidine trial and/or failure places unwarranted burden on providers who are unfamiliar or unwilling to prescribe clonidine off-label. And unnecessary restriction on their patients who otherwise do not have access to the only FDA-approved, non-opioid treatment with proven, evidence-based, standardized dosing and administration instructions. This is especially true for providers, including primary care, who may be uncomfortable or unwilling to prescribe opioid-based treatments to manage withdrawal.

3. There are 4 historical blinded, head-to-head studies that compared clonidine with lofexidine (Lucemyra). All consistently showed similar efficacy and a superior safety profile for lofexidine. A recently published Cochrane Review also concluded no significant efficacy differences between treatment regimens and a better safety profile for lofexidine compared with clonidine. In the

context of opioid withdrawal management, safety and tolerability play a key role in patient retention and increase HCP confidence to engage and manage their patients through this critical treatment step. Note that these four studies are not included in the label.

[Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews 2016*, Issue 5. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub5.], [Carnwath T, Hardman J. Randomised double-blind comparison of lofexidine and clonidine in the outpatient treatment of opiate withdrawal. *Drug and Alcohol Dependence* 1998;50(3):251–4.], [Kahn A, Mumford JP, Rogers GA, Beckford H. Doubleblind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. *Drug and Alcohol Dependence* 1997;44(1):57–61.], [Lin S-K, Strang J, Su L-W, Tsai C-J, Hu W-H. Doubleblind randomised controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal. *Drug and Alcohol Dependence* 1997;48(2):127–33.], [Gerra G, Zaimovic A, Giusti F, Di Gennaro C, Zambelli U, Gardini S, Delsignore R. Lofexidine versus clonidine in rapid opiate detoxification. *J Subst Abuse Treat*. 2001 Jul;21(1):11-7.]

4. A healthcare provider and patient decision to 'tackle' opioid withdrawal is a critical time window that requires the best chance for success. These patients typically are highly sensitive to, and fearful of, opioid withdrawal symptoms. Early and effective withdrawal management is critical to keep patients engaged in withdrawal treatment. Off-label clonidine treatment requires early titration that increases the likelihood of early undertreatment and treatment failure. These are potentially devastating consequences if withdrawal could have been completed but was intentionally inadequate due to step-through restriction of a non-approved medication.

Lucemyra is not a treatment for opioid use disorder (or post-withdrawal addiction treatment). It is the only FDA-approved, non-opioid treatment for mitigation of opioid withdrawal symptoms. Opioid withdrawal symptoms are debilitating and perpetuate opioid use in the majority of chronic opioid users, including patients for whom the initial prescription was for pain.

In summary, we ask the Committee to give patients and their providers the best chance possible to successfully navigate opioid withdrawal.

This includes direct access to Lucemyra as Uniform Formulary and without requirement for step-through of a non-approved medication that lacks standardized, evidence-based dosing and administration for efficacy and safety.

Thank you for your additional consideration of our comments.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUCEMYRA safely and effectively. See full prescribing information for LUCEMYRA.

LUCEMYRA™ (lofexidine) tablets, for oral use
Initial U.S. Approval: 2018

---------- INDICATIONS AND USAGE ----------

LUCEMYRA is a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- The usual LUCEMYRA dosage is three 0.18 mg tablets taken orally 4 times daily at 5- to 6-hour intervals. LUCEMYRA treatment may be continued for up to 14 days with dosing guided by symptoms. (2.1)
- Discontinue LUCEMYRA with a gradual dose reduction over 2 to 4 days. (2.1)
- Hepatic or Renal Impairment: Dosage adjustments are recommended based on degree of impairment. (2.2, 2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 0.18 mg. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Hypotension, Bradycardia, and Syncope: May cause a decrease in blood pressure, a decrease in pulse, and syncope. Monitor vital signs before dosing and advise patients on how to minimize the risk of these cardiovascular effects and manage symptoms, should they occur. Monitor symptoms related to bradycardia and orthostasis. When using in outpatients, ensure that patients are capable of self-monitoring signs and symptoms. Avoid use in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure, as well as in patients with marked bradycardia. (5.1)
- Risk of QT Prolongation: LUCEMYRA prolongs the QT interval. Avoid use in patients with congenital long QT syndrome. Monitor ECG in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, hepatic or renal impairment, or in patients taking other medicinal products that lead to QT prolongation. (5.2)
- Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs: LUCEMYRA potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. (5.3)
- Increased Risk of Opioid Overdose after Opioid Discontinuation: Patients who complete opioid discontinuation are at an increased risk of fatal overdose should they resume opioid use. Use in conjunction with a comprehensive management program for treatment of opioid use disorder and inform patients and caregivers of increased risk of overdose. (5.4)
- Risk of Discontinuation Symptoms: Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy, reduce dose gradually. (5.5)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥ 10% and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds at 1-833-LUCEMYRA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

- Methadone: Methadone and LUCEMYRA both prolong the QT interval. ECG monitoring is recommended when used concomitantly. (7.1)
- Oral Naltrexone: Concomitant use may reduce efficacy of oral naltrexone. (7.2)
- CYP2D6 Inhibitors: Concomitant use of paroxetine resulted in increased plasma levels of LUCEMYRA. Monitor for symptoms of orthostasis and bradycardia with concomitant use of a CYP2D6 inhibitor. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUCEMYRA is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The usual LUCEMYRA starting dosage is three 0.18 mg tablets taken orally 4 times daily during the period of peak withdrawal symptoms (generally the first 5 to 7 days following last use of opioid) with dosing guided by symptoms and side effects. There should be 5 to 6 hours between each dose. The total daily dosage of LUCEMYRA should not exceed 2.88 mg (16 tablets) and no single dose should exceed 0.72 mg (4 tablets).

LUCEMYRA treatment may be continued for up to 14 days with dosing guided by symptoms.

Discontinue LUCEMYRA with a gradual dose reduction over a 2- to 4-day period to mitigate LUCEMYRA withdrawal symptoms (e.g., reducing by 1 tablet per dose every 1 to 2 days) *[see Warnings & Precautions (5.5)]*. The LUCEMYRA dose should be reduced, held, or discontinued for individuals who demonstrate a greater sensitivity to LUCEMYRA side effects *[see Adverse Reactions (6.1), Warnings and Precautions (5.1)]*. Lower doses may be appropriate as opioid withdrawal symptoms wane.

LUCEMYRA can be administered in the presence or absence of food.

2.2 Dosage Recommendations for Patients with Hepatic Impairment

Recommended dosage adjustments based on the degree of hepatic impairment are shown in Table 1. *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

Table 1: Dosage Recommendations in Patients with Hepatic Impairment

	Mild Impairment	Moderate Impairment	Severe Impairment
Child-Pugh score	5-6	7-9	> 9
Recommended dose	3 tablets 4 times daily (2.16 mg per day)	2 tablets 4 times daily (1.44 mg per day)	1 tablet 4 times daily (0.72 mg per day)

2.3 Dosage Recommendations for Patients with Renal Impairment

Recommended dosage adjustments based on the degree of renal impairment are shown in Table 2. LUCEMYRA may be administered without regard to the timing of dialysis *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Table 2: Dosage Recommendations in Patients with Renal Impairment

	Moderate Impairment	Severe Impairment, End-Stage Renal Disease, or on Dialysis
Estimated GFR, mL/min/1.73 m^2	30-89.9	< 30
Recommended dose	2 tablets 4 times daily (1.44 mg per day)	1 tablet 4 times daily (0.72 mg per day)

3 DOSAGE FORMS AND STRENGTHS

LUCEMYRA is available as round, peach-colored, film-coated tablets, imprinted with “LFX” on one side and “18” on the other side. Each tablet contains 0.18 mg lofexidine (equivalent to 0.2 mg of lofexidine hydrochloride).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hypotension, Bradycardia, and Syncope

LUCEMYRA can cause a decrease in blood pressure, a decrease in pulse, and syncope *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*. Monitor vital signs before dosing. Monitor symptoms related to bradycardia and orthostasis.

Patients being given LUCEMYRA in an outpatient setting should be capable of and instructed on self-monitoring for hypotension, orthostasis, bradycardia, and associated symptoms. If clinically significant or symptomatic hypotension and/or bradycardia occur, the next dose of LUCEMYRA should be reduced in amount, delayed, or skipped.

Inform patients that LUCEMYRA may cause hypotension and that patients moving from a supine to an upright position may be at increased risk for hypotension and orthostatic effects. Instruct patients to stay hydrated, on how to recognize symptoms of low blood pressure, and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position). Instruct outpatients to withhold LUCEMYRA doses when experiencing symptoms of hypotension or bradycardia and to contact their healthcare provider for guidance on how to adjust dosing.

Avoid using LUCEMYRA in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, and in patients with marked bradycardia.

Avoid using LUCEMYRA in combination with medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension.

5.2 Risk of QT Prolongation

LUCEMYRA prolongs the QT interval.

Avoid using LUCEMYRA in patients with congenital long QT syndrome.

Monitor ECG in patients with congestive heart failure, bradyarrhythmias, hepatic impairment, renal impairment, or patients taking other medicinal products that lead to QT prolongation (e.g., methadone). In patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), correct these abnormalities first, and monitor ECG upon initiation of LUCEMYRA *[see Dosing and Administration (2.1), Adverse Reactions (6.1), Special Populations (8.6)(8.7), Clinical Pharmacology (12.2)]*.

5.3 Increased Risk of Central Nervous System Depression with Concomitant use of CNS Depressant Drugs

LUCEMYRA potentiates the CNS depressive effects of benzodiazepines and can also be expected to potentiate the CNS depressive effects of alcohol, barbiturates, and other sedating drugs. Advise patients to inform their healthcare provider of other medications they are taking, including alcohol.

Advise patients using LUCEMYRA in an outpatient setting that, until they learn how they respond to LUCEMYRA, they should be careful or avoid doing activities such as driving or operating heavy machinery.

5.4 Increased Risk of Opioid Overdose after Opioid Discontinuation

LUCEMYRA is not a treatment for opioid use disorder. Patients who complete opioid discontinuation are likely to have a reduced tolerance to opioids and are at increased risk of fatal overdose should they resume opioid use. Use LUCEMYRA in patients with opioid use disorder only in conjunction with a comprehensive management program for the treatment of opioid use disorder and inform patients and caregivers of this increased risk of overdose.

5.5 Risk of Discontinuation Symptoms

Stopping LUCEMYRA abruptly can cause a marked rise in blood pressure. Symptoms including diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain have also been observed with LUCEMYRA discontinuation. Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy with LUCEMYRA tablets, gradually reduce the dose *[see Dosing and Administration (2.1)]*.

Symptoms related to discontinuation can be managed by administration of the previous LUCEMYRA dose and subsequent taper.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Hypotension, Bradycardia, and Syncope *[see Warnings and Precautions (5.1)]*
- QT Prolongation *[see Warnings and Precautions (5.2)]*
- Central Nervous System Depression *[see Warnings and Precautions (5.3)]*
- Opioid Overdose *[see Warnings and Precautions (5.4)]*
- Discontinuation Symptoms *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to adverse reaction rates observed for another drug and may not reflect the rates observed in practice.

The safety of LUCEMYRA was supported by three randomized, double-blind, placebo-controlled clinical trials, an open-label study, and clinical pharmacology studies with concomitant administration of either methadone, buprenorphine, or naltrexone.

The three randomized, double-blind, placebo-controlled clinical trials enrolled 935 subjects dependent on short-acting opioids undergoing abrupt opioid withdrawal. Patients were monitored before each dose in an inpatient setting.

Table 3 presents the incidence, rounded to the nearest percent, of adverse events that occurred in at least 10% of subjects treated with LUCEMYRA and for which the incidence in patients treated with LUCEMYRA was greater than the incidence in subjects treated with placebo in a study that tested two doses of LUCEMYRA, 2.16 mg per day and 2.88 mg per day, and placebo. The overall safety profile in the combined dataset was similar.

Orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth were notably more common in subjects treated with LUCEMYRA than subjects treated with placebo.

Table 3: Adverse Reactions Reported by ≥10% of LUCEMYRA-Treated Patients and More Frequently than Placebo

Adverse Reaction	LUCEMYRA 2.16 mg[1] (%) N=229	LUCEMYRA 2.88 mg[1] (%) N=222	Placebo (%) N=151
Insomnia	51	55	48
Orthostatic Hypotension	29	42	5
Bradycardia	24	32	5
Hypotension	30	30	1
Dizziness	19	23	3
Somnolence	11	13	5
Sedation	13	12	5
Dry Mouth	10	11	0

[1] Assigned dose; mean average daily dose received was 79% of assigned dose due to dose-holds for out-of-range vital signs.

Other notable adverse reactions associated with the use of LUCEMYRA but reported in <10% of patients in the LUCEMYRA group included:

- Syncope: 0.9%, 1.4% and 0% for LUCEMYRA 2.16 mg/day and 2.88 mg/day and placebo, respectively
- Tinnitus: 0.9%, 3.2% and 0% for LUCEMYRA 2.16 mg/day and 2.88 mg/day and placebo, respectively

Blood pressure changes and adverse reactions after LUCEMYRA cessation

Elevations in blood pressure above normal values (≥ 140 mmHg systolic) and above a subject's pre-treatment baseline are associated with discontinuing LUCEMYRA, and peaked on the second day after discontinuation, as shown in Table 4. Blood pressure values were evaluated for 3 days following the last dose of a 5-day course of LUCEMYRA 2.88 mg/day.

Table 4: Blood Pressure Elevations after Stopping Treatment

	Abrupt LUCEMYRA Discontinuation 2.88 mg (N = 134)		Placebo (N = 129)	
	N at risk	n (%)	N at risk	n (%)
Systolic Blood Pressure on Day 2 after Discontinuation				
≥ 140 mmHg and ≥ 20 mmHg increase from baseline	58	23 (39.7)	37	6 (16.2)
≥ 170 mmHg and ≥ 20 mmHg increase from baseline	58	5 (8.6)	37	0

Blood pressure elevations of a similar magnitude and incidence were observed in a small number of patients (N=10) that had a one-day, 50% dose reduction prior to discontinuation.

After stopping treatment, subjects that were taking LUCEMYRA also had a higher incidence of diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain compared to subjects who were taking placebo.

Sex-specific adverse event findings

Four out of 101 females (4%) had serious cardiovascular adverse events compared to 3 out of 289 (1%) of males assigned to receive LUCEMYRA 2.88 mg per day.

Discontinuations and dose holds due to bradycardia and orthostatic hypotension, which are the most common adverse reactions associated with LUCEMYRA, occurred with a greater incidence in females assigned to receive the highest studied dose of LUCEMYRA, 2.88 mg per day as shown in Table 5.

Table 5: Discontinuations and Dose Holds for Bradycardia and Orthostatic Hypotension by LUCEMYRA Dose and Sex

	LUCEMYRA 2.16 mg	LUCEMYRA 2.88 mg
Male	22/162 (14%)	29/158 (18%)
Female	9/67 (13%)	20/64 (31%)

6.2 Postmarketing Experience

Lofexidine is marketed in other countries for relief of opioid withdrawal symptoms. The following events have been identified during postmarketing use of lofexidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Since lofexidine's initial market introduction in 1992, the most frequently reported postmarketing adverse event with lofexidine has been hypotension *[see Warnings and Precautions (5.1)]*. There has been one report of QT prolongation, bradycardia, torsades de pointes, and cardiac arrest with successful resuscitation in a patient that received lofexidine and three reports of clinically significant QT prolongation in subjects concurrently receiving methadone with lofexidine.

7 DRUG INTERACTIONS

7.1 Methadone

LUCEMYRA and methadone both prolong the QT interval. ECG monitoring is recommended in patients receiving methadone and LUCEMYRA *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

7.2 Oral Naltrexone

Coadministration of LUCEMYRA and oral naltrexone resulted in statistically significant differences in the steady-state pharmacokinetics of naltrexone. It is possible that oral naltrexone efficacy may be reduced if used concomitantly within 2 hours of LUCEMYRA. This interaction is not expected if naltrexone is administered by non-oral routes *[see Clinical Pharmacology (12.3)]*.

7.3 CNS Depressant Drugs

LUCEMYRA potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. Advise patients to inform their healthcare provider of other medications they are taking, including alcohol *[see Warnings and Precautions (5.3)]*.

7.4 CYP2D6 Inhibitor - Paroxetine

Coadministration of LUCEMYRA and paroxetine resulted in 28% increase in the extent of absorption of LUCEMYRA. Monitor for orthostatic hypotension and bradycardia when an inhibitor of CYP2D6 is used concomitantly with LUCEMYRA *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety of LUCEMYRA in pregnant women has not been established. In animal reproduction studies, oral administration of lofexidine during organogenesis to pregnant rats and rabbits caused a reduction in fetal weights, increases in fetal resorptions, and litter loss at exposures below that in humans. When oral lofexidine was administered from the beginning of organogenesis through lactation, increased stillbirths and litter loss were noted along with decreased viability and lactation indices. The offspring exhibited delays in sexual maturation, auditory startle, and surface righting. These effects occurred at exposures below that in humans *[see Animal Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

Increased incidence of resorptions, decreased number of implantations, and a concomitant reduction in the number of fetuses were observed when pregnant rabbits were orally administered lofexidine hydrochloride during organogenesis (from gestation day [GD] 7 to 19) at a daily dose of 5.0 mg/kg/day (approximately 0.08 times the maximum recommended human dose [MRHD] of 2.88 mg lofexidine base on an AUC basis). Maternal toxicity evidenced by increased mortality was noted at the highest tested dose of 15 mg/kg/day (approximately 0.4 times the MRHD on an AUC basis).

Decreased implantations per dam and decreased mean fetal weights were noted in a study in which pregnant rats were treated with oral lofexidine hydrochloride during organogenesis (from GD 7 to 16) at a daily dose of 3.0 mg/kg/day (approximately 0.9 times the MRHD on an AUC basis). This dose was associated with maternal toxicity (decreased body weight gain and mortality). No malformations or evidence of developmental toxicity were evident at 1.0 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis).

A dose-dependent increase in pup mortality was noted in all doses of lofexidine hydrochloride administered orally to pregnant rats from GD 6 through lactation at an exposure less than the human exposure based on AUC comparisons. Doses higher than 1.0 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis) resulted in incidences of total litter loss and maternal toxicity (piloerection and decreased body weight gain). The highest dose tested of 2.0 mg/kg/day (approximately 0.6 times the MRHD on an AUC basis), increased stillbirths as well as decreased viability and lactation indices were reported. Surviving offspring exhibited lower body weights, developmental delays, and increased delays in auditory startle at doses of 1.0 mg/kg/day or higher. Sexual maturation was delayed in male offspring (preputial separation) at 2.0 mg/kg/day and in female offspring (vaginal opening) at 1.0 mg/kg/day or higher.

8.2 Lactation

Risk Summary

There is no information regarding the presence of LUCEMYRA or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Caution should be exercised when LUCEMYRA is administered to a nursing woman.

The developmental and health benefits should be considered along with the mother's clinical need for LUCEMYRA and any other potential adverse effects on breastfed children from LUCEMYRA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

In animal studies that included some fertility endpoints, lofexidine decreased breeding rate and increased resorptions at exposures below human exposures. The impact of lofexidine on male fertility has not been adequately characterized in animal studies *[see Impairment of Fertility (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of LUCEMYRA have not been established in pediatric patients.

8.5 Geriatric Use

No studies have been performed to characterize the pharmacokinetics of LUCEMYRA or establish its safety and effectiveness in geriatric patients. Caution should be exercised when it is administered to patients over 65 years of age. Dosing adjustments similar to those recommended in patients with renal impairment should be considered *[see Dosage and Administration (2.3), Use in Specific Populations (8.7)]*.

8.6 Hepatic Impairment

Hepatic impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration than on AUC values following a single dose. Dosage adjustments are recommended based on the degree of hepatic impairment. *[see Dosage and Administration (2.2), Clinical Pharmacology (12.2)]*.

Clinically relevant QT prolongation may occur in subjects with hepatic impairment *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.2)]*.

8.7 Renal Impairment

Renal impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration than on AUC values following a single dose. Dosage adjustments are recommended based on the degree of renal impairment *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

Only a negligible fraction of the LUCEMYRA dose is removed during a typical dialysis session, so no additional dose needs to be administered after a dialysis session; LUCEMYRA may be administered without regard to the timing of dialysis *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

Clinically relevant QT prolongation may occur in subjects with renal impairment *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.2)]*.

8.8 CYP2D6 Poor Metabolizers

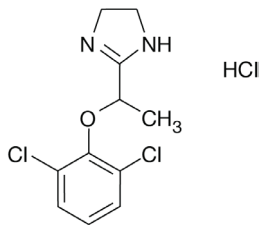
Although the pharmacokinetics of LUCEMYRA have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to LUCEMYRA would be increased similarly to taking strong CYP2D6 inhibitors (approximately 28%). Monitor adverse events such as orthostatic hypotension and bradycardia in known CYP2D6 poor metabolizers. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Overdose with LUCEMYRA may manifest as hypotension, bradycardia, and sedation. In the event of acute overdose, perform gastric lavage where appropriate. Dialysis will not remove a substantial portion of the drug. Initiate general symptomatic and supportive measures in cases of overdosage.

11 DESCRIPTION

LUCEMYRA tablets contain lofexidine, a central alpha-2 adrenergic agonist, as the hydrochloride salt. Lofexidine hydrochloride is chemically designated as 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5 dihydro-1*H*- imidazole monohydrochloride with a molecular formula of $C_{11}H_{12}Cl_2N_2O$•HCl. Its molecular weight is 295.6 g/mole and its structural formula is:



Lofexidine hydrochloride is a white to off-white crystalline powder freely soluble in water, methanol, and ethanol. It is slightly soluble in chloroform and practically insoluble in n-hexane and benzene.

LUCEMYRA is available as round, convex-shaped, peach-colored, film-coated tablets for oral administration. Each tablet contains 0.18 lofexidine, equivalent to 0.2 mg of lofexidine hydrochloride, and the following inactive ingredients: 92.6 mg lactose, 12.3 mg citric acid, 1.1 mg povidone, 5.7 mg microcrystalline cellulose, 1.4 mg calcium stearate, 0.7 mg sodium lauryl sulphate, and Opadry OY S 9480 (contains indigo carmine and sunset yellow).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lofexidine is a central alpha-2 adrenergic agonist that binds to receptors on adrenergic neurons. This reduces the release of norepinephrine and decreases sympathetic tone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Single LUCEMYRA doses of 1.44 to 1.8 mg produced maximum mean change from baseline in QTcF (ΔQTcF) of 14.4 msec (upper two-sided 90% CI: 22.3 msec) and 13.6 msec (17.4 msec) for 1.44 and 1.8 mg respectively in healthy normal volunteers.

In a Phase 3 placebo-controlled, dose response study in opioid dependent subjects, LUCEMYRA was associated with a maximum mean prolongation of the QTcF interval 7.3 (8.8) and 9.3 (10.9) msec at doses of 2.16 and 2.88 mg/day, respectively.

Patients with hepatic impairment

Administration of LUCEMYRA to subjects with hepatic impairment was associated with prolongation of the QTc interval, which was more pronounced in subjects with severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

Patients with renal impairment

Administration of LUCEMYRA to subjects with renal impairment was associated with prolongation of the QTc interval, which was more pronounced in subjects with severe renal impairment *[see Use in Specific Populations (8.7)]*

LUCEMYRA coadministered with methadone

LUCEMYRA (2.88 mg/day) coadministered with methadone in 18 methadone-maintained patients (80-120 mg/day) resulted in a maximum mean increase from methadone-alone baseline in QTcF of 9.1 (14.2) msec.

LUCEMYRA coadministered with buprenorphine

LUCEMYRA (2.88 mg/day) coadministered with buprenorphine in 21 buprenorphine-maintained patients (16-24 mg/day) resulted in a maximum mean QTcF increase in QTcF of 15 (5.6) msec compared to a buprenorphine-alone baseline.

In Vitro Binding

LUCEMYRA exhibits *in vitro* binding affinity and functional agonist activity with alpha-2A and alpha-2C adrenoreceptors at concentrations within clinical exposure plasma levels (K_i values of approximately 7.2 nM and 12 nM, and EC_{50} values of 4.9 nM and 0.9 nM, respectively).

12.3 Pharmacokinetics

Absorption

LUCEMYRA is well absorbed and achieves peak plasma concentration 3 to 5 hours after administration of a single dose.

LUCEMYRA shows approximately dose-proportional pharmacokinetics. Administration of LUCEMYRA with food does not alter its pharmacokinetics.

The absolute bioavailability of a single oral LUCEMYRA dose (0.36 mg in solution) compared with an intravenous infusion (0.2 mg infused for 200 minutes) was 72%. Mean LUCEMYRA C_{max} after the oral dose and intravenous infusion was 0.82 ng/mL (at median T_{max} of 3 hours) and 0.64 ng/mL (at median T_{max} of 4 hours), respectively. Mean estimates of overall systemic exposure (AUC_{inf}) were 14.9 ng•h/mL and 12.0 ng•h/mL, respectively.

Distribution

Mean LUCEMYRA apparent volume of distribution and volume of distribution values following the administration of an oral dose and an intravenous dose were 480.0 L and 297.9 L, respectively, which are appreciably greater than total body volume, suggesting extensive LUCEMYRA distribution into body tissue.

LUCEMYRA protein binding is approximately 55%.

LUCEMYRA is not preferentially taken up by blood cells. In a study comparing LUCEMYRA concentrations in plasma and whole blood at the time of peak LUCEMYRA concentrations in human volunteers, it was determined that red blood cells contain approximately 27% the LUCEMYRA concentration of the plasma.

Elimination

Metabolism

From absolute bioavailability results, approximately 30% of the administered LUCEMYRA dose is converted to inactive metabolites during the first pass effect associated with drug absorption from the gut.

LUCEMYRA and its major metabolites did not induce or inhibit any CYP450 isoforms, with the exception of a slight inhibition of CYP2D6 by LUCEMYRA, with an IC_{50} of 4551 nM (approximately 225 times the steady-state C_{max} for LUCEMYRA with 0.72 mg 4 times daily dosing). Any LUCEMYRA interaction with CYP2D6 substrates is not expected to be clinically significant.

LUCEMYRA is metabolized when incubated *in vitro* with human liver microsomes, the major contributor to the hepatic metabolism of LUCEMYRA is CYP2D6, with CYP1A2 and CYP2C19 also capable of metabolizing LUCEMYRA.

Excretion

The elimination half-life is approximately 12 hours and mean clearance is 17.6 L/h following an IV infusion.

LUCEMYRA has a terminal half-life of approximately 11 to 13 hours following the first dose. At steady-state, the terminal half-life is approximately 17 to 22 hours. Accumulation occurs up to 4 days with repeat dosing, following the recommended dosing regimen.

A mass balance study of LUCEMYRA showed nearly complete recovery of radiolabel in urine (93.5%) over 144 hours postdose, with an additional 0.92% recovered in the feces over 216 hours postdose. Thus, it appears that all, or nearly all, of the dose was absorbed, and that the primary route of elimination of the parent drug and its metabolites is via the kidney. Renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose.

Specific Populations

Hepatic Impairment

Hepatic impairment slows the elimination of LUCEMYRA, but exhibits less effect on the peak plasma concentration following a single dose. In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in mild, moderate, and severe hepatically impaired subjects to subjects with normal hepatic function (6 subjects in each hepatic function group), mean C_{max} values were similar for subjects with normal, mild, and moderate hepatic impairment as shown in Table 6.

Table 6: LUCEMYRA Pharmacokinetics in Subjects with Hepatic Impairment

	Normal	Mild Impairment	Moderate Impairment	Severe Impairment
Child-Pugh Class & Score	Normal Function	Class A 5-6	Class B 7-9	Class C 10-15
C_{max} % of normal	100	114	117	166
AUC_{last} % of normal	100	127	190	304
AUC_{∞} % of normal	100	117	185	260
$t_{1/2}$ % of normal	100	139	281	401

Renal Impairment

Renal impairment slows the elimination of LUCEMYRA but exhibits less effect on the peak plasma concentration following a single dose. In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in 8 end-stage renal disease subjects on 3 times weekly hemodialysis to 8 subjects with normal renal function matched for sex, age, and body mass index, mean C_{max} values were similar for end-stage renal disease and normal renal function subjects, indicating no change in maximum LUCEMYRA exposure with renal impairment as shown in Table 7.

The impact of dialysis on the overall pharmacokinetics of LUCEMYRA during a typical 4-hour dialysis was minimal; the drop in LUCEMYRA plasma concentrations produced during the dialysis session was transient, with a rebound to nearly predialysis concentrations after re-equilibration within a few hours following completion of the dialysis cycle *[see Dosage and Administration (2.3), Use in Specific Populations (8.7)]*.

In a study comparing the pharmacokinetics of LUCEMYRA (0.36 mg) in 6 subjects each with normal renal function, mild renal impairment, and moderate renal impairment as well as 5 subjects with severe renal impairment but not requiring dialysis, there were similar increases in mean C_{max} values in subjects with mild and moderate renal impairment in comparison to subjects with normal renal function with additional increase in mean C_{max} values in subjects with severe renal impairment. Mean AUC_{last}, AUC_{∞}, and $t_{1/2}$ increased with severity of renal impairment as shown in Table 7.

Table 7: LUCEMYRA Pharmacokinetics in Subjects with Renal Impairment

	Normal	Mild Impairment	Moderate Impairment	Severe Impairment	ESRD or on dialysis
eGFR (mL/min/1.73 m^2)	≥ 90	60-89	30-59	15-29	< 15
C_{max} % of normal	100	124	117	154	104
AUC_{last} % of normal	100	157	187	272	181
AUC_{∞} % of normal	100	144	173	243	171
$t_{1/2}$ % of normal	100	111	145	157	137

Drug Interaction Studies

LUCEMYRA coadministered with methadone

In a double-blind placebo-controlled study of 23 patients maintained on a methadone dose of 80-120 mg/day and concomitantly administered LUCEMYRA up to 2.88 mg/day, LUCEMYRA did not alter the pharmacokinetics of methadone. LUCEMYRA concentrations may be slightly increased when coadministered with methadone; however, the increase at concentrations expected with recommended dosing is not clinically meaningful *[see Drug Interactions (7.1)]*.

LUCEMYRA coadministered with buprenorphine

In a double-blind placebo-controlled study of 30 subjects maintained on buprenorphine (16-24 mg/day) concomitantly administered LUCEMYRA up to 2.88 mg/day, no pharmacokinetic or pharmacodynamic interactions between LUCEMYRA and buprenorphine were seen.

LUCEMYRA coadministered with oral naltrexone

In an open-label, single-arm study of 24 healthy subjects, oral naltrexone (50 mg/day) did not significantly alter the single-dose pharmacokinetics of LUCEMYRA (0.36 mg). The alteration in steady-state pharmacokinetics of oral naltrexone was statistically significant in the presence of LUCEMYRA. The t_{max} was delayed for both naltrexone and 6ß-naltrexol (2-3 hours), and overall exposure was slightly reduced when naltrexone was administered with LUCEMYRA *[see Drug Interactions (7.2)]*.

LUCEMYRA coadministered with paroxetine

In an open-label, single-sequence study of 24 healthy subjects, the strong CYP2D6 inhibitor paroxetine (40 mg/day) increased LUCEMYRA (0.36 mg) C_{max} and AUC_{∞} by approximately 11% and 28%, respectively *[see Drug Interactions (7.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No adequate long-term animal studies have been completed to evaluate the carcinogenic potential of lofexidine.

Mutagenesis

Lofexidine tested positive in the *in vitro* mouse lymphoma assay. Lofexidine tested negative in the *in vitro* bacterial reverse mutation assay (Ames assay) and in the *in vivo* rat micronucleus assay.

Impairment of Fertility

In a female fertility study in rabbits, fertility was not adversely impacted by administration of lofexidine hydrochloride up to 6.4 mg/kg/day (approximately 0.1 times the MRHD of 2.88 mg on an AUC basis) when administered orally to female rabbits starting 2 weeks prior to mating and through gestation and lactation. However, decreased breeding rate and higher post-implantation loss was observed at this dose, which correlated with higher resorptions and reduced litter size. Maternal toxicity, which included increased mortality rate, reduced body weight gain, and moderate sedation was observed at 6.4 mg/kg/day. The NOAEL for female fertility was 6.4 mg/kg/day and the NOAEL for female-mediated developmental parameters was 0.4 mg/kg/day (approximately 0.005 times the MRHD on an AUC basis).

In a fertility study in rats, fertility was unaffected by administration of lofexidine up to 0.88 mg/kg/day (approximately 0.2 times the MRHD on an AUC basis) via diet to male and female rats prior to mating and to the dams through gestation and lactation. No evidence of maternal toxicity was observed. However, no assessment of sperm or reproductive organs were performed in this study.

Reduced testes, epididymis, and seminiferous tubule weights, as well as delayed sexual maturation of males and females and decreases in the number of corpora lutea and implantations after mating, were noted in offspring of pregnant rats administered lofexidine hydrochloride orally from GD 6 through lactation at exposures less than the human exposure based on AUC comparisons.

14 CLINICAL STUDIES

Two randomized, double-blind, placebo-controlled trials supported the efficacy of LUCEMYRA.

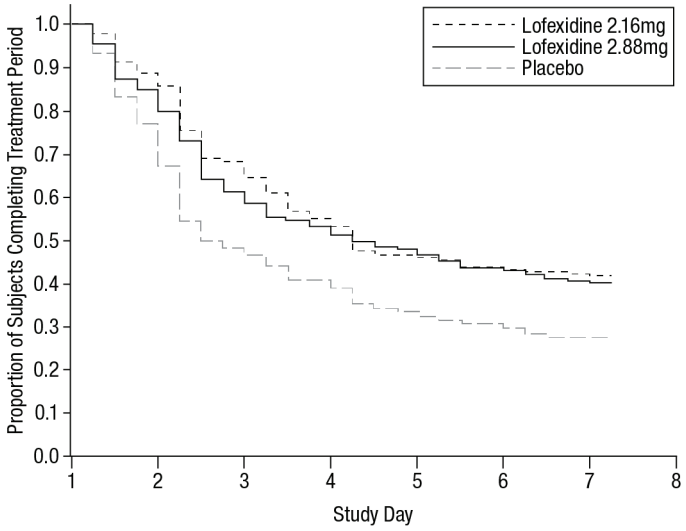
Study 1, NCT01863186

Study 1 was a 2-part efficacy, safety, and dose-response study conducted in the United States in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). The first part of the study was an inpatient, randomized, double-blind, placebo-controlled design consisting of 7 days of inpatient treatment (Days 1 – 7) with LUCEMYRA 2.16 mg total daily dose (0.54 mg 4 times daily) (n=229), LUCEMYRA 2.88 mg total daily dose (0.72 mg 4 times daily) (n=222), or matching placebo (n=151). Patients also had access to a variety of support medications for withdrawal symptoms (guaifenesin, antacids, dioctyl sodium sulfosuccinate, psyllium hydrocolloid suspension, bismuth sulfate, acetaminophen, and zolpidem). The second part of the study (Days 8 – 14) was an open-label design where all patients who successfully completed Days 1 – 7 were eligible to receive open-label treatment with variable dose LUCEMYRA treatment (as determined by the investigator, but not to exceed 2.88 mg total daily dose) for up to an additional 7 days (Days 8 – 14) in either an inpatient or outpatient setting as determined by the investigator and the patient. No patient received LUCEMYRA for more than 14 days.

The two endpoints to support efficacy were the mean Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) total score on Days 1 – 7 of treatment and the proportion of patients that completed 7 days of treatment. The SOWS-Gossop, a patient-reported outcome (PRO) instrument, evaluates the following opioid withdrawal symptoms: feeling sick, stomach cramps, muscle spasms/twitching, feeling of coldness, heart pounding, muscular tension, aches and pains, yawning, runny eyes and insomnia/problems sleeping. For each opioid withdrawal symptom, patients are asked to rate their symptom severity using four response options (none, mild, moderate, and severe). The SOWS-Gossop total score ranges from 0 to 30 where a higher score indicates a greater withdrawal symptom severity. The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on Days 1 – 7.

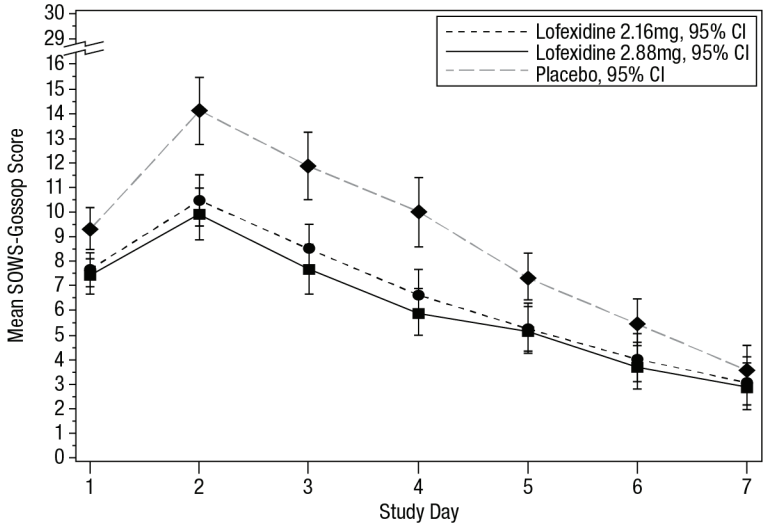
Of the randomized and treated patients, 28% of placebo patients, 41% of LUCEMYRA 2.16 mg and 40% of LUCEMYRA 2.88 mg patients completed 7 days of treatment. The difference in proportion in both LUCEMYRA groups was significant compared to placebo. See Figure 1. Patients in the placebo group were more likely to drop out of the study prematurely due to lack of efficacy than patients treated with LUCEMYRA.

Figure 1: Completion of treatment period for Study 1



The mean SOWS-Gossop scores for Days 1 – 7 were 8.8, 6.5, and 6.1 for placebo, LUCEMYRA 2.16 mg and LUCEMYRA 2.88 mg, respectively. Results are shown in Figure 2. The mean difference between LUCEMYRA 2.16 mg and placebo was -2.3 with a 95% CI of (-3.4, -1.2). The mean difference between LUCEMYRA 2.88 mg and placebo was -2.7 with a 95% CI of (-3.9, -1.6). They were both significant. Symptoms assessed on the SOWS-Gossop were recorded as absent or mild for almost all patients remaining to the end of the assessment period.

Figure 2: Mean SOWS-Gossop Scores for Days 1 – 7 in Study 1



Study 2, NCT00235729

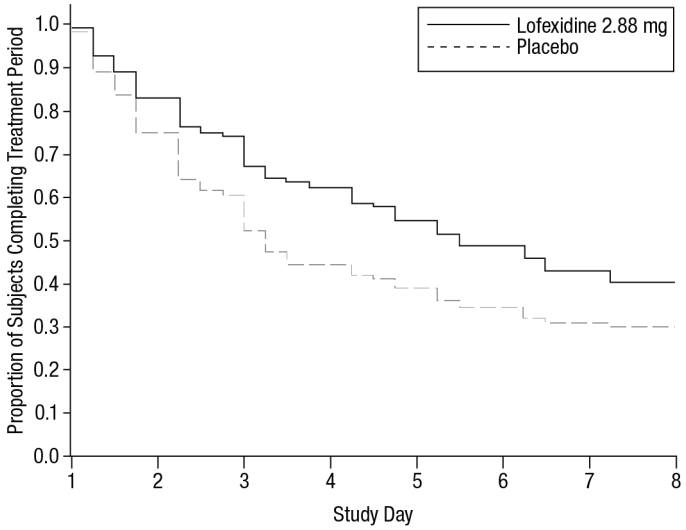
Study 2 was an inpatient, randomized, multicenter, double-blind, placebo-controlled study carried out in the United States in patients meeting DSM-IV criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). Patients were treated with LUCEMYRA tablets (2.88 mg/day [0.72 mg four times daily]) or matching placebo for 5 days (Days 1 – 5). Patients also had access to a variety of support medications for withdrawal symptoms (guaifenesin, antacids, dioctyl sodium sulfosuccinate, psyllium hydrocolloid suspension, bismuth sulfate, acetaminophen, and zolpidem). All patients then received placebo on Days 6 and 7 and were discharged on Day 8.

The two endpoints to support efficacy were the mean SOWS-Gossop total score on Days 1 – 5 of treatment and the proportion of patients that completed 5 days of treatment. The SOWS-Gossop was administered at baseline and once daily 3.5 hours after the first morning dose on Days 1 – 5.

A total of 264 patients were randomized into the study. Of these, 134 patients were randomized to LUCEMYRA 2.88 mg/day and 130 patients to placebo.

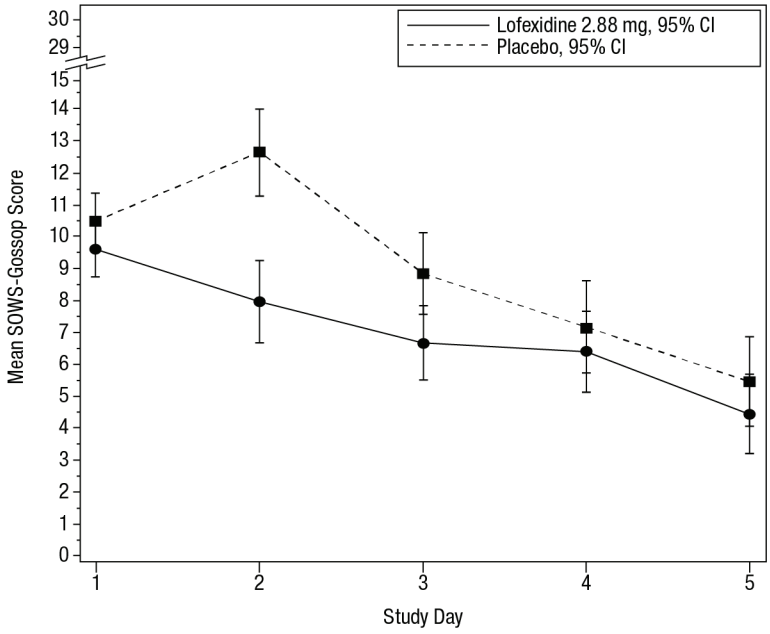
Of the randomized and treated patients, 33% of placebo patients and 49% of LUCEMYRA patients completed 5 days of treatment. The difference in proportion between the two groups was significant. See Figure 3. Patients in the placebo group were more likely to drop out of the study prematurely due to lack of efficacy than patients treated with LUCEMYRA.

Figure 3: Completion of treatment period in Study 2



The mean SOWS-Gossop scores for Days 1 – 5 were 8.9 and 7.0 for placebo and LUCEMYRA 2.88 mg, respectively. Results are shown in Figure 4. The mean difference was -1.9 with a 95% CI of (-3.2, -0.6) and was statistically significant.

Figure 4: Mean SOWS-Gossop Scores for Days 1 – 5 in Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Available as 0.18 mg round, convex-shaped, peach colored, film-coated tablets, imprinted with “LFX” on one side and “18” on the other side; approximately 7 mm in diameter.

Bottles of 36 tablets . . . . . NDC 27505-050-36

Bottles of 96 tablets . . . . . NDC 27505-050-96

Storage

Store in original container at controlled room temperature, 25°C (77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep LUCEMYRA away from excess heat and moisture both in the pharmacy and after dispensing. Do not remove desiccant packs from bottles until all tablets are used. Keep LUCEMYRA and all medicines out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

LUCEMYRA may mitigate, but not completely prevent, the symptoms associated with opioid withdrawal syndrome, which may include feeling sick, stomach cramps, muscle spasms or twitching, feeling of cold, heart pounding, muscular tension, aches and pains, yawning, runny eyes and sleep problems (insomnia). Patients should be advised that withdrawal will not be easy. Additional supportive measures should be clearly advised, as needed.

Hypotension and Bradycardia

Inform patients to be alert for any symptoms of low blood pressure or pulse (e.g., dizziness, lightheadedness, or feelings of faintness at rest or on abruptly standing). Advise patients on how to reduce the risk of serious consequences should hypotension occur (sit or lie down, carefully rise from a sitting or lying position).

Patients being given LUCEMYRA in an outpatient setting should be capable of and instructed on self-monitoring for hypotension, orthostasis and bradycardia and advised to withhold LUCEMYRA doses and contact their healthcare provider for instructions if they experience these signs or related symptoms *[see Warnings and Precautions (5.1)]*.

Advise patients to avoid becoming dehydrated or overheated, which may potentially increase the risks of hypotension and syncope *[see Warnings and Precautions (5.1)]*.

Concomitant Medications

Review with patients all concomitant medications being taken and request that they immediately inform their healthcare provider of any changes in concomitant medications, including any other medications that may be used to treat individual symptoms of withdrawal.

Increased Risk of CNS Depression with Concomitant use of CNS Depressant Drugs

Inform patients of the increased risk of CNS depression with concomitant use of benzodiazepines, alcohol, barbiturates, or other sedating drugs *[see Warnings and Precautions (5.3)]*.

Advise patients using LUCEMYRA in an outpatient setting that, until they learn how they respond to LUCEMYRA, they should be careful or avoid doing activities such as driving or operating heavy machinery.

Sudden Discontinuation of LUCEMYRA

Inform patients not to discontinue LUCEMYRA without consulting their healthcare provider *[see Warnings and Precautions (5.5)]*.

Risk of Opioid Overdose After Discontinuation of Opioids

Advise patients that after a period of not using opioid drugs, they may be more sensitive to the effects of opioids and at greater risk of overdosing *[see Warnings and Precautions (5.4)]*.

US WorldMeds

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360-10020

PATIENT INFORMATION

LUCEMYRA™ (LEW-sem-EER-uh)
(lofexidine)
tablets

What is the most important information I should know about LUCEMYRA and discontinuing opioid drugs?

LUCEMYRA can cause serious side effects, including low blood pressure (hypotension), slow heart rate (bradycardia), and fainting.

If you get any of the following signs or symptoms, tell your healthcare provider right away:

- low blood pressure
- slow heartbeat
- dizziness
- lightheadedness
- feeling faint at rest or when standing up

If you take LUCEMYRA at home and have any of these signs and symptoms, do not take your next dose of LUCEMYRA until you have talked to your healthcare provider. You should avoid becoming dehydrated or overheated during treatment with LUCEMYRA, which may increase your risk of low blood pressure and fainting. You should also be careful not to stand up too suddenly from lying down or sitting.

When your treatment is complete you will need to stop taking LUCEMYRA gradually or your blood pressure could increase. For more information about side effects, see **"What are the possible side effects of LUCEMYRA?"**

Increased risk of opioid overdose. After a period of time of not using opioid drugs, you can become more sensitive to the effects of opioids if you start using opioids again. This may increase your risk of overdose and death.

What is LUCEMYRA?

LUCEMYRA is a non-opioid prescription medicine used in adults to help with the symptoms of opioid withdrawal that may happen when you stop taking an opioid suddenly.

LUCEMYRA will not completely prevent the symptoms of opioid withdrawal, which may include feeling sick, stomach cramps, muscle spasms or twitching, feeling of cold, heart pounding, muscular tension, aches and pains, yawning, runny eyes and sleep problems (insomnia).

LUCEMYRA is not a treatment for opioid use disorder. If you have been diagnosed with opioid use disorder (opioid addiction), your healthcare provider may prescribe LUCEMYRA as part of a complete treatment program for your opioid use disorder (opioid addiction).

It is not known if LUCEMYRA is safe and effective in children.

Before taking LUCEMYRA, tell your healthcare provider about all of your medical conditions, including if you:

- have low blood pressure
- have a slow heart rate
- have any heart problems, including history of heart attack or a condition called long QT syndrome
- have liver or kidney problems
- drink alcohol
- are pregnant or plan to become pregnant. It is not known if LUCEMYRA can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LUCEMYRA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with LUCEMYRA.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements, and any medications you may take for the individual symptoms of opioid withdrawal (such as pain relievers or medications for upset stomach).

Especially tell your healthcare provider if you take benzodiazepines, barbiturates, tranquilizers, or sleeping pills. Taking LUCEMYRA with these medicines can cause serious side effects. Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines.

How should I take LUCEMYRA?

- Take LUCEMYRA exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose if needed.
- Do not change your dose or stop taking LUCEMYRA without talking to your healthcare provider.
- Take LUCEMYRA with or without food.
- If you take too much LUCEMYRA, go to the nearest hospital emergency room right away.

LUCEMYRA™ (lofexidine) tablets

What should I avoid while taking LUCEMYRA?

Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how LUCEMYRA affects you.

What are the possible side effects of LUCEMYRA?

The most common side effects of LUCEMYRA include:

- low blood pressure or symptoms of low blood pressure such as lightheadedness
- slow heart rate
- dizziness
- sleepiness
- dry mouth

These are not all the possible side effects of LUCEMYRA.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to US WorldMeds at 1-833-LUCEMYRA.

How should I store LUCEMYRA?

- Store LUCEMYRA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep LUCEMYRA in its original container.
- Keep LUCEMYRA away from heat and moisture.
- LUCEMYRA bottles contain desiccant packs to help keep the tablets dry. Do not remove the desiccant packs until all the tablets are used.

Keep LUCEMYRA and all medicines out of the reach of children.

General information about the safe and effective use of LUCEMYRA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LUCEMYRA for a condition for which it was not prescribed. Do not give LUCEMYRA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about LUCEMYRA that is written for health professionals.

What are the ingredients of LUCEMYRA?

Active ingredient: lofexidine.

Inactive ingredients: lactose, citric acid, povidone, microcrystalline cellulose, calcium stearate, sodium lauryl sulphate, and Opadry OY S 9480 (contains indigo carmine and sunset yellow).

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US WorldMeds, LLC is the exclusive licensee and distributor of LUCEMYRA™ in the United States and Its territories.

For more information, go to www.LUCEMYRA.com or call 1-833-LUCEMYRA

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 05/2018

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AMERICA • ASIA PACIFIC • EUROPE

September 20, 2018

By Federal Express and Email

Beneficiary Advisory Panel
Designated Federal Officer
Colonel Paul J. Hoerner, USAF
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101
Email: dha.ncr.healthit.mbx.baprequests@mail.mil

Re: September 27, 2018 Beneficiary Advisory Panel Background Information (H.P. Acthar® Gel)

Dear Beneficiary Advisory Panel Members:

We write on behalf of Mallinckrodt Pharmaceuticals (Mallinckrodt) to provide the members of the Beneficiary Advisory Panel (BAP) with comments on the coverage restrictions proposed by the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee for H.P. Acthar® Gel (repository corticotropin injection) (Acthar), which will be discussed at the BAP meeting currently scheduled for September 27, 2018. In summary, Mallinckrodt vigorously opposes the proposed coverage restrictions, which are not evidence-based and threaten grievous harm to vulnerable TRICARE beneficiaries.

The comments discussed below should seem familiar to BAP members. The same flawed coverage restrictions for Acthar were rejected by the BAP in April 2018. The P&T Committee seeks a "mulligan" and is re-presenting the same proposals. By doing so, the P&T Committee hopes to obtain a more favorable outcome than the rejection that it received from the BAP less than six months ago. The BAP should once again reject the P&T Committee's flawed proposals. No new data or information has been produced, and the P&T Committee's background materials are misleading at best.

BACKGROUND

Acthar is the only drug in the class known as adrenocorticotropic hormones (ACTH) that is approved by the U.S. Food and Drug Administration (FDA) for therapeutic use in the United States. Acthar is widely known as the standard of care (and the preferred first-line treatment) for West Syndrome, also known as infantile spasms (IS), a rare but potentially fatal neurologic condition affecting young children. Another key indication is the treatment of acute exacerbations

of multiple sclerosis (MS), where Acthar is often prescribed to patients who are intolerant of, or do not respond to, other medications. In addition, Acthar is an important later-line treatment for a broad array of conditions, such as proteinuria in nephrotic syndrome; dermatomyositis / polymyositis; rheumatoid arthritis; systemic lupus erythematosus; ophthalmic disease; and symptomatic sarcoidosis.

The present dispute dates to the P&T Committee's first consideration of Acthar in 2013. At that time, the P&T Committee adopted limited prior authorization (PA) criteria regarding the use of Acthar to treat IS.[1] However, the P&T Committee determined that certain other indications (including exacerbations of MS and nephrotic syndrome) would be covered on appeal only, while other indications would be excluded from coverage altogether. "Appeal only" coverage, however, is inconsistent with Defense Health Agency (DHA) regulations. It also led to widespread confusion among TRICARE providers and patients, who were not informed that "appeal only" coverage existed for MS, nephrotic syndrome, or other uses. In fact, TRICARE's prime vendor falsely described the coverage rules applicable to Acthar in denial notices, which undermined the affected beneficiaries' appeal rights.

For these and other reasons, Mallinckrodt engaged with DHA to seek a clear and more appropriate coverage policy for Acthar. On or about November 6, 2017, the agency told Mallinckrodt that its concerns would be addressed by the P&T Committee in its February 2018 meeting.

That did not occur. Instead, the P&T Committee proposed additional coverage restrictions. First, the P&T Committee proposed to impose a new PA criteria regarding IS that would require all pediatric patients to first try and fail "off-label" steroid treatment before being prescribed Acthar, the recognized first line therapy for IS.[2] Second, the P&T Committee proposed to require that patients try and fail treatment with steroids prior to each individual exacerbation of MS. Finally, the P&T Committee proposed to deny all coverage for all remaining uses—including conditions, like nephrotic syndrome, that had been covered as a result of appeals by beneficiaries.

These proposals were firmly opposed by stakeholders. Multiple groups and healthcare providers wrote to DHA to voice their opposition—including the Child Neurology Foundation, Multiple Sclerosis Association of America, Nephcure Kidney International, the National Kidney Foundation, and leading pediatric neurologists from the University of Tennessee Health Science

[1] The 2013 PA criteria for IS were that the patient was less than 24 months old, that the IS diagnosis had been confirmed, and that the patient has not previously been treated with Acthar. These criteria are consistent with the model criteria that Acthar urges all payors to adopt.

[2] Go C.Y. et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society – Neurology, 2012;78:1974-1980.

Center, the Children's Hospital of Orange County, and the Children's Hospital of Pittsburg. These materials are provided for consideration by the BAP as Exhibit A to these comments.

Importantly, the BAP rejected these proposals. The P&T Committee presented its recommendations to the BAP on April 5, 2018. During that presentation, BAP members asked probing questions regarding the recommendation to eliminate coverage for uses currently covered on appeal. The BAP members quite correctly pointed out that the P&T Committee failed to support its position to eliminate coverage for those uses. On the contrary, BAP members noted that the P&T Committee had effectively conceded that clinicians and patients needed access to Acthar as an alternative where prior treatments had been ineffective. The BAP ultimately voted 3-1 to not concur in the P&T Committee's flawed recommendations.

Despite the BAP's rejection and broad stakeholder opposition, the DHA Director adopted the P&T Committee's recommendations, without change, on April 24, 2018. After that decision, Mallinckrodt again raised the procedural and substantive defects in the new coverage restrictions and was informed, on July 10, 2018, that the P&T Committee would be conducting another review of Acthar at its meeting on August 8-9, 2018. The P&T Committee now seeks to present the same, rejected proposals to the BAP on September 27, 2018.

DISCUSSION

It is disappointing that the P&T Committee has reiterated the same flawed proposals. We fear that it reflects that the P&T Committee is wedded to a result and is searching for a justification. Such a "result first" approach is a disservice to military families and the antithesis of the reasoned decision-making required of all federal agencies. We have included our prior presentation to the BAP as Exhibit B to these comments. The BAP should reject the current proposals for largely the same reasons it rejected the prior iteration. In brief summary:

- Infantile Spasms. The prior authorization criteria for the IS indication should not include a requirement that patients first receive a 2-week course of high-dose prednisone/prednisolone. It is clearly inappropriate to prefer an unapproved use of steroids over Acthar, which is the accepted standard of care.

  First, a two-week course of steroids threatens grievous harm to vulnerable patients by delaying the onset of treatment with Acthar. Infantile Spasms is a rare but catastrophic syndrome characterized by both spasms and hypsarrhythmic EEG patterns. Delayed treatment that exposes infants to even a few weeks of hypsarrhythmia can cause increased impairment.[3] Thus, the approach proposed by the P&T Committee threatens unnecessary, permanent disability.

[3] Mackay MT, et al. Neurology. 2004;62(10):1668-1681; Goh S, et al. Neurology. 2005;65(2):235-238.

Second, Acthar's status as the standard of care for infantile spasms is well established. That status was recognized by the FDA in 2010. It is supported by the joint clinical guidelines of the American Academy of Neurology and the Child Neurology Society, which not only endorse Acthar as a first line therapy, but also conclude that there is insufficient evidence to recommend preferential use of steroids.[4] Similarly, a 2010 meeting of knowledge leader concluded that a high-dose regimen of Acthar "continues to be the clinical standard of treatment of infantile spasms in the United States and several other countries."[5]

Third, robust clinical evidence supports the use of Acthar as the first-line treatment. Thus, a study published in 2016 by the National Infantile Spasms Consortium found that ACTH appeared to be a more effective treatment for Infantile Spasms than other standard therapies.[6] Similarly, a randomized trial published in 1996, which found that a 2-week course of high-dose ACTH (86.6% efficacy) was superior to 2 weeks of what would now be considered low-dose prednisone (28.6%) for treatment of infantile spasms as assessed by both clinical and EEG criteria.[7]

- Exacerbations of MS. The prior authorization criteria for the MS indication should not require treatment failure with steroids for each individual exacerbation. It is plainly inappropriate to require a failed treatment for each individual exacerbation as it occurs. Forcing patients to endure multiple, repeated treatment failures would be an entirely unreasonable barrier to access to an established second line therapy.

  Repeated steroid treatments also pose quality of life problems for patients. During the time it takes for a steroid trial to fail, patients can experience a range of harms, from difficulty walking to optic neuritis and cognitive delays. A steroidal treatment also typically requires the patient to visit a clinic every day to receive the infusion, as opposed to Acthar, which can be administered by the patient in the home. For a patient in an exacerbation, with limited or no mobility, that is a very real and very serious barrier to treatment and recovery.

- Other Conditions. TRICARE should not deny coverage for other uses of Acthar, including nephrotic syndrome, that previously have been covered on appeal. A policy

[4] Go C.Y. et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society – Neurology, 2012;78:1974-1980.

[5] Stafstrom CE et al. Treatment of IS insights from clinical & basic science perspectives - J Child Neurol 2011 26(11) 1411-1421.

[6] Knupp K.G. et al. Response to Treatment in a Prospective National Infantile Spasms Cohort – Ann Neurol 2016;79:475-484.

[7] Barram TZ et al. High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study – Pediatrics 1996;97(3):375-379.

of no coverage under any circumstances, no matter how severe the patient need and no matter how extensively other therapies have been tried and failed, is plainly arbitrary and capricious.

In addition, the P&T Committee failed to explain in any manner how new evidence justified the departure from its prior coverage policies, which did cover these uses in appropriate circumstances. While we have many concerns about providing coverage only on appeal, that policy did enable at least some patients to receive coverage. For instance, between January 2014 and March 2018, at least 113 naïve patients received coverage for Acthar for protein-wasting nephropathies. The P&T Committee's recommendation will severely harm these patients, as well as similarly-situated patients in the future.

We do not believe that the P&T Committee has offered a meaningful rebuttal to any of the above points. Indeed, in several respects, the P&T Committee's second review of Acthar has served only to exacerbate the errors and highlight the flaws in its proposals.

1. <u>Procedural Irregularities Prevented Stakeholder Participation</u>.

The simple fact that the P&T Committee chose to review Acthar for a second time in six months is highly unusual. But the way the second review was implemented violated DHA policies and procedures and prevented public participation.

Typically, the public receives months of advance notice to prepare and submit information to the P&T Committee. Here, the documentation related to the August 2018 meeting was posted to the internet on May 1, 2018; the industry teleconference was scheduled for May 14, 2018; sponsor presentations were to occur in May and June; and cost proposals were due on June 22, 2018. All of those dates had passed by the time Mallinckrodt was informed that Acthar would be re-reviewed. Other stakeholders received no notice whatsoever. As of this writing, the DHA website ***still*** fails to reveal that the ACTH or Acthar was discussed at the August meeting in direct violation of by Health Affairs Policy 04-032, which requires advance public notice of the P&T Committee's agenda via the website.[8] This violation is particularly troubling given the significant number of stakeholders who objected to the February 2018 proposals regarding Acthar.

2. The P&T Committee still has not responded to stakeholder opposition or <u>Mallinckrodt's proposal</u>.

To our knowledge, the P&T has not acknowledged, much less responded to, any of the stakeholder correspondence collected in Exhibit A to these comments. Nor is there any indication that the P&T Committee considered Mallinckrodt's prior submissions, which included model

[8] https://www.health.mil/About-MHS/OASDHA/Defense-Health-Agency/Operations/Pharmacy-Division/DoD-Pharmacy-and-Therapeutics-Committee.

coverage policies that include step edits that could be used to develop clinically appropriate prior authorization criteria for ***each*** relevant indication.

3. The P&T Committee still has not addressed the relevant clinical evidence and practice guidelines.

Mallinckrodt has repeatedly directed the P&T Committee to the relevant clinical practice guidelines and published studies regarding Acthar (see, e.g., footnotes 2-7 above). At no point has the P&T Committee addressed those materials, despite repeated claims of having conducted a "comprehensive review" of the relevant evidence.

4. The P&T Committee continues to prefer "off-label" use of steroids in violation of DHA regulations.

As before, the P&T Committee continues to recommend that all patients with IS first receive off-label treatment with steroids prior to being prescribed Acthar, which is FDA-approved for that use. As we have previously explained to the agency, DHA regulations hold that off-label uses may only be ***covered*** (let alone ***preferred***) when there has been a "demonstration[] from medical literature, national organizations, or technology assessment bodies that the off-label use of the drug or device is safe, effective, and in accordance with nationally accepted standards of practice in the medical community." 32 C.F.R. § 199.4 (emphasis added). Section 9.1 of Chapter 8 of the TRICARE Policy Manual contains the same requirement.

We are aware of no evidence that could support a "demonstration" that an unapproved use of oral steroids as a first-line treatment for infantile spasms is "in accordance with nationally accepted standards of practice." The P&T Committee's background materials do not attempt to make the demonstration required by the regulation or the corresponding manual provision. Instead, the P&T Committee suggests that it is appropriate to prefer off-label use of steroids for infantile spasms because the P&T Committee previously proposed, in 2017, to prefer off-label use of steroids for another rare disease affecting vulnerable children, namely, Duchene's muscular dystrophy. The fact that the P&T Committee could only identify ***one*** prior coverage policy that favors an unapproved treatment over an FDA-approved product indicates that such proposals are contrary to 32 C.F.R. § 199.4.

5. The P&T Committee still refuses to identify many of the materials on which it purports to rely.

The P&T Committee continues to make unsupported claims. For example, the P&T Committee claims to have received "additional information … from providers and the FDA as it relates to the clinical effectiveness and safety of [Acthar]." But the P&T Committee does not disclose who supposedly provided this alleged information, what information allegedly was provided, or what it purported to show about the safety or efficacy of Acthar. Similarly, the P&T Committee claims that it reviewed "[f]undamentals of inflammation," without identifying the materials reviewed or explaining how they are supposed to show that it is appropriate to require

TRICARE beneficiaries living with MS to repeat a failed steroid treatment potentially ten or more times over the course of their lives.

By far the most egregious example, however, involves unfounded allegations regarding safety. The P&T Committee writes that "[n]ew data … cause[d] the Committee to have more safety concerns than previously concluded." Yet the P&T Committee did not disclose the purported "new data" at issue, did not identify the source, and did not even specify the nature of the supposed safety concerns. These vague and unfounded references to safety are inappropriate and irresponsible. If the P&T Committee has ***actual*** safety concerns regarding Acthar, it must disclose what they are (and the data supporting them) so that Mallinckrodt and other stakeholders can evaluate and respond to them. Significantly, FDA has approved Acthar as safe and effective for all of the uses at issue here.

6. <u>The P&T Committee's materials reflect an effort to mislead.</u>

In the few instances in which the P&T Committee discloses the information on which it purports to rely, the P&T Committee misstates its content. In other places, the P&T Committee makes assertions that are misleading.

- First, the P&T Committee claims claims that "9 health care plans" do not cover Acthar "for any indication," but does not identify the plans in question. We believe the reference to "9 health care plans" may be referring to certain self-insured employers that do not cover Acthar. Even if there are such plans—and the information provided is insufficient to evaluate that point—it is well known that these types of self-insurance plans do not and cannot offer the same quality of care as national plans.[9] There is no showing that these plans operate under the statutory and regulatory mandates that apply to the TRICARE program, and it would be plainly inappropriate to reduce TRICARE benefits for active-duty service members and their families to the level of benefits provided by self-insured employers.

- Second, the P&T Committee asserts that the Intermountain Health System in Utah requires "a trial of oral corticosteroids prior to using [Acthar] for infantile spasms." We believe that assertion to be false. The public PA form used by Intermountain for commercial and Medicaid patients is specific to infantile spasms and it ***does not*** require

[9] See Kaiser Family Foundation, Employer Health Benefits, 2017 Summary of Findings, available at http://files.kff.org/attachment/Summary-of-Findings-Employer-Health-Benefits-2017 (stating "Despite continuing economic improvement, with lower rates of unemployment, and the ACA employer mandate, there are no signs that the longterm declines in the offer and coverage rates are reversing.")

a prior trial of steroids. That form is attached to these comments as Exhibit C for consideration by the BAP.[10]

- Third, the P&T Committee similarly contends that UCLA and Johns Hopkins also require a failed steroid trial before administering Acthar to patients with IS. Mallinckrodt has not been able to confirm the P&T Committee's assertion regarding Johns Hopkins, which appears to be based on non-public and undisclosed information. However, Mallinckrodt queried UCLA regarding its coverage policy and was told that—contrary to the P&T Committee's claim—UCLA does not impose the restriction asserted.

- Fourth, the P&T Committee asserts that steroids "better facilitate[]" urgent treatment of infantile spasms. This assertion is not supported by any citation. And for good reason: There is absolutely no support in the literature for the implicit claim that steroids are a superior (i.e., more effective) treatment for IS.

  The P&T Committee relatedly asserts that treatment with Acthar can be delayed because the distribution system for Acthar allegedly is "administratively burdensome." Again, the P&T Committee offers no support or explanation for the claim of burden. Mallinckrodt believes that Acthar is readily available for use in TRICARE facilities or distribution to TRICARE families and that it is TRICARE's policies that have imposed burdens on patients and providers.

- Fifth, the P&T Committee claims that its review "reaffirmed" that steroids should be "a frontline treatment ***alongside*** [Acthar] and vigabatrin." But that is not an accurate description of what the P&T Committee proposes to do. Acthar and steroids stood "alongside" each other as frontline treatments for IS under the prior coverage policy that was adopted in 2013. Since February 2018, the P&T Committee has been determined to place steroids ***in front of***, not alongside, Acthar in the armamentarium. That change is both critical and the genesis of this dispute.

Finally, we note that the above statements—each disturbing in its own right—build upon false assertions in the P&T Committee's prior recommendations in February 2018. At that time, the P&T Committee recommended against coverage of important uses of Acthar, including nephrotic syndrome, based on the factually incorrect premise that Acthar was only approved "in 1952, prior to the higher standards demonstrating clinical effectiveness." In truth, Acthar was approved ***for***

[10] In contrast, an Intermountain PA form for Medicare beneficiaries does inquire regarding prior trials with steroids. *See* Exhibit D. Medicare is plainly irrelevant—there is virtually no set of facts pursuant to which the Medicare program would ever be the responsible payor for an infant diagnosed with IS. Moreover, the Intermountain form for Medicare makes clear that the prior authorization questions being asked apply to a broad array of indications other than IS, as one would expect for an adult beneficiary population.

efficacy in the 1970s, *see* 42 Fed. Reg. 11891 (Mar. 1, 1977), and again in 2010 when FDA comprehensively reexamined and modernized the drug's labeling.

* * *

Thank you for your time. We greatly appreciate your review and consideration of these comments.

Best regards,

William A. Sarraille
Sean C. Griffin
SIDLEY AUSTIN LLP

EXHIBIT A

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Child Neurology FOUNDATION
Creating a Community of Support

201 Chicago Avenue, Suite 200
Minneapolis, MN 55415
612.928.6325

Vice Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101

May 1, 2018

Dear Vice Admiral Raquel C. Bono,

Thank you for the opportunity to comment on Tricare's proposed policy changes to health care benefits. The Child Neurology Foundation (CNF) serves as a collaborative center for patient education and support for the children and families living with the over 300 neurologic conditions. We are governed by board-certified child neurologists, allied health professionals, and parents. We utilize this multi-stakeholder expertise to guide our advocacy efforts.

Since 2016, CNF has convened the Infantile Spasms Action Network (ISAN); which is a collaborative advocacy model in which 25 national and international entities are actively engaged (www.childneurologyfoundation.org/infantilespasms). ISAN's goal is to increase awareness for the necessity for prompt and accurate diagnosis for infantile spasms (IS) and urgent and appropriate treatment for every child diagnosed with IS. As you may know, IS is associated with significantly elevated risk of developmental impairment, lifelong intractable epilepsy, autism, and death. To be clear, delays in diagnosis and treatment pose a grave threat to children with IS. Even short delays—as brief as 7 days—in receiving effective treatment have been associated with substantial and enduring intellectual harm. For further information, please note the recent position statement on "Immediate Access to Accepted Treatments for Infantile Spasms" by the American Epilepsy Society (www.aesnet.org/about_aes/position_statements/position_infantile_spasms) .

Whereas treatment protocols for IS vary among health care providers, there is tremendous consensus around:

1) A physician's right to treat infantile spasms as he/she deems appropriate
2) The critical need for the treating provider to have access to the appropriate treatment immediately

The proposed Tricare policy changes conflict with this established consensus and provide systematic opportunity for further delay in children receiving appropriate treatment for IS.

Therefore, our request is that you do not approve the proposed policy changes to Tricare's coverage as it relates to infantile spasms treatment.

Child Neurology FOUNDATION
Creating a Community of Support

201 Chicago Avenue, Suite 200
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Feel free to reach out to us if we may provide you with further information.

Respectfully,

Ann Tilton, MD
President, CNF

Amy Brin Miller, MSN, MA, PCNS-BC
Executive Director, CNF

cc: Shaun Hussain, MD – CNF Chair of Content Review Committee
Scott Pomeroy, MD, PhD – CNF Secretary
William H. Trescher, MD – CNF Past President
Mary Zupanc, MD – CNF Board of Director

UT Le Bonheur
Pediatric Specialists

April 10, 2018

Vice-Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Blvd, Suite #5101
Falls Church, VA 22042-5101

RE: Tricare and the Treatment of Infantile Spasms

Dear Vice-Admiral Bono,

I am writing to you regarding your recent decision that Tricare has made recommending high-dose prednisolone therapy for two weeks as initial treatment for infantile spasms. I was one of the lead authors in the United States that was part of a special report (The Infantile Spasms Working Group) that reviewed the diagnosis, evaluation and treatment of infantile spasms. (I have enclosed a copy of this document for you).

As you can see, when this document was published in 2010, there were only two FDA approved treatments for Infantile Spasms in the United States, ACTH gel, and vigabatrin. Since that time, no other products have received FDA approval as initial treatment, and none have demonstrated superiority. As such, it caused me concern when your group recommended high-dose prednisolone as initial therapy. Since our study was published, other studies have also confirmed the superior efficacy of ACTH gel over the high dose prednisolone. Additionally, the studies have shown the delay in treatment of ongoing infantile spasms has negative developmental consequences for the infant that cannot be recovered from.

I would hope that you would consider these items and consider revision of your policy. I would be happy to discuss this with you at any time, and a phone call can be coordinated through my office if needed. Please do not hesitate to contact me if I can answer any questions.

Sincerely,

James W. Wheless, M.D., FAAP, FACP, FAAN, FAES
Professor and Chief of Pediatric Neurology
Le Bonheur Chair in Pediatric Neurology
University of Tennessee Health Science Center
Director, Le Bonheur Comprehensive Epilepsy Program & Neuroscience Institute
Le Bonheur Children's Hospital
Memphis, TN

enclosure

JWW/mwa

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Division of Neurology

Mary L. Zupanc, M.D., Division Chief
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Jonathan T. Megerian, M.D. • Andrew Mower, M.D. • Donald Phillips, M.D., MPH
Daniel Shrey, M.D. • Maija Steenari, M.D. • Sharief Taraman, M.D. • Minodora Totoiu, M.D., PhD
Anne Tournay, M.D. • Lily Tran, M.D.
Aliza Riba, CPNP

April 12, 2018

Vice-Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
770 Arlington Blvd., Suite #5101
Falls Church, VA 22042-5101

RE: Tricare and the Treatment of Infantile Spasms

Dear Vice-Admiral Bono,

I am writing to you regarding your recent decision that Tricare has made recommending high-dose prednisolone therapy for two weeks as initial treatment for infantile spasms. Please see the attached article entitled "Infantile Spams: A US Consensus Report". Although I was not one of the lead authors for this particular article, I have authored multiple articles on infantile spasms, have participated in clinical studies using ACTH, and am recognized as a national expert on infantile spasms and its treatment.

As you can see, when this document was published in 2010, there were only two FDA approved treatments for Infantile Spasms in the United States, ACTH gel, and vigabatrin. Since that time, no other products have received FDA approval as initial treatment and none have demonstrated superiority. As such, I am very concerned that your group has recommended high-dose prednisolone as initial therapy. Since this study was published, other studies have also confirmed the superior efficacy of ACTH gel over the high dose prednisolone. Additionally, the studies have shown the delay in treatment of ongoing infantile spasms has negative developmental consequences for the infant that cannot be recovered from.

I hope that you will consider these items and consider revision of your policy. I would be happy to discuss this with you at any time, and a phone call can be coordinated through my office if needed. Please do not hesitate to contact me if I can answer any questions.

Sincerely,

Mary L. Zupanc MD

Mary L. Zupanc, MD, FAAP, FAAN
Professor and Chief of Neurology
Director of the Pediatric Epilepsy Program
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Children's Hospital of Pittsburgh | of UPMC

Yoshimi Sogawa, MD

Associate Professor of Pediatrics
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Division of Child Neurology
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April 13, 2018

Vice-Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Blvd, Suite #5101
Falls Church, VA 22042-5101

RE: Tricare and the Treatment of Infantile Spasms

Dear Vice-Admiral Bono,

I am writing to you regarding your recent decision that Tricare has made recommending high-dose prednisolone therapy for two weeks as initial treatment for infantile spasms. I would like to point out that the most recent practice guideline (2012) published by the American Academy of Neurology clearly stated that " the evidence is insufficient to recommend the use of prednisolone as being as effective as ACTH (Level U)" In more detail, the response rate to prednisolone was 50-70%, which is much lower than 87% from high-dose ACTH. The reason for insufficient evidence is not due to the small difference in efficacy but to lack of sufficient number of patients on these studies to reach statistical significance.

In the United States, ACTH gel and vigabatrin are the FDA approved initial treatment for infantile spasms, and no other agents (including prednisolone) have demonstrated superiority. I am concerned that Tricare is recommending non-FDA approved agent as initial therapy for infantile spasms, which has devastating long-term neurological outcome if seizures are not controlled quickly.

I would hope that you would consider revision of your policy. I would be happy to discuss this with you at any time. Please feel free to contact me if I could answer any questions.

Sincerely,

Yoshimi Sogawa, MD

MULTIPLE SCLEROSIS
ASSOCIATION OF AMERICA
800-532-7667
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EMAIL: msaa@msassociation.org

Vice Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101

May 1, 2018

Dear Vice Admiral Bono:

The Multiple Sclerosis Association of America is a national 501(c)(3) patient advocacy organization that serves the more than 400,000 US residents diagnosed with multiple sclerosis. Founded 49 years ago, MSAA has established an excellent record of reasoned, fair and balanced public positions on various MS issues focusing on the needs of the patient. As a leading resource for the entire MS community, improving lives through vital services and support, we are strong advocates for patient access to all needed and appropriate treatments.

Our organization is extremely troubled by the Department of Defense Pharmacy and Therapeutic Committee's April recommendations for new manual prior authorization criteria for Adrenocorticotropic Hormones (ACTH), also known as HP Acthar Gel, in Tricare beneficiaries. According to this new criterion, patients with multiple sclerosis who are experiencing a disease relapse would be required to utilize IV/PO corticosteroids and fail each time an exacerbation has been determined by their treating physician before approval of ACTH is granted.

This is a worrying decision, as ACTH is typically used in MS patients who have displayed intolerance for corticosteroids, have struggled with the numerous side-effects present in the same, have found them ineffective in treating disease relapses, and may simply be unable to take medication through their veins. These barriers to treatment in the use of steroids make prescription of ACTH a vital option for exacerbations that have an immense impact on an individual's quality of life.

Signs of a disease relapse or "MS Attack" may include, but are not limited to: loss of or blurry vision, spasticity in various extremities, speech changes, leg/foot weakness, balance and walking difficulty, bowel and bladder issues, and extreme pain. These exacerbations, if left untreated, can lead to a deterioration of not only quality of life, but also increase the likelihood of long-term disability, and carry the risk of hospitalization and potential rehabilitative periods.

While it is common for an MS patient to face step-therapy requirements for ACTH during their initial relapse period, it is highly unusual for the individual in question to face the same requirement in each instance of recurrent disease activity. **MSAA urges for the betterment of all Tricare beneficiaries living with MS, that the Pharmacy and Therapeutics Committee reconsider this recommendation and instead amend it to allow for prescription of ACTH in perpetuity after the first corticosteroid failure has been determined.**

I would be happy to provide further insight in to our concerns about the negative impact that this might have on MS patients' long-term health outcomes. I can be reached at (800) 532-7667, x160 or kpinion@mymsaa.org. Thank you in advance for your attention to this matter.

Respectfully,

Kyle Pinion
Senior Director of Education, Healthcare Relations & Advocacy

NEPHCURE®
Kidney International

April 30, 2018

Via Electronic Delivery
Vice Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042-5101
Chief of Staff: Col Daniel E. Lee, USAF, MSC
Daniel.e.Lee8.mil@mail.mil
Re: Recommended Coverage Policy for H.P. Acthar® Gel

Dear Vice Admiral Bono:

On behalf of NephCure Kidney International, we would like to share concerns regarding the recent recommendations of the Department of Defense's Pharmacy & Therapeutics Committee regarding coverage for Acthar Gel. As the only organization committed exclusively to support research seeking the cause of the diseases that cause Nephrotic Syndrome, we believe these patients should have access to all available treatment options in all appropriate circumstances. NephCure is driven by a panel of respected medical experts and a dedicated band of patients and families.

Every patient's nephrotic syndrome journey is unique. This disease often involves a complex set of symptoms that varies significantly by patient. Because of the disease's complexities, patients' responses to the available therapies also varies. Therefore, it is critical that patients have access to the full range of treatment options, so that the appropriate medication for that patient is available to meet his or her needs. No patient should be denied any therapy appropriately prescribed by their physician without any consideration of their unique needs.

We understand that the P&T Committee's recommendations include serious restrictions to existing Acthar coverage criteria by, in part, determining that the use of Acthar for nephrotic syndromes is "unsupported" and not approved. It is not clear why the P&T Committee made this recommendation, especially given that veterans with nephrotic syndromes currently have access to Acthar through an appeal process. We are deeply concerned that the recommendations, if approved, may harm the patients we serve.

We understand that you will either approve or reject the P&T Committee's recommendations. We ask that you reject the recommendation to protect patients of this nephrotic syndrome and ensure that they have appropriate access to all treatment options.

We appreciate your consideration of these comments. If you have any questions about these comments or if we can be of any assistance, please let us know.

Sincerely,

Joshua M. Tarnoff
Chief Executive Officer

National Kidney Foundation™

30 E. 33rd Street
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Tel 212.889.2210
Fax 212.689.9261
www.kidney.org

May 2, 2018

Vice Admiral Raquel C. Bono
Director, Defense Health Agency
Defense Health Agency
7700 Arlington Boulevard, Suite 5101
Falls Church, VA 22042

Subject: Coverage for Nephrotic Syndrome Therapies

Dear Vice Admiral Bono,

The National Kidney Foundation (NKF) is America's largest and oldest health organization dedicated to the awareness, prevention, and treatment of kidney disease for hundreds of thousands of healthcare professionals, millions of patients and their families, and tens of millions of people at risk. In addition, NKF has provided evidence-based clinical practice guidelines for all stages of chronic kidney disease (CKD), since 1997 through the NKF Kidney Disease Outcomes Quality Initiative (NKF KDOQI). NKF has divisions and affiliates delivering education, programs, and services in all 50 states, to provide patients and professionals with the best available information and to help them make informed and appropriate treatment choices

It has come to our attention that you are considering reducing the coverage options available to patients suffering from nephrotic syndrome (NS) whose health benefits are covered by Tri Care, by eliminating NS as an approved indication for Acthar gel, repository corticotropin injection. NS is a serious disorder that can lead to chronic disability and to expensive renal replacement therapy. NS is a complex condition, caused by a variety of glomerular disorders that affect both adults and children. Fortunately, there are pharmaceutical interventions that can result in partial or complete remissions, thereby slowing progression and reducing the incidence of ESRD, as well as other adverse outcomes.

The first line treatment for primary NS is often corticosteroids, with other immunosuppressive agents added depending on the pathologic diagnosis. These agents may fail or cause significant adverse events. NKF believes that clinical outcomes for our patients are optimal when they have

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access to all FDA-approved therapies that their physicians prescribe. In order for this to be true the therapies need to be covered by insurance, even if in some cases step therapy approaches or other utilization review techniques are required prior to authorization

The NKF therefore respectfully requests that you cover all therapeutic agents, including Acthar, when prescribed for the treatment of steroid-resistant NS.

Sincerely,

Kerry Willis, PhD
Chief Scientific Officer

CC David W. Bobb, RPH, JD, Chief, Pharmacy Operations Division
CAPT Edward Norton, U.S. Navy, BAP Designated Federal Officer (DFO)
Bryan Wheeler, Deputy General Counsel

EXHIBIT B

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Mallinckrodt Pharmaceuticals
Comments on DoD P&T Committee Proposal

I. Introduction

- My name is Sean Griffin, and I am an attorney with the law firm Sidley Austin LLP.
- I am here today on behalf of Mallinckrodt Pharmaceuticals.
- Mallinckrodt has asked me to address a mix of clinical and legal concerns regarding the P&T Committee's recent recommendations regarding the class of drugs known as Adrenocorticotropic Hormones or ACTH.
- Mallinckrodt manufacturers Acthar Gel, which is the only ACTH product currently approved for therapeutic use in the United States.
- Acthar Gel is widely recognized as a medically necessary product and has the distinction of being FDA approved for 19 different indications.
- We have not had much time to review the Committee's recommendations, so my comments today are necessarily at a high-level.
- Mallinckrodt is concerned, however, that certain of the PA criteria recommended for the Infantile Spasm (IS) and Multiple Sclerosis (MS) indications are inappropriate and will harm patients by delaying access to an important and effective therapy.
- Mallinckrodt also is concerned about the omission of any prior authorization criteria for the other FDA-approved indications. That omission appears to be based on a false premise—namely, that those indications have not been evaluated or approved by FDA for effectiveness. That is false. Each of the current labeled uses was approved for effectiveness in 1977 and again in 2010.
- These clinical and factual issues also raise serious legal issues. Under the Administrative Procedures Act (or APA), agency decisions must be evidence-based and supported by a reasoned explanation.[1] Those requirements take on special force when, as now, an agency proposes to substantially revise a policy that has been in place for several years.[2] At a minimum, the Committee should have acknowledged that it was changing the coverage policy for IS and other uses, explained why the change is justified based on specific, reliable evidence, and addressed the legitimate reliance that patients, providers,

[1] *Motor Vehicle Mfrs. Assn. of United States, Inc. v. State Farm Mut. Automobile Ins. Co.*, 463 U.S. 29, 43 (1983) ("[T]he agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'").

[2] *FCC v. Fox Television Stations, Inc.*, 129 S. Ct. 1800, 1811 (2009) (An agency must "provide a more detailed justification … when, for example, its new policy rests upon factual findings that contradict those which underlay its prior policy.").

and Mallinckrodt have placed on the prior policies.[3] The Committee appears not to have followed these important APA requirements.

- In light of these concerns, we request that the Panel modify the Committee's recommendations in three ways.
    - First, we believe that the PA criteria for the IS indication should not include a requirement that patients first receive a 2-week course of high-dose prednisone/prednisolone. This will harm patients and is inconsistent with nationally-accepted clinical practice guidelines.
    - Second, we believe that the PA criteria for the MS indication should be edited to remove the words "for the present exacerbation." It is plainly inappropriate to require a failed steroid treatment for each individual exacerbation as it occurs. Forcing patients to endure multiple, repeated treatment failures would be an entirely unreasonable barrier to access to an established second line therapy.
    - Finally, we believe that the Panel should strike the Committee's language describing other FDA-approved uses of Acthar Gel as "unsupported" or "unproven" and adopt appropriate PA criteria for at least those uses that previously have been covered "on appeal." The Committee failed to explain in any manner how new evidence justified the departure from its prior coverage policies, which did cover these uses in appropriate circumstances. A policy of no coverage under any circumstances, no matter how severe the patient need and no matter how extensively other therapies have been tried and failed, is plainly arbitrary and capricious.
- I will now address our three concerns in greater detail.

II. Infantile Spasms

- We have several concerns regarding the Committee's proposal that patients be required to receive 2 weeks of steroids before receiving Acthar Gel. First and foremost, we are concerned that a two-week course of steroids will harm patients by delaying the onset of treatment with Acthar Gel.
    - Infantile Spasms is a rare but catastrophic syndrome that typically onsets within the first year of life and is characterized by both spasms and hypsarrhythmic EEG patterns.
    - The condition very frequently results in neurological delay or impairment.

[3] *Perez v. Mortgage Bankers Ass'n*, 135 S. Ct. 1199, 1209 (2015) ("It would be arbitrary and capricious to ignore" "serious reliance interests that must be taken into account."); *accord Smiley v. Citibank (South Dakota), N.A.*, 517 U.S. 735, 742 (1996).

- Delayed treatment that exposes infants to three or more weeks of hypsarrhythmia has been shown to cause increased impairment.[4]

- We are concerned that a two-week delay before commencing treatment with Acthar Gel could result in unnecessary, permanent disability.

- Our concerns are underscored by the fact that neither prednisone nor prednisolone has been approved by FDA for the treatment of IS.

  - We think it is plainly inappropriate to rely on unapproved uses of these steroids as a first-line treatment for such a serious and time-sensitive condition.

  - Indeed, we are not aware of any government payor or major commercial payor that currently requires patients suffering from Infantile Spasms to receive steroid treatment prior to receiving Acthar Gel.

- To the contrary, Acthar Gel is widely recognized as the standard of care for IS.

- Mallinckrodt previously submitted a comprehensive set of articles and studies related to the use of Acthar Gel as a treatment for IS. We would particularly like to draw the Panel's attention to:

  - The current evidence-based clinical guidelines from the American Academy of Neurology / Child Neurology Society, which not only endorse Acthar Gel as a first line therapy but also conclude that there is insufficient evidence to recommend the use of prednisolone or other therapies.[5]

  - A 2010 meeting of knowledge leaders, which concluded that a high-dose regimen of Acthar Gel "continues to be the clinical standard of treatment of infantile spasms in the United States and several other countries."[6]

  - A study published in 2016 by the National Infantile Spasms Consortium, which found that ACTH appeared to be a more effective treatment for Infantile Spasms than other standard therapies.[7]

  - A randomized trial published in 1996, which found that a 2-week course of high-dose ACTH (86.6% efficacy) was superior to 2 weeks of what would now be

[4] Mackay MT, et al. Neurology. 2004;62(10):1668-1681; Goh S, et al. Neurology. 2005;65(2):235-238.

[5] Go C.Y. et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society – Neurology, 2012;78:1974-1980.

[6] Stafstrom CE et al. Treatment of IS insights from clinical & basic science perspectives - J Child Neurol 2011 26(11) 1411-1421.

[7] Knupp K.G. et al. Response to Treatment in a Prospective National Infantile Spasms Cohort – Ann Neurol 2016;79:475-484.

considered low-dose prednisone (28.6%) for treatment of infantile spasms as assessed by both clinical and EEG criteria.[8]

- We believe that the Committee's recommendation would not survive judicial review under the APA.
    - The Committee's recommendation does not appear to be evidence based. Although there are oblique statements regarding a review of the evidence, the Committee does not cite any particular source that supports its position.
    - The Committee also appears to have ignored the materials I've mentioned, none of which are acknowledged in the decision, and all of which contradict the recommendation.
    - The Committee's recommendation does not acknowledge that the 2 weeks of steroids requirement is a substantial change in policy. The PA criteria that have been in place since 2013 do not require prior steroid treatment. No new evidence is presented, and we are not aware of new evidence that would be sufficient to outweigh or contradict the settled view that Acthar Gel is the standard of care for this condition.
    - Last, the Committee did not consider the reliance interests of patients, providers, and Mallinckrodt surrounding the prior policy.
    - Each of these issues is independently a basis to conclude that the Committee's recommendation is arbitrary and capricious under the APA.
- Accordingly, we ask the Panel to remove the PA criteria that all patients with IS first try a 2 week course of steroids.

III. Multiple Sclerosis

- With respect to the MS indication, we agree that prior authorization is appropriate and that patients should try and fail treatment with steroids prior to receiving Acthar Gel for MS exacerbations.
- Our objection is only to the requirement that patients must have failed steroid treatment in connection with "the present exacerbation," which seems plainly unreasonable.
    - MS patients often experience multiple exacerbations or relapses, with many experiencing more than one exacerbation a year.
    - If steroids failed in a prior exacerbation, there should be no reason to force the patient to repeat the failed therapy again.

[8] Barram TZ et al. High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study – Pediatrics 1996;97(3):375-379.

- If the Committee's recommendation is adopted, veterans theoretically could be forced to try steroid treatments 5, 6, 7 or more times beyond the first failure, with each exacerbation forcing a new trial and failure.

- We cannot believe that was the Committee's intent.

- Repeated steroid treatments also pose quality of life problems for MS patients:

  - During an exacerbation without appropriate treatment, patients can experience a range of harms, from difficulty walking to optic neuritis, a painful vision issue, and cognitive delays.

  - A steroidal treatment also typically requires the patient to visit a clinic every day to receive the infusion, as opposed to Acthar Gel, which can be administered by the patient in the home. For a patient in an exacerbation, with limited or no mobility, that is a very real and very serious barrier to care.

- Accordingly, we ask the Committee to remove the requirement that steroids must be used first in the "present exacerbation."

IV. All Other Uses

- For all remaining indications of Acthar Gel, the P&T Committee recommends that all other uses "are unsupported and excluded from TRICARE coverage."

- We have several concerns about this recommendation.

- First, the recommendation is based on a plain misunderstanding of the facts and the law.

  - The Committee document (at page 13) asserts that all indications other than IS and MS have not been approved by FDA for clinical effectiveness because the drug was originally approved prior to the 1962 Amendments to the FDCA.

  - That is false.

  - ACTH was considered through the Drug Efficacy Study Implementation Program. Through that program, Acthar Gel was reviewed and approved as effective in 1977 for a large number of indications and in 1978 for MS.

  - FDA then re-reviewed the drug in 2010 as part of a supplemental NDA filing, and reaffirmed 19 approved indications. Each of those indications have been approved by FDA for both safety and effectiveness.

  - The APA does not permit an agency to base a decision on a false premise.

- Second, the recommendation is a break from existing coverage policy.
    - Previously, the program provided coverage for indications like lupus and protein-wasting nephropathies on "appeal only."
    - While we have many concerns about the legality of "appeal only" coverage, that policy did enable at least some patients to receive coverage.
    - For instance, between January 2014 and March 2018, at least 113 naïve patients received coverage for Acthar Gel for protein-wasting nephropathies on appeal.
    - By statute, this means that the Department has recognized that these uses were medically necessary in those particular cases.[9]
- Thus, the Committee articulated a change of position, but without any explanation, such as new evidence that could support the decision to cut off coverage for uses that were previously covered. The change therefore is subject to challenge under the APA.
- Finally, we are very concerned that the recommendation does not address the legal concerns that we have raised over the past several months.
    - Previously, we raised a serious of concerns in which some patients who had been prescribed Acthar Gel for these uses were not given initial determinations that they are entitled to receive under applicable law.
    - They were instead given appeal rights, but were falsely told by DoD's contractor that the appeal would necessarily fail. Not only did this result in delay, it strongly disincented patients from pursuing their appeal rights.
    - We were told that the P&T Committee review would address these serious issues, but the current recommendation makes the problem worse.
    - There is no mechanism to correct for past patients to receive the initial coverage determination that they were deprived. Nor is there a process to correct the false statements made to patients regarding their appeals.
    - And, for future patients, there is no indications that they will even receive appeal rights, let alone an initial determination.
- Accordingly, we believe the Panel should establish PA criteria for the uses previously covered on appeal.
- Thank you for your time. The company will be following up with an additional letter and we can address the questions in that letter.

[9] TRICARE's coverage is limited to services and supplies that "are medically or psychologically necessary for the diagnosis or treatment of a covered illness . . . or injury . . . ." 32 CFR 199.4(g)(1).

EXHIBIT C

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PRIOR AUTHORIZATION FORM
Acthar - Commercial/Medicaid

Unless otherwise indicated below, authorization quantities are limited to the manufacturer recommended dosage

selecthealth
P.O. Box 30192
Salt Lake City, UT 84130-0192
SELECTHEALTH.ORG

Phone: 801-442-4912 or 800-442-3129	**Fax back to: 801-442-3006**
Patient Information	
Patient's Name:	Patient's Date of Birth:
Patient's ID:	Patient's Phone #:
Diagnosis Code(s):	
Requesting Provider Information	
Name:	Phone #:
NPI/DEA:	Fax #:
Address:	Supervising Physician (if requesting provider bills under a different provider)
	Name:
	NPI/DEA:
Servicing Provider Information (if different than requesting provider)	
Name of provider or facility:	Phone number:
NPI/DEA:	Address:

Drug Name and Strength:	Directions / SIG:

Q1. Is the prescribing physician a neurologist?
☐ Yes ☐ No

Q2. Has the patient been diagnosed with infantile spasms as confirmed by EEG?
☐ Yes ☐ No

Q3. Is the patient less than 24 months old?
☐ Yes ☐ No

Q4. Please supply infant's body surface area (BSA):

Q5. Additional Comments:

This form is intended for SelectHealth members only. All requests for preauthorization should be sent via fax to 1-801-442-3006. Missing, inaccurate, or incomplete information may cause a delay or denial of authorization.

Prescriber Signature

Date

EXHIBIT D

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PRIOR AUTHORIZATION FORM
Acthar - Medicare

Unless otherwise indicated below, authorization quantities are limited to the manufacturer recommended dosage

selecthealth ADVANTAGE
P.O. Box 30196
Salt Lake City, UT 84130-0196
SELECTHEALTHADVANTAGE.ORG

Phone: 801-442-9988 or 855-442-9988	**Fax back to: 801-442-0413**
Patient Information	
Patient's Name:	Patient's Date of Birth:
Patient's ID:	Patient's Phone #:
Diagnosis Code(s):	
Requesting Provider Information	
Name:	Phone #:
NPI/DEA:	Fax #:
Address:	Supervising Physician (if requesting provider bills under a different provider)
	Name:
	NPI/DEA:
Servicing Provider Information (if different than requesting provider)	
Name of provider or facility:	Phone number:
NPI/DEA:	Address:

Drug Name and Strength:	Directions / SIG:
☐ Urgent Request (24 hours)	☐ Standard Request (72 hours)

Q1. What is Acthar being prescribed to treat?

- ☐ Infantile Spasms
- ☐ Multiple Sclerosis
- ☐ Nephrotic Syndrome
- ☐ Systemic Lupus Erythematosus (Rheumatic disorder)
- ☐ Rheumatoid Arthritis (Rheumatic disorder)
- ☐ Psoriatic Arthritis (Rheumatic disorder)
- ☐ Ankylosing Spondylitis (Rheumatic disorder)
- ☐ Severe Erythema Multiforme (Dermatalogic disorder)
- ☐ Stevens-Johnson Syndrome (Dermatalogic disorder)
- ☐ Systemic Dermatomyositis
- ☐ Symptomatic Sarcoidosis
- ☐ Serum Sickness
- ☐ Other

Q2. If other, does the patient have keratitis; iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis; or anterior segment inflammation? ☐ Yes ☐ No
Q3. If no, please provide the diagnosis and rationale for request:
Q4. For Infantile Spasms, is the prescribing physician a neurologist? ☐ Yes ☐ No
Q5. Has the patient been diagnosed with infantile spasms as confirmed by electroencephalogram (EEG)? ☐ Yes ☐ No
Q6. Is the patient less than 24 months old? ☐ Yes ☐ No
Q7. Has the patient failed treatment with prednisone, prednisolone, hydrocortisone, or dexamethasone? ☐ Yes ☐ No
Q8. Has the patient failed treatment with vigabatrin and/or cosyntropin? ☐ Yes ☐ No
Q9. For Exacerbations of Multiple Sclerosis, is the prescribing physician a neurologist? ☐ Yes ☐ No
Q10. Has the patient failed at least two courses of treatment with Solu-Medrol for two separate multiple sclerosis exacerbations? ☐ Yes ☐ No
Q11. For Nephrotic Syndrome, is the prescribing physician a nephrologist? ☐ Yes ☐ No
Q12. Has the patient failed therapy with at least two corticosteroids? ☐ Yes ☐ No
Q13. Has the patient failed therapy with either cyclophosphamide or cyclosporine? ☐ Yes ☐ No
Q14. For Rheumatic Disorders, Is the prescribing physician a rheumatologist? ☐ Yes ☐ No
Q15. Has the patient failed therapy with oral corticosteroids? ☐ Yes ☐ No
Q16. Has the patient failed therapy with an oral disease-modifying antirheumatic drug (DMARD)? ☐ Yes ☐ No
Q17. For Dermatologic Disorders, is the prescribing physician a dermatologist? ☐ Yes ☐ No
Q18. Has the patient failed therapy with methylprednisolone? ☐ Yes ☐ No
Q19. Additional Comments:

This form is intended for SelectHealth members only. All requests for preauthorization should be sent via fax to 1-801-442-3006. Missing, inaccurate, or incomplete information may cause a delay or denial of authorization.

Prescriber Signature

Date