EXECUTIVE SUMMARY

Uniform Formulary Beneficiary Advisory Panel
Meeting January 26, 2022

For the August 2021 DoD Pharmacy and Therapeutics Committee

The Uniform Formulary Beneficiary Advisory Panel (UFBAP) convened at 9:00 A.M. on January 26, 2022 via teleconference, due to the ongoing COVID pandemic. The Secretary of Defense directed a zero-based review of all DoD Advisory Committees in January 2021, as a result, the UF BAP did not meet in 2021.

The current meeting took place over two days on January 25-26, 2022. The information presented on January 25th included the recommendations from the February 2021 DoD Pharmacy and Therapeutics Committee (P&T) meeting (presented in the morning) and May 2021 DoD P&T meeting (presented in the afternoon). The information presented on January 26th included the recommendations from the August 2021 (presented in the morning) and November 2021 (presented in the afternoon) DoD P&T Committee meetings

The detailed meeting information is found starting on page 7.

UNIFORM FORMULARY (UF) DRUG CLASS REVIEWS

I. UF DRUG CLASS REVIEWS— Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass

A. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass—UF/Tier 4/Not Covered Recommendation

- UF
  - Calquence
  - Imbruvica
  - Brukinsa

- NF – None
- Tier 4 – None

Summary of Panel Questions and Comments
There were no questions from the Panel.

- **Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0**

B. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass —Manual PA Criteria

Summary of Panel Questions and Comments
There were no questions from the Panel.

- **Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0**

C. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass —UF, PA and Implementation Plan of two weeks

Summary of Panel Questions and Comments
There were no questions from the Panel.

- **Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0**

II. UF CLASS REVIEWS—Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass

A. Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass —UF Recommendation

- UF
  - Colyte, GoLYTELY, Galvilyte-A, Galvilyte-C, GalviLyte-G, generics
  - NuLYTELY, TriLyte, generics
  - Moviprep
  - Plenvu
  - Clenpiq *(moves from NF to UF)*
- NF
  - None Suprep *(moves from UF to NF)*
  - Sutab
  - Osmoprep *(moves from UF to NF)*
  - Prepopik *(moves from UF to NF)*

- Tier 4 – None

Summary of Panel Questions and Comments
There were no questions from the Panel.

- **Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0**

B. Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass —UF Implementation Period of two weeks

Summary of Panel Questions and Comments
There were no questions from the Panel.

- **Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0**

III. NEWLY APPROVED DRUGS PER 32 CFR 199.21(g)(5)

A. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF/Tier 4 Recommendation

- UF
  - Zegalogue
  - Truseltiq
  - Xolair syringe
  - Empaveli
  - Myfembree
  - Exservan oral film
  - Wegovy injection
  - Lumakras
- NF
  - Nextstellis
  - Accrufer
  - Qelbree
- Tier 4/Not Covered
  - Roszet

Summary of Panel Questions and Comments
Mr. Ostrowski remarked that it was good to see several new drugs becoming available for our beneficiaries.

Mr. DuTeil appreciated the discussion on Accrufer by Dr. Kugler, as he had wondered why four people had voted no (*refer to page 10 – the opposing votes were because the Committee wanted Tier 4 status rather than nonformulary status)*

- **Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0**

B. Newly Approved Drugs per 32 CFR 199.21(g)(5) — PA Criteria for Wegovy, Lumakras, Truseltiq, Xolair syringe, Myfembree, Exservan film, Accrufer, Empaveli, Nextstellis, and Qelbree

Summary of Panel Questions and Comments
Dr. Guzman questioned (*in reference to the Myfembree PA criteria that it is not approved for the off-label use of endometriosis*) that if Myfembree does get the indication for endometriosis, can it be used if the patient has symptoms. Dr. Allerman responded yes, and that there is monitoring for new indications and that PAs are updated accordingly. Dr. Allerman also relayed that there is the avenue of an appeal's process, if the formal indication is not yet approved yet by the FDA.

- **Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0**

C. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF, Tier 4/Not Covered and PA Implementation Plan of two weeks for the UF and NF drugs, and 120 days for the Tier 4 drugs

Summary of Panel Questions and Comments
There were no questions from the Panel.

- **Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0**

IV. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA

A. New Manual PA Criteria for Omnipod and Omnipod DASH in new and current users, for Kristalose packets in new users, and for Neonatal-DHA and Neonatal FE prenatal vitamins in new users

Summary of Panel Questions and Comments
Dr. Peloquin asked with regard to the PA criteria for Omnipod and Omnipod DASH if the PA renewal criteria matches the TRICARE Policy Manual Criteria. Dr. Lugo responded that the criteria do not necessarily follow the TPM criteria, but are to ensure

appropriate use. For example, patients may need to go on to an insulin pump, rather than using these devices.

Dr. Peloquin asked if there was inappropriate use of these devices. Dr. Lugo said yes, MTFs had let the Formulary Management Branch staff know about some inappropriate use.

Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0

B. New Manual PA Criteria—Implementation Plan for Omnipod and Omnipod DASH for 90 days and that DHA will send letters; and for 60 days for for Kristalose packets

Summary of Panel Questions and Comments
There were no questions from the Panel.

Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0

V. UTILIZATION MANAGEMENT—UPDATED MANUAL PA CRITERIA

A. Updated PA Criteria for Zeposia, Nurtec ODT, Ubrelvy, and Reyvow in new users

Summary of Panel Questions and Comments
Dr. Peloquin asked if the migraine drugs were all on the same PA form. CDR Raisor responded that they are on separate PA forms.

Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0

B. Updated PA Criteria—Implementation Plan at 30 days for Zeposia, and 60 days for the migraine drugs

Summary of Panel Questions and Comments
There were no questions from the Panel.

Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0

VI. UTILIZATION MANAGEMENT—UPDATED MANUAL PA CRITERIA FOR NEW FDA-APPROVED INDICATIONS, NCCN GUIDELINE UPDATES, OR AGE RANGES

A. Updated PA Criteria for Ayvakit, Cosentyx, Myrbetriq, Toviaz, Epclusa and authorized generic, Mavyret, Evekeo ODT, and Ocaliva

Summary of Panel Questions and Comments

There were no questions from the Panel.

Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0

B. Updated PA Criteria—Implementation Plan of 60 days

Summary of Panel Questions and Comments
There were no questions from the Panel.

Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0

VII. COPAYMENT CHANGE – TIER 1 for the PULMONARY 3 AGENTS: COMBINATIONS SUBCLASS—BREZTRI INHALER COPAYMENT CHANGE

A. Breztri Tier 1 Copayment and Implementation Plan upon signing

Summary of Panel Questions and Comments
There were no questions from the Panel. Mr. Ostrowski commented that the copay change was good news for the beneficiaries

Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0

VIII. BRAND OVER GENERIC AUTHORIZATION and TIER 1 (GENERIC) COPAYMENT PULMONARY ARTERIAL HYPERTENSION (PAH) AGENTS: AMBRISENTAN (LETAIRIS)

A. Ambrisentan (Letairis) brand over generic authorization and Tier 1 Copayment and Implementation Plan upon signing

Summary of Panel Questions and Comments
Mr. Du Tiel commented that he was pleased with the copay change.
Mr. Ostrowski asked if we can administratively switch back to the usual generic requirements when the supply is stable. CDR Raisor responded that is correct. Mr. Ostrowski then commented that he has seen this happen before.

Concur: 7 Non-Concur: 0 Abstain: 0 Absent: 0

Director, DHA:
_____ The comments outlined above were taken under consideration prior to my final decision.

Uniform Formulary Beneficiary Advisory Panel
Virtual Meeting Summary Minutes
January 26, 2022

Panel Members Present

- Mr. Jon Ostrowski, Non-Commissioned Officer Association, Chair
- Dr. Karen Dager, PharmD, Health Net Federal Services
- Mr. John Du Teil, U.S. Army Warrant Officers Association
- Dr. Betsaida Guzman, PharmD, Veterans of Foreign Wars
- Dr. Joseph McKeon, MD, Humana Military
- Dr. Jay Peloquin, Pharm D, Express Scripts
- Dr. Jennifer Soucy, PharmD, U.S. Family Health Plan, Martins Point Services

Panel Members Absent

- Dr. Richard Bertin, Ph. D., Commissioned Officer Association of the U.S. Public Health Service
- Ms. Holly Dailey, the Association of the United States Army
- Ms. Catherine Seybold, U.S. Coast Guard Chief Petty Officers Association
- Ms. Patricia Orfini, National Family Member Association
- Ms. Amanda Meyers – Military Officers Association of America (MOAA)
- Mr. Keith Reed—Air Force Sergeants Association

Acting Designated Federal Officer (Non-Voting): Colonel Paul Hoerner, BSC

DHA Participants (Non-Voting)

- Dr. John Kugler, Division Chief, J-6; DoD P&T Committee Chair
- CDR Scott Raisor, Interim Chief, Pharmacy Operations Division Formulary Management Branch (POD FMB)
- Angela Allerman, PharmD, BCPS, POD FMB
- MAJ Adam Davies POD FMB
- LCDR Elizabeth Hall POD FMB
- LCDR Todd Hansen POD FMB
- Amy Lugo, PharmD, BCPS, POD FMB
- Mr. Bryan Wheeler Office of General Counsel
- Ms. Meghan Gemunder Office of General Counsel

Agenda is found starting on page 12

- Panel Discussions

  The Beneficiary Advisory Panel members will have the opportunity to ask questions to each of the presenters. Upon completion of the presentation and any questions, the Panel will concur or non-concur on the recommendations of the P&T Committee concerning the establishment of the UF and subsequent recommended changes. The

Panel will provide comments on their vote as directed by the Panel Chairman. Comments to the Director, DHA, or their designee will be considered before making a final UF decision.

Opening Remarks

This is a continuation of the meeting that started on the previous day - see the January 25th BAP meeting information corresponding to the February 2021 P&T Committee meeting for the full regulatory language regarding the purpose of the BAP meeting. Col Paul Hoerner stated that the Panel has convened for its second day to comment on the DoD P&T Committee meetings from August 4-5th 2021, and November 3-4th Nov 2021

Written comments were forwarded to the Panel for their review and consideration from the following:

1. Dr. Frank Lopez
2. Braintree Laboratories, Inc.
3. Supernus Pharmaceuticals
4. AstraZeneca

The meeting was then handed over to the Panel Chair for his opening remarks.

Chairman's Opening Remarks

Mr. Ostrowski welcomed everyone to the second day of meetings. He also thanked the Panel for taking time out of their busy schedule. He then turned the meeting over to CDR Raisor.

CDR Raisor's Opening Remarks

CDR Raisor introduced himself. He then continued by thanking the panel for their involvement yesterday and today. He stated there is a lot of information to cover in the two meetings today. He next introduced everyone on the line (see list above). There will be two drug classes discussed in the AM, the BTKIs to treat lymphoma and leukemia and the bowel prep classes; and also 12 new drugs

The full presentations then started. Following each section, the DoD P&T Committee physician perspective was provided by Dr. John Kugler, and is included starting on page 10. The information starting on page 17 includes the full meeting information.

Closing Remarks

Col Hoerner stated the morning meeting was concluded, and that the afternoon session would start after lunch.

The Meeting Adjourned at 10:36 AM EST.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

Jon R. Ostrowski

Digitally signed by Jon R. Ostrowski
Date: 2022.02.07 18:10:54 -05'00'

Jon R. Ostrowski
Chairperson, UFBAP

Appendices (starting on page 59)

- Appendix 1 – Written Comments Dr. Frank Lopez
- Appendix 2 – Written Comments Braintree Laboratories, Inc.
- Appendix 3 – Written Comments Supernus Pharmaceuticals
- Appendix 4 – Written Comments AstraZeneca

DoD P&T Committee Physician Perspective

Dr. John Kugler's comments on the formulary recommendations followed each individual section, and are outlined below.

Drug Class Reviews

Leukemia and Lymphoma drugs (BTKis)

- This is the second oncology drug class that was reviewed in 2021. The three products in the class were all designated as formulary, so providers and patients can select whichever product best meets their needs in terms of side effect profiles or patient comorbidities.
- Since we didn't choose a preferred product, if there are investigational agents that reach the market, then they can also be added to the formulary, based on clinical and cost effectiveness.
- We've had PA criteria in place for a while, and only minor updates were done here.

Bowel Preps

- We did receive input for the formulary recommendation from several providers. There will be 4 products designated as nonformulary. One of the drugs that was recommended for NF status is Osmoprep. Providers frequently mentioned the safety concerns with this drug, which is the main reason it will move the NF status.
- These products are primarily for one-time use, so for the drugs moving to nonformulary status, only new patients will be affected by the increased copay. We also won't be mailing letters, because of the acute use nature of the drugs.
- For the 5 drugs that will be designated as Uniform Formulary, they do cover special populations, such as for young children, or those with heart failure or kidney impairment. Low volume preparations were also designated as uniform formulary. So overall, a wide variety of products will be available.

Newly Approved Drugs

- There were 12 drugs reviewed, with 1 drug moving to Tier 4, 8 drugs moving to formulary status, and 3 drugs moving to nonformulary status.
- For the new weight loss drug Wegovy, it was added to the formulary and has PA criteria similar to another weight loss drug with the same mechanism of action (Saxenda). The endocrinologist on the Committee did say that the PA was appropriate and that the other drugs should be tried first.
- For the iron replacement drug Accrufer, the 4 opposing votes were because they felt this drug should be designated as Tier 4, rather than non formulary.

- The one drug recommended for Tier 4 status (Roszet) contains two ingredients which are available in low cost generic formulations. One of the ingredients, rosuvastatin, is available for no copay, since it is part of a medication adherence pilot. So far there have been 3 patients receiving prescriptions for this drug.

Utilization Management – New PA Criteria

- **Insulin devices – Omnipod and Omnipod DASH**
    - These products are insulin devices that are now covered under the pharmacy benefit. For the PA, it will follow similar requirements as is required if the products were obtained with the DME process. We are seeing increasing utilization, so the PA will ensure that the most appropriate patients are using these products.

Utilization Management – Updated PA Criteria – new clinical data

- **Zeposia- MS drug now approved for Ulcerative colitis; oral migraine drugs**
    - The PA updates here are based on the available clinical evidence that we have. They updates also take into account the preferred therapies for these disease states. If any new data is published, the PAs can be re-examined and updated as needed.

Pulmonary 3 Agents Tier 1 Copay for Breztri

- The Committee is able to recommend lower copays, and the decision here will allow for an immediate copay reduction for those patients already receiving Breztri, plus any new patients starting therapy will be able to take advantage of this lower copay.

PAH drugs- Letairis Brand Over Generic and Tier 1 copay

- This an example of where we continue to monitoring pricing and availability of generics. Here we will be preferring the branded product, and lowering the copay. Patients will notice this copay reduction the next time they fill their prescription after signature.

AGENDA

Uniform Formulary Beneficiary Advisory Panel (BAP)
For the August 2021 DoD Pharmacy and Therapeutics Committee Meetings
January 26, 2022 at 9:00 AM Eastern Daylight Time

Virtual Meeting

Note that the UF BAP meeting occurring on January 25th and 26th will include information presented at the February 2021, May 2021, August 2021 and November 2021 DoD Pharmacy and Therapeutics (P&T) Committee meetings. The information presented on January 25th will include the recommendations from the February 2021 (presented in the morning) and May 2021 (presented in the afternoon) P&T meetings. The information presented on January 26th will include the recommendations from the August 2021 (presented in the morning) and November 2021 (presented in the afternoon) P&T meetings.

Information from the August 2021 DoD P&T Committee Meeting

- **Administrative Meeting: 8:00 AM – 9:00 AM Eastern Daylight Time (General session starts at 9:00 AM Eastern Daylight Time)**
- **Roll Call**
- **Therapeutic Class Reviews**

  Members of the DHA Pharmacy Operations Division (POD) Formulary Management Branch (FMB) will present relative clinical and cost-effective analyses along with the DoD Pharmacy & Therapeutics Committee (P&T) recommendations for the Uniform Formulary (UF) and any recommended Tier 4/Not Covered candidates.

  The P&T Committee made recommendations for the following drugs/drug classes during the August 2021 meeting:

  - **Drug Class Reviews**

    - *Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass*
    - *Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass*

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

    - *dasiglucagon injection (Zegalogue) Binders-Chelators-Antidotes Overdose Agents: Hypoglycemia Agents for severe hypoglycemia*
    - *drospirenone/estetrol (Nextstellis) Contraceptive agents: Monophasics with 20 mcg estrogen*
    - *ferric maltol (Accrufer) Electrolyte Mineral Trace Element Replacement for iron deficiency*
    - *infigratinib (Truseltiq)-Oncological agent for cholangiocarcinoma*

- *omalizumab syringe (Xolair) Respiratory Interleukin for asthma, nasal polyps and chronic idiopathic urticaria (CIU)*
- *pegcetacoplan injection (Empaveli) Hematological agent for paroxysmal nocturnal hemoglobinuria (PNH)*
- *relugolix/estradiol/norethindrone (Myfembree) Luteinizing Hormone Releasing Hormone (LHRH) Agonists Antagonists*
- *riluzole oral film (Exservan) Miscellaneous neurological agent for amyotrophic lateral sclerosis (ALS)*
- *rosuvastatin/ezetimibe (Roszet) Antilipidemic I*
- *semaglutide injection (Wegovy) Weight loss agent and a GLP-1 receptor antagonist for the treatment of obesity*
- *sotorasib (Lumakras) Oncological agent for non-small cell lung cancer (NSCLC)*
- *viloxazine extended release (Qelbree) Non-Stimulant for Attention Deficient Hyperactivity Disorder (ADHD) in pediatric patients ages 6 to 17 years of age*

- **Utilization Management Issues**
  - ***Prior Authorization Criteria—New Manual PA Criteria***
    - *Miscellaneous Insulin Devices – Omnipod and Omnipod DASH*
    - *Laxatives-Cathartics-Stool Softeners – Lactulose Packets (Kristalose, generics)*
    - *Vitamins: Prenatal – Prenatal Multivitamins (Neonatal-DHA, Neonatal FE)*
  - ***Prior Authorization Criteria—Updated PA and Step Therapy Criteria***
    - *Multiple Sclerosis Agents: ozanimod (Zeposia)*
    - *Migraine Agents: rimegepant (Nurtec ODT), ubrogepant (Ubrelvy),lasmiditan (Reyvow)*
  - ***Prior Authorization Criteria—Updated PA Criteria for New FDA-Approved Indications, National Comprehensive Cancer Network Guideline Updates, or Age Ranges***

- *Oncological Agents: avapritinib (Ayvakit)*
- *Targeted Immunomodulatory Biologics (TIBs): secukinumab (Cosentyx)*
- *Overactive Bladder Agents*
  - *mirabegron (Myrbetriq)*
  - *fesoterodine (Toviaz)*
- *Hepatitis C Agents: Direct Acting Agents*
  - *sofosbuvir/velpatasvir (Epclusa) and authorized generic*
  - *glecaprevir/pibrentasvir (Mavyret)*
- *ADHD Agents: Stimulants*
  - *amphetamine sulfate ODT (Evekeo ODT)*
- *Gastrointestinal 2 Agents: obeticholic (Ocaliva)*

➢ **Copayment Change: Tier 1 (Generic)**

- *Pulmonary 3 Agents: Combinations Subclass-budesonide/glycopyrrolate/formoterol inhaler (Breztri)*

➢ **Brand Over Generic Authorization and Tier 1 (Generic) Copayment**

- *Pulmonary Arterial Hypertension (PAH) Drugs: ambrisentan (Letairis)*

➢ **Panel Discussions**

The Beneficiary Advisory Panel members 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.

(Break for Lunch)

Information from the November 2021 DoD P&T Committee Meeting

➢ **Roll Call**

➢ **Therapeutic Class Reviews**

Members of the DHA Pharmacy Operations Division (POD) Formulary Management Branch (FMB) will present relative clinical and cost-effective analyses along with the DoD Pharmacy & Therapeutics Committee (P&T) recommendations for the Uniform Formulary (UF) and any recommended Tier 4/Not Covered candidates.

The P&T Committee made recommendations for the following drugs/drug classes during the November 2021 meeting:

- **Drug Class Reviews**
  - *Continuous Glucose Monitoring Systems (CGMs)*
  - *Subcutaneous Immunoglobulins (SCIG)*
- **Newly Approved Drugs per 32 CFR 199.21(g)(5)**
  - *belumosudil (Rezurock) – Immunosuppressive for chronic graft-vs-host disease*
  - *belzutifan (Welireg) – Oncological agent for von Hippel Lindau disease*
  - *dihydroergotamine mesylate nasal spray (Trudhesa) – Another DHE nasal spray for acute treatment of migraine in adults with or without aura*
  - *finerenone (Kerendia) – Miscellaneous cardiovascular agent for kidney failure associated with diabetes*
  - *ibrexafungerp (Brexafemme) – Antifungal for vulvovaginal candidiasis*
  - *lorazepam extended-release capsules (Loreev XR) – Extended release lorazepam capsules for anxiety in adults already stabilized*
  - *mirabegron extended release granules for oral suspension (Myrbetriq Granules) – Overactive bladder agent for neurogenic detrusor overactivity (NDO)*
  - *mobocertinib (Exkivity) – Oncological agent for non-small cell lung cancer (NSCLC)*
  - *naloxone nasal 8 mg (Kloxxado) – Narcotic antagonist for opioid overdose*
  - *odevixibat (Bylvay) – Miscellaneous metabolic agent for progressive familial intrahepatic cholestasis (PFIC)*
  - *olanzapine/samidorphan (Lybalvi) – Combination atypical antipsychotic for schizophrenia and bipolar I disorder*
  - *ruxolitinib 1.5% cream (Opzelura) – Topical corticosteroid immune modulator for atopic dermatitis*
  - *serdexmethylphenidate/dexmethylphenidate (Azstarys) – Stimulant ADHD agent*
- **Utilization Management Issues**
  - ***Prior Authorization Criteria—New Manual PA Criteria***

- *Antihistamine-1s: First Generation and Combinations—clemastine 0.5 mg/mL oral syrup*

a) *Pain Agents: NSAID – diclofenac potassium 25 mg tablet (Lofena)*

b) *Anti-Emetic/Anti-Vertigo Agents – meclizine 50 mg tablet (Antivert)*

c) *Antilipidemics-1 – niacin 500 mg tablet*

d) *Vitamins: Prenatal – Prenatal Multivitamin (Neonatal Complete)*

e) *Antidepressant and Non-Opioid Pain Syndrome Agents: Selective serotonin reuptake inhibitors (SSRIs) – sertraline 150 mg and 200 mg capsules*

- *Skeletal Muscle Relaxants and Combinations—tizanidine capsules (Zanaflex, generics***)**

- ***Prior Authorization Criteria—Updated PA Criteria for New FDA-Approved Indications, National Comprehensive Cancer Network Guideline Updates, or Age Ranges, or Safety***

  - *Antilipidemics-1: PCSK9–inhibitors: evolocumab (Repatha)*
  - *Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors–zanubrutinib (Brukinsa)*
  - *Oncological Agents: Acute Myelogenous Leukemia–ivosidenib (Tibsovo)*
  - *Respiratory Interleukins–mepolizumab injection (Nucala)*
  - *Sleep Disorders: Wakefulness Promoting Agents–sodium oxybate/calcium/magnesium/potassium oral solution (Xywav)*
  - *Targeted Immunomodulatory Biologics: Tumor Necrosis Factor Inhibitors–adalimumab (Humira)*
  - *Targeted Immunomodulatory Biologics (TIBs): Janus Kinase (JAK) inhibitors: baricitinib (Olumiant) and upadacitinib (Rinvoq)*

- **Panel Discussions**

The Beneficiary Advisory Panel members 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.

DEPARTMENT OF DEFENSE
PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS FROM THE AUGUST 2021 MEETING

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. UNIFORM FORMULARY REVIEW PROCESS

Under 10 United States Code § 1074g, as implemented by 32 Code of Federal Regulations 199.21, the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee is responsible for developing the Uniform Formulary (UF). Recommendations to the Director, Defense Health Agency (DHA) or their designee, on formulary or Tier 4/not covered status, prior authorization (PA), pre-authorizations, and the effective date for a drug's change from formulary to non-formulary (NF) or Tier 4 status are received from the Beneficiary Advisory Panel (BAP), which must be reviewed by the Director or their designee before making a final decision.

II. UF DRUG CLASS REVIEWS—Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass

P&T Comments

A. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass — Relative Clinical Effectiveness Analysis and Conclusion

Background—The P&T Committee evaluated the relative clinical effectiveness of the three agents in the BTK inhibitor subclass, comprised of ibrutinib (Imbruvica), acalabrutinib (Calquence), and zanubrutinib (Brukinsa). The Committee comprehensively reviewed the evidence including what was reviewed when Imbruvica, Calquence, and Brukinsa were presented as innovators in May 2018, February 2018, and February 2020, respectively.

The BTK inhibitors are indicated for use in chronic lymphocytic leukemia (CLL) and a variety of non-Hodgkin lymphoma subtypes including small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), non-germinal center B-Cell diffuse large B-Cell lymphoma (non-GCB-DLBCL), and Waldenström macroglobulinemia (WM).

The comprehensive evidence review included information from individual clinical trial data; guidelines from the National Cancer Comprehensive Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO); meta-analyses; FDA labeling; current Military Health System (MHS) patterns of use; and MHS provider comments.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following:

- Ibrutinib (Imbruvica) has the greatest number of FDA-approved indications, guideline-recommended uses, and the most voluminous and validated evidence base. In the Military Health System, it is the most utilized and the de facto preferred agent by oncologists.

- Where data is available, by indirect comparison, via network meta-analysis, and in head-to-head trials, all three agents appear to be equally clinically effective.

- While their safety profiles largely overlap, each agent has unique features. Specialists will tailor their choice of agent based on patient comorbidities.

- Acalabrutinib (Calquence) and zanubrutinib (Brukinsa) have favorable safety profiles relative to ibrutinib (Imbruvica) among certain clinically significant adverse events. Some providers prefer acalabrutinib over ibrutinib, either for specific patient comorbidities or indications.

- Zanubrutinib (Brukinsa) is the newest of the three agents, and has an immature evidence base and generally lower rankings where guidelines recommend use, when compared to the other two drugs.

- The ibrutinib (Imbruvica) capsule formulation allows for more flexible dosage titration, either for increasing the dose or reducing the dose due to adverse events, compared to the ibrutinib tablets.

- Once a patient's disease becomes refractory to one BTK inhibitor, it tends to be refractory to all BTK inhibitors.

B. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass — Relative Cost Effectiveness Analysis and Conclusion

Relative Cost-Effectiveness Analysis and Conclusion—Cost minimization analysis (CMA) and budget impact analysis (BIA) were performed. The P&T Committee concluded (18 for, 0 opposed, 0 abstained, 0 absent) the following:

- CMA results showed that acalabrutinib (Calquence), ibrutinib (Imbruvica), and zanubrutinib (Brukinsa) were all cost effective, when compared to each other. For Imbruvica, the capsule formulations are more cost effective than the tablet formulations.

- BIA was performed to evaluate the potential impact of designating selected agents as formulary, NF, or Tier 4 on the UF. BIA results showed that designating acalabrutinib (Calquence), ibrutinib (Imbruvica), and zanubrutinib (Brukinsa) as UF demonstrated the greatest cost avoidance for the MHS.

C. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass—UF/Tier 4/Not Covered Recommendation

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) the following:

- UF
    - acalabrutinib (Calquence)
    - ibrutinib (Imbruvica)
    - zanubrutinib (Brukinsa)
- NF – None
- Tier 4/Not Covered – None

D. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass—Manual PA Criteria

Existing PA criteria currently apply to all three drugs. For the ibrutinib tablets, further justification is required on the PA to state why the capsules cannot be used, due to more flexible dosage titration with the capsules. The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) minor updates to the ibrutinib PA criteria to reflect the clinical and cost differences of the capsules and tablets, and recommended maintaining the current PA criteria for acalabrutinib and zanubrutinib.

The PA criteria are as follows:

1. **ibrutinib (Imbruvica)**

    Updates from the August 2021 meeting are in bold

    Manual PA is required for new users of Imbruvica capsules and tablets, and is approved if all criteria are met.

    Imbruvica capsules are **more cost effective than Imbruvica tablets for DoD**.

    - The provider acknowledges that Imbruvica capsules are more cost effective than Imbruvica tablets for DoD
    - If the prescription is for Imbruvica tablets, please state why the patient cannot take the capsule formulation_____, then continue with the PA criteria below
    - If the prescription is for the Imbruvica capsules, please continue with the PA criteria below.
    - Patient is 18 years of age or older
    - Imbruvica is prescribed by or in consultation with a hematologist/oncologist
    - Imbruvica will be used in one of the following contexts:
        - Pretreatment to limit the number of cycles of RhyperCVAD/rituximab maintenance therapy for Mantle Cell Lymphoma

- Second line (or subsequent therapy) for Mantle Cell Lymphoma
- Second line (or subsequent therapy) for Marginal Zone Lymphoma
- Second line (or subsequent therapy) for non-germinal center B cell-like Diffuse Large B Cell Lymphoma if unable to receive chemotherapy
- Frontline or relapsed refractory therapy for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) without del(17p)/TP53 mutation
  - Patient fits one of the following categories:
    - Frail patient with significant comorbidity (not able to tolerate purine analogues)
    - Patient ≥ 65 years old with significant comorbidity
    - Patients < 65 years old
- Frontline or relapsed/refractory therapy for CLL/SLL with del(17p)/TP53 mutation
- Waldenström macroglobulinemia
- Chronic Graft versus Host Disease
- The patient will be monitored for bleeding, infection, hypertension, cardiac arrhythmias, cytopenias, and Tumor Lysis Syndrome
- If the patient is female, she is not pregnant or planning to become pregnant
- Breastfeeding female patients will be advised that the potential harm to the infant is unknown
- All patients (males and females) of reproductive potential will use effective contraception during treatment and for at least 30 days after discontinuation
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.

Other non-FDA-approved uses are not approved.

PA does not expire.

2. acalabrutinib (Calquence)

Note that no changes were made to the PA criteria at the August 2021

Manual PA Criteria: Calquence is approved if all criteria are met:

- Age 18 years of age or older
- Calquence is prescribed by or in consultation with a hematologist/oncologist
- Patient meets one of the following categories:
    - Patient must have pathologically confirmed relapsed or refractory mantle cell lymphoma (MCL) with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1 that had a short response duration to prior therapy (< median progression-free survival).
    - Patient will use acalabrutinib as relapsed refractory therapy for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) without del(17p)/TP53 mutation
        - Patient fits one of following categories:
            - Frail patient with significant comorbidity (not able to tolerate purine analogues)
            - Patient ≥ 65 years old with significant comorbidity
            - Patients < 65 years old
    - Patient will use acalabrutinib as relapsed refractory therapy for CLL/SLL with del(17p)/TP53 mutation
- If the patient has CLL, the patient's disease has no evidence of a BTK C481S mutation nor prior ibrutinib-refractory disease
- Patient must not have significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec
- The patient will be monitored for bleeding, infection, cardiac arrhythmias, and cytopenias
- If the patient is female and of childbearing potential, advise the patient of the risk of significant fetal harm
- Female patients will not breastfeed during treatment and for at least 2 weeks following cessation of treatment
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.

Other non-FDA-approved uses are not approved.

PA does not expire

3. zanubrutinib (Brukinsa)

Note that Brukinsa received new FDA indications following the August 2021 P&T Committee meeting, and prior to the BAP meeting and P&T Committee minutes' singing. The new indications are noted below in bold.

Manual PA Criteria applies to all new patients and Brukinsa is approved if all criteria are met:

- Patient is 18 years if age or older
- Brukinsa is prescribed by or in consultation with a hematologist/oncologist
- Patient has pathologically confirmed relapsed or refractory mantle cell lymphoma (MCL) or
- **Patient has Waldenström's macroglobulinemia (WM) or**
- **Patient has relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 anti-CD20-based regimen**
- The patient will be monitored for bleeding, infection (including opportunistic infection), cardiac arrhythmias, secondary primary malignancies, and cytopenias
- Patient will use sun protection in sun-exposed areas
- Female patients of childbearing age and are not pregnant confirmed by (-) HCG.
- Female patients will not breastfeed during treatment and for at least 2 weeks after the cessation of treatment
- Female patients of childbearing potential agree to use effective contraception during treatment and for at least 1 week after the cessation of treatment
- The diagnosis Is NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis:_____.

Other non-FDA-approved uses are not approved.

PA does not expire.

E. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass – UF, PA and Implementation Plan

The P&T Committee recommended (18 for, 0 opposed, 0 abstained, 0 absent) an effective date of the first Wednesday two weeks after signing of the minutes in all points of service.

III. UF DRUG CLASS REVIEWS- Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass

BAP Comments

A. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass—UF/Tier 4/Not-Covered Recommendations

The P&T Committee recommended the formulary status for the BTK inhibitors as discussed above.

- UF
  - Calquence
  - Imbruvica
  - Brukinsa
- NF
  - None
- Tier 4/Not Covered
  - None

BAP Comment:	□ Concur	□ Non-concur

B. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass— PA Criteria

The P&T Committee recommended updating the PA criteria as outlined above.

BAP Comment:	□ Concur	□ Non-concur

C. Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors Subclass—UF, PA and Implementation Plan

The P&T Committee recommended the implementation plan of the first Wednesday two weeks after signing of the minutes in all points of service.

BAP Comment: ☐ Concur ☐ Non-concur

IV. UF DRUG CLASS REVIEWS—Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass

P&T Comments

A. Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass—Relative Clinical Effectiveness Analysis and Conclusion

Background—The P&T Committee evaluated the relative clinical effectiveness of the bowel preparations indicated for colon cleansing in preparation for colonoscopy. Drugs in the class include generic preparations comprised of polyethylene glycol (PEG) 3350 with and without additional electrolytes. Six branded products are marketed, Osmoprep, Plenvu, Clenpiq, Suprep, Sutab, and Moviprep. The class has not been previously reviewed for formulary status, although Clenpiq, Plenvu and Sutab were evaluated as newly approved drugs at the February 2018, November 2018, and February 2021, respectively.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 1 abstained, 0 absent) the following:

- Several different dosage formulations are available, including powders for reconstitution, oral solutions, and tablets. The bowel preparations vary in the amount of liquid that is required for consumption, ranging from 2 to 4 liters.
    - Full-volume (standard volume) preparations require consumption of 4 liters (L) of total volume and include Colyte, GoLYTELY, NuLYTELY, and TriLyte and their generics.
    - Low-volume preparations range from 2 to 3.5 liters of total volume consumed and include Osmoprep (2 L), Plenvu (2 L), Clenpiq (2.2 L), Suprep (3 L), Sutab (3 L), and Moviprep (3 L). Although the tablet formulations (Osmoprep and Sutab) do not require mixing of solutions, significant additional water consumption is still required.

- There do not appear to be clinically relevant differences in efficacy, based on indirect evidence. Compared with standard-volume preparations, low volume products demonstrate superior bowel prep completion rate, improved adenoma detection rates, improved patient satisfaction for the prep and procedure, and increased likelihood that the patient will undergo future colonoscopy.

- Professional treatment guidelines recommend split-dose regimens over single dose traditional regimens (which are administered the day before the colonoscopy), due to improved cleansing. However, no one specific agent is recommended over another.

- Tolerability issues, including poor palatability and the requirement for large volumes of liquid may result in an inadequate bowel prep. Safety concerns vary by product and include gastrointestinal obstruction/perforation, gastric retention, and electrolyte disturbances, potentially exacerbating heart failure or renal dysfunction. PEG products are preferred in patients with heart failure, renal dysfunction or liver disease.

- Specific clinical considerations for the products are as follows:

    - **PEG 3350 with electrolytes powder for solution (Colyte, GoLYTELY, TriLyte, NULYTELY)** advantages include availability in generic formulations; approval for children as young as 6 months of age (TriLyte and NuLYTELY); additional indications for bowel cleansing prior to barium enema X-ray examinations (Colyte and GoLYTELY); and availability in sulfate-free formulations (TriLYTE and NULYTELY). Disadvantages include the large volumes required (4 L), poor taste, and tolerability issues.

    - **PEG 3350 with electrolytes powder for solution (MoviPrep**) is a low volume preparation (3 L) that has high MHS utilization, is well tolerated in elderly patients, and was frequently mentioned by providers as requiring inclusion on the formulary. MoviPrep should be used with caution in patients with phenylketonuria.

    - **PEG 3350 with electrolytes powder for solution (Plenvu)** is a low volume (2 L) preparation that is similar to MoviPrep.

    - **Sodium picosulfate, magnesium oxide, anhydrous citric acid oral solution (Clenpiq)** is a low volume formulation (2.2 L) indicated for patients 9 years of age and older that is already constituted and well-tolerated. Electrolyte disturbances can occur.

- **Sodium sulfate, potassium sulfate, magnesium sulfate, concentrated oral solution (Suprep)** is a low volume (3 L) product indicated for patients 12 years of age and older. Safety concerns include a higher risk of nausea, vomiting and abdominal distension compared to other products. Overall Suprep offers no compelling clinical advantages relative to the other bowel prep agents.

- **Sodium sulfate, potassium chloride, magnesium sulfate tablets (Sutab):** Although Sutab provides the convenience of a tablet, it requires consumption of 24 tablets and 3 L of extra volume. Overall Sutab offers no compelling clinical advantages relative to the other bowel prep agents.

- **Sodium phosphate tablets (Osmoprep)** requires 32 tabs and 2 L of extra volume and has existing low utilization in the MHS. Significant safety concerns include the boxed warning for acute phosphate nephropathy. Overall Osmoprep offers no compelling clinical advantages relative to the other bowel prep agents.

- **Sodium picosulfate, magnesium oxide, anhydrous citric acid power packets (Prepopik)** is an older formulation that was voluntarily discontinued from the market.

- In order to meet the needs of MHS beneficiaries, at least one product approved in young children, and at least one low volume product is required.

B. Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass — Relative Cost Effectiveness Analysis and Conclusion

Relative Cost-Effectiveness Analysis and Conclusion—CMA and BIA were performed. The P&T Committee concluded (17 for, 0 opposed, 1 abstained, 0 absent) the following:

- CMA results showed that the generic standard volume PEG formulations (Colyte, GoLYTELY, NULYTELY, TriLYTE) were the most cost effective bowel preparations, followed by the branded products (ranked from most cost effective to least cost effective) MoviPrep, Plenvu, Clenpiq, Suprep, Sutab and Osmoprep.

- BIA was performed to evaluate the potential impact of designating selected agents as formulary, NF, or Tier 4 on the UF. BIA results

showed that designating the generic PEG formulations, MoviPrep, Plenvu, and Clenpiq as UF, and designating Suprep, Sutab, Osmoprep and Prepopik as NF, demonstrated significant cost avoidance for the MHS.

C. Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass — UF/Tier 4/Not-Covered Recommendation

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) the following:

- UF
  - PEG 3350, sodium sulfate, sodium bicarbonate, sodium chloride and potassium chloride powder for oral solution (Colyte, GoLYTELY, Galvilyte-A, Galvilyte-C, GalviLyte-G, generics)
  - PEG 3350, sodium bicarbonate, sodium chloride and potassium chloride powder for oral solution (NuLYTELY, TriLyte, generics)
  - PEG 3350, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, and sodium ascorbate powder for oral solution (Moviprep)
  - PEG 3350, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, and sodium ascorbate powder for solution (Plenvu)
  - sodium picosulfate, magnesium oxide, and anhydrous citric acid oral solution (Clenpiq) *(moves from NF to UF)*
- NF
  - sodium sulfate, potassium sulfate, and magnesium sulfate concentrated oral solution (Suprep) *(moves from UF to NF)*
  - sodium sulfate, potassium chloride and magnesium sulfate tablets (Sutab)
  - sodium phosphate tablets (Osmoprep) *(moves from UF to NF)*
  - sodium picosulfate, magnesium oxide, and anhydrous citric acid power packets (Prepopik) *(moves from UF to NF)*
- Tier 4/Not Covered: None

D. Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass—UF and Implementation Plan

The P&T Committee recommended (17 for, 0 opposed, 1 abstained, 0 absent) 1) an effective date of the first Wednesday two weeks after signing of the minutes in all

points of service. Note that letters won't be sent to patients who have received Suprep, Sutab, Osmoprep or Prepopik, due to the acute use of these drugs, and since the majority of prescriptions are for one-time use.

V. UF DRUG CLASS REVIEWS- Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass

BAP Comments

A. Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass— UF/Tier 4/Not-Covered Recommendation

The P&T Committee recommended the formulary status for the Bowel Preparations as discussed above:

- UF
  - Colyte, GoLYTELY, Galvilyte-A, Galvilyte-C, GalviLyte-G, generics
  - NuLYTELY, TriLyte, generics
  - Moviprep
  - Plenvu
  - Clenpiq *(moves from NF to UF)*
- NF
  - Suprep *(moves from UF to NF)*
  - Sutab
  - Osmoprep *(moves from UF to NF)*
  - Prepopik *(moves from UF to NF)*
- Tier 4/Not Covered: None

BAP Comment: ☐ Concur ☐ Non-concur

B. Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass—UF and Implementation Plan

The P&T Committee recommended an effective date of the first Wednesday two weeks after signing of the minutes in all points of service.

BAP Comment:	☐ Concur	☐ Non-concur

VI. NEWLY APPROVED DRUGS PER 32 CFR 199.21(g)(5)

P&T Comments

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

The P&T Committee agreed for group 1: (16 for, 0 opposed, 1 abstained, 1 absent); group 2: (14 for, 1 opposed, 1 abstained, 2 absent), with the relative clinical and cost-effectiveness analyses presented for the newly approved drugs reviewed according to 32 CFR 199.21(g)(5).

B. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF/Tier 4/Not Covered Recommendation

The P&T Committee recommended (for group 1: 16 for, 0 opposed, 1 abstained, 1 absent; group 2: 14 for, 1 opposed, 1 abstained, 2 absent; and for Accrufer 12 for, 4 opposed, 1 abstained, 1 absent) the following:

- UF:
  - dasiglucagon injection (Zegalogue) – Binders-Chelators-Antidotes-Overdose Agents: Hypoglycemia Agents for severe hypoglycemia
  - infigratinib (Truseltiq) – Oncological agent for cholangiocarcinoma
  - omalizumab syringe (Xolair) – Respiratory Interleukin for asthma, nasal polyps, and chronic idiopathic urticaria (CIU)
  - pegcetacoplan injection (Empaveli) – Hematological agent for paroxysmal nocturnal hemoglobinuria (PNH)

- relugolix/estradiol/norethindrone (Myfembree) – Luteinizing Hormone-Releasing Hormone (LHRH) Agonists-Antagonists for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women
- riluzole oral film (Exservan) – Miscellaneous neurological agent for amyotrophic lateral sclerosis (ALS)
- semaglutide injection (Wegovy) – Weight loss agent and a GLP-1 receptor antagonist for the treatment of obesity
- sotorasib (Lumakras) – Oncological agent for non-small cell lung cancer (NSCLC)

- NF:
  - drosperinone/estetrol (Nextstellis) – Contraceptive Agents: Monophasics with 20 mcg estrogen
  - ferric maltol (Accrufer) – Electrolyte-Mineral-Trace Element Replacement for iron deficiency
  - viloxazine extended release (Qelbree) – Non-Stimulant for Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients ages 6 to 17 years of age

- Tier 4/Not Covered:
  - rosuvastatin/ezetimibe (Roszet) – Antilipidemic 1
    - Roszet was recommended as Tier 4 as it has little to no additional clinical effectiveness relative to the statins that are combined with ezetimibe, and the needs of TRICARE beneficiaries are met by available alternative agents. Formulary alternatives include taking rosuvastatin and ezetimibe separately, atorvastatin with ezetimibe, simvastatin/ezetimibe (Vytorin), and the PCSK-9 inhibitors.

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

The P&T Committee recommended (for group 1: 16 for, 0 opposed, 1 abstained, 1 absent; group 2 14 for, 0 opposed, 2 abstained, 2 absent, and for Accrufer (12 for, 4 opposed, 1 abstained, 1 absent) the following:

- Weight loss drugs: Applying manual PA criteria to new users of Wegovy, consistent with the requirements for Saxenda and the other weight loss drugs. A trial of all the other weight loss drugs except Saxenda will be required before Wegovy.
- Oncologic drugs: Applying manual PA criteria to new users of Lumakras and Truseltiq, consistent with PA requirements in general for oncology drugs.

- Respiratory Interleukins: Applying manual PA criteria to new users of the Xolair syringe, consistent with the requirements for the other respiratory biologics intended for patient self-administration.
- LHRH Agonists-Antagonists: Applying manual PA criteria to new users of Myfembree, similar to the requirements for Oriahnn.
- ALS Drugs: Applying manual PA criteria to new users of Exservan oral film, consistent with the requirements for riluzole oral suspension (Tiglutik).
- Applying manual PA criteria to new users of Accrufer, Empaveli, Nextstellis, and Qelbree.

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

1. **drospirenone/estetrol (Nextstellis)**

   Manual PA criteria apply to all new users of Nextstellis and is approved if all criteria are met:

   - Provider acknowledges that ethinyl estradiol/drospirenone (Yaz, Yasmin) and numerous other contraceptives are available for TRICARE patients and do not require a PA. Providers are encouraged to consider changing the prescription to Yaz, Yasmin, or another formulary contraceptive
   - Patient has tried an ethinyl estradiol containing oral contraceptive and has had significant adverse effects attributed to the ethinyl estradiol component
   - Provider acknowledges that Nextstellis may be less effective in females with a body mass index (BMI) ≥ 30 kg/m^2 per the FDA label

   Non-FDA-approved uses are not approved.

   Prior authorization does not expire.

2. **ferric maltol (Accrufer)**

   Manual PA criteria apply to all new users of Accrufer and is approved if all criteria are met:

   - Patient has a documented diagnosis of iron deficiency
   - Patient is 18 years of age or older

- Patient has tried and failed two oral iron products (must be different salts e.g., ferrous sulfate, ferrous gluconate, ferrous fumarate) for at least six weeks in duration for each product, unless contraindicated or clinically significant adverse effects are experienced.
    - The provider must provide the date of when the patient previously tried each medication, or the contraindication or clinically significant adverse effect that the patient experienced:
    - Oral iron product:_____Date:_____ Contraindication or clinically significant adverse effect: _____
    - Oral iron product:_____Date:_____ Contraindication or clinically significant adverse effect: _____
- Provider acknowledges there is insufficient data on drug interactions at this time.

Non-FDA-approved uses are not approved.

Prior authorization expires in 6 months.

Renewal criteria: Note that initial TRICARE PA approval is required for renewal. Coverage will be approved for an additional 6 months for continuation of therapy if:

- Patient is still iron deficient
- Documentation of clinically significant improvement in patient's iron deficiency required.

3. infigratinib (Truseltiq)

Manual PA criteria apply to all new users of Truseltiq and is approved if all criteria are met:

- Patient is 18 years of age or older
- Patient has previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.
- The patient will be monitored for retinal pigment epithelial detachment, hyperphosphatemia, and soft-tissue mineralization
- The drug is prescribed by or in consultation with a hematologist/oncologist

- Female patients of childbearing age are not pregnant confirmed by (-) HCG
- Female patients will not breastfeed during treatment and for at least 1 month after the cessation of treatment
- Both male and female patients of childbearing potential agree to use effective contraception during treatment and for at least 1 month after cessation of therapy
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.

Other non-FDA-approved uses are not approved.

Prior authorization does not expire.

4. pegcetacoplan injection (Empaveli)

Manual PA criteria apply to all new users of Empaveli and is approved if all criteria are met:

- Patient is 18 years of age or older
- Patient has a documented diagnosis of paroxysmal nocturnal hemoglobinuria (PNH)
- Patient has been counseled on the appropriate administration of the drug via infusion pump
- Patient has been vaccinated against certain encapsulated bacteria (e.g., *Streptococcus pneumoniae, Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B)

Non-FDA-approved uses are not approved.

Prior authorization does not expire.

5. riluzole oral film (Exservan)

Manual PA criteria apply to all new users of Exservan and is approved if all criteria are met:

- Patient is diagnosed with amyotrophic lateral sclerosis (ALS)
- Patient has dysphagia/swallowing dysfunction

Non-FDA-approved uses are not approved.

Prior authorization does not expire.

6. relugolix/estradiol/ norethindrone (Myfembree)

Manual PA criteria apply to all new users of Myfembree and is approved if all criteria are met. Note that the PA criteria are similar to Oriahnn, with differences bolded below.

- Patient is 18 years of age or older
- Patient is a premenopausal woman with diagnosed heavy menstrual bleeding associated with uterine leiomyomas (fibroids)
- Patient has had inadequate relief after at least three months of first-line therapy with a hormonal contraceptive or Intrauterine Device (IUD)
- Medication is prescribed by a reproductive endocrinologist or obstetrics/gynecology specialist
- Patient is not pregnant. Pregnancy test required.
- Patient agrees to use non-hormonal contraception throughout treatment and for one week after discontinuation of treatment
- Patient does not have current or a history of thrombotic or thromboembolic disorders or an increased risk for these events
- Patient is not a smoker over the age of 35
- Provider agrees to discontinue treatment if a thrombotic, cardiovascular, or cerebrovascular event occurs or if the patient has a sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions
- Patient does not have uncontrolled hypertension
- Provider agrees to monitor blood pressure and discontinue treatment if blood pressure rises significantly
- Patient does not have osteoporosis
- Provider agrees to advise the patient to seek medical attention for suicidal ideation, suicidal behavior, new onset or worsening depression, anxiety, or other mood changes
- Patient does not have a history of breast cancer or other hormonally-sensitive malignancies
- Patient does not have known liver impairment or disease
- Provider agrees to counsel patients on the signs and symptoms of liver injury
- Patient does not have undiagnosed abnormal uterine bleeding
- Patient is not using Oriahnn concomitantly with cyclosporine or gemfibrozil or other organic anion transporting polypeptide [(OATP)1B1] inhibitors

- **Patient is not using Myfembree with oral P-gp inhibitors (e.g., erythromycin) or combined P-gp and strong CYP3A inducers (e.g., rifampin)**

Non-FDA-approved uses are not approved including **contraception** or pain associated with endometriosis.

Prior authorization expires after 24 months (lifetime expiration). **Cumulative treatment with Oriahnn and Myfembree will not exceed 24 months during the patient's lifetime**

7. semaglutide injection (Wegovy)

Manual PA criteria apply to all new users of Wegovy and is approved if all criteria are met:

- Patient is 18 years of age or older
- Patient has a BMI ≥ to 30, or a BMI ≥ to 27 for those with risk factors in addition to obesity (diabetes, impaired glucose tolerance, dyslipidemia, hypertension, sleep apnea)
- Patient has engaged in behavioral modification and dietary restriction for at least 6 months and has failed to achieve the desired weight loss, and will remain engaged throughout course of therapy
- Patient has tried and failed or has a contraindication to all of the following agents (generic phentermine, Qsymia, Xenical, and Contrave). (Note: provider must include the date of use and duration of therapy or contraindication to the drug)
  - Phentermine: Date_____ Duration of therapy_____
  - Qsymia: Date_____ Duration of therapy_____
  - Xenical: Date _____ Duration of therapy_____
  - Contrave: Date _____ Duration of therapy_____
- If the patient is diabetic, they must have tried and failed metformin and the DoD's preferred GLP1RAs (Trulicity and Bydureon Bcise)
- If the patient is an Active Duty Service Member, the individual is enrolled in a Service-specific Health/Wellness Program AND will adhere to Service policy, AND will remain engaged throughout course of therapy
- Patient is not pregnant
- Concomitant use of Wegovy with other GLP1RA drugs is not allowed (e.g., Bydureon, Trulicity, Byetta, Adlyxin, Victoza, Soliqua, Xultophy)

- The patient does not have a history of or does not have a family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2

Non-FDA approved uses are NOT approved including for diabetes mellitus and for those less than 18 years of age.

Initial prior authorization expires after 4 months and then annually.

Renewal PA Criteria: Wegovy will be approved for an additional 12 months if the following are met:

- The patient is currently engaged in behavioral modification and remains on a reduced calorie diet
- Wegovy will be discontinued if a 4% decrease in baseline body weight is not achieved at 16 weeks
- The patient is not pregnant

Additionally, for Active Duty Service Members: The individual continues to be enrolled in a Service-specific Health/Wellness Program AND adheres to Service policy AND will remain engaged throughout course of therapy.

8. sotorasib (Lumakras)

Manual PA criteria apply to all new users of Lumakras and is approved if all criteria are met:

- Patient is 18 years of age or older
- Patient has laboratory evidence of KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test
- The patient will be monitored for interstitial lung disease and hepatotoxicity
- The drug is prescribed by or in consultation with a hematologist/oncologist
- Female patients will not breastfeed during treatment and for at least 1 week after the cessation of treatment
- The diagnosis IS NOT listed above but IS cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation. If so, please list the diagnosis: _____.

Other non-FDA-approved uses are not approved.

Prior authorization does not expire.

9. viloxazine (Qelbree)

Manual PA criteria apply to all new users of Qelbree and is approved if all criteria are met:

- Patient is 6 to 17 years of age
- Patient has a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD)
- Patient has tried and failed, had an inadequate response, OR contraindication to amphetamine salts XR (Adderall XR, generic) or other long acting amphetamine or derivative drug
- Patient has tried and failed, had an inadequate response, OR contraindication to methylphenidate OROS and other (Concerta, generic) or other long acting methylphenidate or derivative drug
- Patient has tried and failed, had an inadequate response, OR contraindication to at least one non-stimulant ADHD medication (generic formulations of Strattera, Kapvay, or Intuniv)

Non-FDA-approved uses are not approved (to include depression and anxiety).

Prior authorization does not expire.

10. omalizumab syringe (Xolair)

Manual PA criteria apply to all new users of Xolair syringe and is approved for initial therapy for 12 months if all criteria are met:

For all indications:

- Provider ensures that patient has no prior history of anaphylaxis, including to Xolair or other agents, such as foods, drugs, biologics, etc.
- Patient has received at least 3 doses of Xolair under the guidance of a healthcare provider without experiencing any hypersensitivity reactions
- Provider agrees to ensure that the patient or caregiver is able to recognize symptoms of anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Provider agrees to counsel the patient that anaphylaxis has occurred up to 2 hours post administration and appropriate monitoring will occur.

- Provider agrees to ensure that the patient or caregiver is able to treat anaphylaxis appropriately and consider co-prescribing epinephrine.
- Provider agrees to ensure that the patient or caregiver is able to perform subcutaneous injections with Xolair prefilled syringe with proper technique according to the prescribed dosing regimen
- For all indications the patient is not currently receiving another immunobiologic (e.g., benralizumab [Fasenra], mepolizumab [Nucala], or dupilumab [Dupixent])

For Asthma:

- The patient is 6 years of age or older
- The drug is prescribed by an allergist, immunologist, pulmonologist, or asthma specialist
- The patient has moderate to severe asthma with baseline IgE levels that are greater than 30 IU/ml
- The patient has tried and failed an adequate course (3 months) of two of the following while using a high-dose inhaled corticosteroid:
    - Long-acting beta agonist (LABA e.g., Serevent, Striverdi)
    - Long-acting muscarinic antagonist (LAMA e.g. Spiriva, Incruse), or
    - Leukotriene receptor antagonist (e.g., Singulair, Accolate, Zyflo)

For chronic rhinosinusitis with nasal polyposis:

- The patient is 18 years of age or older
- The drug is prescribed by allergist, immunologist, pulmonologist, or otolaryngologist
- The patient has chronic rhinosinusitis with nasal polyposis defined by all of the following:
    - Presence of nasal polyposis is confirmed by imaging or direct visualization AND
    - At least two of the following: mucopurulent discharge, nasal obstruction and congestion, decreased or absent sense of smell, or facial pressure and pain
- Xolair will only be used as add-on therapy to standard treatments, including nasal steroids and nasal saline irrigation
- The symptoms of chronic rhinosinusitis with nasal polyposis must continue to be inadequately controlled despite all of the following treatments

- Adequate duration of at least two different high-dose intranasal corticosteroids AND
- Nasal saline irrigation AND
- The patient has a past surgical history or endoscopic surgical intervention or has a contraindication to surgery

For chronic idiopathic urticaria (CIU):

- The patient is 12 years of age or older
- The drug is prescribed by an allergist, immunologist, or dermatologist
- Xolair is not indicated for any other form of urticaria
- Patient has symptoms lasting for greater than 6 weeks
- Patient remains symptomatic despite trial of at least 4 weeks with recommended urticarial dosing of a second generation H1 antihistamine (i.e., cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine)

Non-FDA-approved uses are not approved.

Prior authorization expires after 12 months. Renewal PA criteria will be approved indefinitely.

Renewal Criteria; (initial TRICARE PA approval is required for renewal) AND

- Asthma: The patient has had a positive response to therapy with a decrease in asthma exacerbations or improvements in forced expiratory volume in one second (FEV1)
- Chronic rhinosinusitis with nasal polyposis: There is evidence of effectiveness as documented by decrease in nasal polyps score or nasal congestion score
- Chronic Idiopathic Urticaria: The patient has had a positive response to therapy and improvement in clinical symptoms to warrant maintenance of therapy

D. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF, Tier 4/Not Covered, PA, and Implementation Plan

The P&T Committee recommended group 1 (16 for, 0 opposed, 1 abstained, 1 absent); group 2 (14 for, 0 opposed, 2 abstained, 2 absent) an effective date of the following:

- **New Drugs Recommended for UF or NF Status:** An effective date of the first Wednesday two weeks after signing of the minutes in all points of service.

- **New Drugs Recommended for Tier 4/Not Covered Status:** 1) An effective date of the first Wednesday120 days after signing of the minutes in all points of service, and 2) DHA send letters to beneficiaries who are affected by the Tier 4/Not Covered recommendation at 30 days and 60 days prior to implementation.

VII. NEWLY APPROVED DRUGS PER 32 CFR 199.21(g)(5)

BAP Comments

A. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF/Tier 4 Recommendation

The P&T Committee recommended the formulary status for the newly approved drugs as discussed above:

- **UF**
  - Zegalogue
  - Truseltiq
  - Xolair syringe
  - Empaveli
  - Myfembree
  - Exservan oral film
  - Wegovy injection
  - Lumakras

- NF:
  - Nextstellis
  - Accrufer
  - Qelbree

- Tier 4/Not Covered:

  Roszet

BAP Comment: ☐ Concur ☐ Non-concur

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

The P&T Committee recommended the PA criteria for the new drugs as stated previously.

BAP Comment: ☐ Concur ☐ Non-concur

C. Newly Approved Drugs per 32 CFR 199.21(g)(5)—UF, Tier 4/Not Covered and PA Implementation Plan

The P&T Committee recommended the following implementation plans as described above.

BAP Comment: ☐ Concur ☐ Non-concur

VIII. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA

P&T Comments

A. New Manual PA Criteria

1.) Miscellaneous Insulin Devices—Omnipod and Omnipod DASH

The Omnipod and Omnipod DASH cartridge pods are wearable, tubeless insulin management systems that are controlled using a personal diabetes manager (PDM).

These FDA-approved medical devices must be filled with insulin by the patient, and supply up to 3 days (72 hours) of insulin. Omnipod systems are meant for those who require multi-day injections of insulin (defined as at least three times daily). The smartphone-like PDM allows for remote management of basal and bolus insulin dosing.

The Omnipod and Omnipod DASH are covered under the TRICARE pharmacy benefit, but the starter kit is packaged with the actual device and is not a pharmacy benefit. Prior authorization was recommended to reflect current TRICARE Policy Manual coverage requirements for external infusion pumps (EIPs).

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) manual PA criteria for new and current users of Omnipod and Omnipod DASH cartridge pods to ensure appropriate use in the expected patient population, as well as to ensure continued monitoring of blood glucose levels and proper patient education on the device.

a) Omnipod and Omnipod DASH PA criteria: The manual PA criteria apply to all new and current users of Omnipod and Omnipod DASH, and these devices will be approved if all the following are met:

- The patient has diabetes mellitus and requires insulin therapy
- The patient is on an insulin regimen of 3 or more injections per day and has failed to achieve glycemic control after six months of Multiple Daily Injection (MDI) therapy
- The patient performs 4 or more blood glucose tests per day or is using a Continuous Glucose Monitoring (CGM) system
- The patient has completed a comprehensive diabetes education program
- The patient has demonstrated willingness and ability to play an active role in diabetes self-management

Initial prior authorization expires after 1 year.

Renewal criteria: Note that initial TRICARE PA approval is required for renewal.

- Omnipod or Omnipod DASH is approved for 1 year for continuation of therapy if all criteria are met:
- Patient has been successful with therapy
- Patient does not require changing the Omnipod DASH unit more frequently than every 72 hours (e.g., changing the unit every 48 hours is not allowed)

b) Omnipod and Omnipod DASH Manual PA Criteria—Implementation Plan

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) the new PA criteria will become effective the first Wednesday 90 days after the signing of the minutes. DHA will send letters to beneficiaries affected by the new PA requirements for these products, as new and current users will be subject to the PA.

2) Laxatives-Carthartics-Stool Softeners – Lactulose Packet (Kristalose, generics) PA criteria and implementation plan

Lactulose formulated in packets (Kristalose brand and generic) are not cost effective relative to other formulary lactulose products or other laxatives (i.e., glycerin, lactitol, polyethylene glycol 3350, sorbitol), which are all available in low-cost formulations.

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) manual PA criteria for lactulose packets (Kristalose, generics) in new users, due to the significant cost differences compared with numerous available alternative agents. The new PA will become effective the first Wednesday 60 days after the signing of the minutes.

Lactulose packets (Kristalose packets) Manual PA criteria apply to new users and is approved if all criteria are met:

- Provider acknowledges that lactulose solution and other laxatives (i.e., glycerin, lactitol, polyethylene glycol 3350, sorbitol) are available to DoD beneficiaries without the need of prior authorization
- The provider must explain why patient requires Kristalose packets as opposed to available alternatives.

Non-FDA approved uses are not approved.

Prior Authorization does not expire

3) Vitamins Prenatal – Prenatal Vitamins (Neonatal-DHA, Neonatal FE) PA criteria and implementation plan

Neonatal-DHA and Neonatal FE are prenatal dietary supplements manufactured by a single company and require a prescription prior to dispensing. The primary ingredients of Neonatal-DHA and Neonatal FE are similar to that found in other prenatal vitamins (Azesco, Zalvit, Trinaz) which require manual PA. Several prescription prenatal multivitamins are included in the TRICARE pharmacy benefit for women younger than the age of 45 and do not require prior authorization criteria.

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) manual PA criteria for Neonatal-DHA and Neonatal FE (regardless of the woman's age) in new users, due to the significant cost differences compared with numerous available alternative agents. The new PA will become effective the first Wednesday 90 days after the signing of the minutes.

Neonatal-DHA or Neonatal-FE Manual PA criteria apply to new users and is approved if all criteria are met:

- Provider acknowledges that Prenatal Vitamins Plus Low I, Prenatal Plus, Preplus, Prenatal, Prenatal Vitamins, Prenatal Multi plus DHA, Prenatal Vitamin plus Low Iron, and Prenatal Plus DHA are the preferred products and are covered without a prior authorization for women who are under the age of 45 years and planning to become pregnant or who are pregnant. The provider is encouraged to consider changing the prescription to one of these agents.
- The provider must explain why the patient requires Neonatal DHA or Neonatal FE and cannot take the available alternatives.

Non-FDA-approved uses are not approved.

PA does not expire.

IX. UTILIZATION MANAGEMENT—NEW MANUAL PA CRITERIA

BAP Comments

A. New Manual PA Criteria for Omnipod, Omnipod DASH, Kristalose packets, and Neonatal-DHA and Neonatal-FE prenatal vitamins:

The P&T Committee recommended manual PA criteria for Omnipod and Omnipod DASH in new and current users, for Kristalose packets in new users, and for Neonatal-DHA and Neonatal FE prenatal vitamins in new users, as outlined above.

BAP Comment: ☐ Concur ☐ Non-concur

B. New Manual PA Criteria Implementation Plan

The P&T Committee recommended the new PA criteria for Omnipod and Omnipod DASH become effective at 90 days and that DHA will send letters; the new PA for Kristalose packets become effective at 60 days, and the new PA for the prenatal vitamins become effective at 90 days.

BAP Comment: □ Concur □ Non-concur

X. UTILIZATION MANAGEMENT—UPDATED PA AND STEP THERAPY CRITERIA

P&T Comments

A. Updated PA and Step Therapy Criteria:

Updates to the manual PA criteria and step therapy were recommended for the following products, due to availability of cost-effective alternative treatments, results from clinical trial data, clinical practice guideline updates, or provider recommendation. The updated PAs and step therapy outlined below will apply to new users.

1.) Multiple Sclerosis Agents—ozanimod (Zeposia) PA criteria and implementation plan

Zeposia is a sphingosine-1 phosphate receptor modulator originally approved for treating relapsing forms of multiple sclerosis. It recently gained approval for ulcerative colitis (UC), another type of immune-mediated inflammatory disorder. At the time of review the trial supporting Zeposia for UC was not published. Other treatments, including non-biologics (e.g., azathioprine, sulfasalazine) and the targeted immunomodulatory biologic (TIBs) adalimumab (Humira) are well-established therapies for UC, and are more cost effective than Zeposia. The Zeposia PA was updated to allow for treatment of UC after a trial of non-biologic systemic therapy and trial of Humira.

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) updating the current PA criteria for Zeposia to require more clinically established and cost effective treatments first. Updates to the current PA criteria in new users for Zeposia will become effective the first Wednesday 30 days after the signing of the minutes.

Zeposia Manual PA criteria apply to all new users and will be approved if all criteria are met: (Note that the updates for UC are in bold)

- All recommended Zeposia monitoring has been completed and patient will be monitored throughout treatment as recommended in the label. Monitoring includes CBC, LFT, varicella zoster virus (VZV) antibody serology, ECG, and macular edema screening as indicated.
- **Patients of childbearing potential agree to use effective contraception during treatment and for 3 months after stopping therapy**
- Zeposia will not be used in patients with significant cardiac history, including:
  - Patients with a recent history (within the past 6 months) of class Ill/IV heart failure, myocardial infarction, unstable angina, stroke, transient ischemic attack, or decompensated heart failure requiring hospitalization
  - Those with a history or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless they have a functioning pacemaker

For relapsing Multiple Sclerosis

- Zeposia is prescribed by a neurologist
- Patient has a documented diagnosis of relapsing forms of MS
- There is no concurrent use of other MS disease-modifying therapy
- Patient has not failed a course of another S1p receptor modulator (e.g., Gilenya, Mayzent)

For Ulcerative Colitis

- **The patient has a diagnosis of moderate to severe active Ulcerative Colitis**
- **The patient is 18 years of age or older**
- **The provider acknowledges that Humira is the Department of Defense's preferred targeted immunomodulatory biologic agent for ulcerative colitis.**
- **The patient must have tried Humira AND:**
  - Had an inadequate response to Humira OR
  - Experienced an adverse reaction to Humira that is not expected to occur with Zeposia OR
  - Has a contraindication to Humira
- **The patient is not receiving oral immunomodulatory or biologic therapies concomitantly**

- **The patient has had an inadequate response to non-biologic systemic therapy. (For example - methotrexate, aminosalicylates [e.g., sulfasalazine, mesalamine], corticosteroids, immunosuppressant's [e.g. azathioprine], etc.)**

Non-FDA-approved uses are not approved.

Prior authorization does not expire

2.) Migraine Agents—rimegepant (Nurtec ODT), ubrogepant (Ubrelvy), lasmiditan (Reyvow) PA criteria and implementation plan

These three oral drugs were originally approved for acute treatment of migraine headache, and were reviewed at the May 2020 P&T Committee meeting. PA criteria currently apply. Rimegepant orally disintegrating tablets (Nurtec ODT) is now FDA-approved for preventive treatment of episodic migraine in adults. Other migraine preventive medications (e.g., antiepileptics, beta blockers, antidepressants, and the injectable calcitonin gene-related peptide [CGRP] antagonists) are available that have shown greater reductions in monthly migraine days than Nurtec ODT, based on indirect comparison, and are more cost-effective.

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) updating the current PA criteria for Nurtec ODT, Ubrelvy, and Reyvow to require a trial of other preventive medications (oral agents, and injectable CGRPs) first. PAs for Nurtec ODT, Ubrelvy, and Reyvow were also updated to include renewal criteria, to assess for efficacy. Updates to the current PA criteria in new users for Nurtec ODT, Ubrelvy, and Reyvow will become effective the first Wednesday 60 days after the signing of the minutes.

a.) rimegepant (Nurtec ODT) Manual PA criteria apply to all new users and will be approved if all criteria are met: (Note that updates from the August 2021 meeting are in bold.)

- The patient is 18 years of age or older
- The medication is prescribed by or in consultation with neurologist
- Concurrent use with any other small molecule CGRP targeted medication (i.e., another gepant [Ubrelvy]) is not allowed
- Not approved for patients who have clinically significant or unstable cardiovascular disease

<u>For Acute Treatment</u>

- Patient has a contraindication to, intolerability to, or has failed a trial of at least TWO of the following medications
  - sumatriptan (Imitrex), rizatriptan (Maxalt), zolmitriptan (Zomig), eletriptan (Relpax)

<u>For Prevention of Episodic Migraine</u>

- **The patient has episodic migraine as defined by one of the following:**
  - **Patient has episodic migraines at a rate of 4 to 7 migraine days per month for 3 months and has at least moderate disability shown by Migraine Disability Assessment (MIDAS) Test score > 11 or Headache Impact Test-6 (HIT-6) score > 50 OR**
  - **Patient has episodic migraine at a rate of 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, timolol**
  - **Prophylactic antidepressants: amitriptyline, duloxetine, nortriptyline, venlafaxine**
- **Patient has a contraindication to, intolerability to, or has failed a 2-month trial of at least ONE of the following CGRP injectable agents**
  - **erenumab-aooe (Aimovig)**
  - **fremanezumab-vfrm (Ajovy)**
  - **galcanezumab-gnlm (Emgality)**

Non-FDA-approved uses are NOT approved.

PA expires after 6 months

Renewal Criteria: Coverage will be approved indefinitely for continuation of therapy if one of the following apply (Note that initial TRICARE PA approval is required for renewal):

Acute Treatment

- **Patient has a documented positive clinical response to therapy**

Preventive Treatment

- **The patient has had a reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline (as shown by patient diary documentation or healthcare provider attestation) OR**

- **The patient has shown a clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:**
  - **Migraine Disability Assessment (MIDAS)**
    - **Reduction of ≥ 5 points when baseline score is 11–20**
    - **Reduction of ≥ 30% when baseline score is > 20**
  - **Headache Impact Test (HIT-6)**
    - **Reduction of ≥ 5 points**
  - **Migraine Physical Functional Impact Diary (MPFID)**
    - **Reduction of ≥ 5 points**

b.) ubrogepant (Ubrelvy) Manual PA criteria apply to all new users and will be approved if all criteria are met: (Note that updates from the August 2021 meeting for the renewal criteria are in bold.)

- The patient is 18 years of age or older
- The medication is prescribed by or in consultation with neurologist
- Concurrent use with any other small molecule CGRP targeted medication (i.e., another gepant [Nurtec ODT]) is not allowed
- Not approved for patients who have clinically significant or unstable cardiovascular disease
- Patient has a contraindication to, intolerability to, or has failed a trial of at least TWO of the following medications
  - sumatriptan (Imitrex), rizatriptan (Maxalt), zolmitriptan (Zomig), eletriptan (Relpax)
- Patient has had a contraindication to, intolerability to, or has failed a 2-month trial of Nurtec ODT

Non-FDA-approved uses are NOT approved.

PA expires after 6 months

Renewal Criteria: Coverage will be approved indefinitely for continuation of therapy if one of the following apply (Note that initial TRICARE PA approval is required for renewal):

Acute Treatment

- **Patient has a documented positive clinical response to therapy**

c.) lasmiditan (Reyvow) Manual PA criteria apply to all new users and will be approved if all criteria are met: (Note that updates from the August 2021 meeting for the renewal criteria are in bold.)

- The patient is 18 years of age or older
- The medication is prescribed by or in consultation with neurologist
- Reyvow is not approved for patients with a history of hemorrhagic stroke
- Reyvow is not approved for patients with a history of epilepsy or any other condition with increased risk of seizure
- Not approved for patients who have clinically significant or unstable cardiovascular disease
- Patient has a contraindication to, intolerability to, or has failed a trial of at least TWO of the following medications
  - sumatriptan (Imitrex), rizatriptan (Maxalt), zolmitriptan (Zomig), eletriptan (Relpax)
- Patient has had a contraindication to, intolerability to, or has failed a 2-month trial of Nurtec ODT
- If Reyvow is used with a triptan, the provider acknowledges Reyvow and the triptan should not be used within 24 hours of each other.
- Reyvow will be used with caution in patients with low heart rate and/or those using beta blockers, such as propranolol

Non-FDA-approved uses are NOT approved.

PA expires after 6 months

Renewal Criteria: Coverage will be approved indefinitely for continuation of therapy if one of the following apply (Note that initial TRICARE PA approval is required for renewal):

Acute Treatment

- **Patient has a documented positive clinical response to therapy**

XI. UTILIZATION MANAGEMENT—UPDATED PA AND STEP THERAPY CRITERIA

BAP Comments

A. Updated PA and Step Therapy Criteria:

The P&T Committee recommended the update PA criteria for Zeposia, Nurtec ODT, Ubrelvy, and Reyvow in new users, as outlined above.

BAP Comment: ☐ Concur ☐ Non-concur

B. Updated PA Criteria and Implementation Plan

The P&T Committee recommended the updated PA criteria for Zeposia become effective the first Wednesday 30 days after the signing of the minutes, and for the migraine drugs at 60 days after signing.

BAP Comment: ☐ Concur ☐ Non-concur

XII. UTILIZATION MANAGEMENT—UPDATED PA CRITERIA FOR NEW FDA-APPROVED INDICATIONS OR EXPANDED AGE RANGES

P&T Comments

A. Updated PA Criteria for Expanded Uses and implementation plan:

Updates to the PA criteria for several drugs were recommended due to new FDA-approved indications and expanded age ranges. The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) updates to the manual PA criteria for Ayvakit, Cosentyx, Myrbetriq, Toviaz, Epclusa and authorized generic, Mavyret, Evekeo ODT, and Ocaliva, due to new FDA-approved indications and expanded age ranges. The updated PA criteria summarized below will apply to new users.

Note that since these types of updates expand the patient population eligible for the drug, only a summary of the PA criteria is provided here; the current full PA criteria can be found on the TRICARE Formulary Search Tool at https://www.express-scripts.com/frontend/open-enrollment/tricare/fst/#/. The updated PA criteria will become effective the first Wednesday 60 days after the signing of the minutes.

1.) **Oncologic Agents Target –avapritinib (Ayvakit)**—Includes the new indication for adult patients with advanced systemic mastocytosis (comprises patients with aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, and mast cell leukemia)

2.) **Targeted Immunomodulatory Biologics —secukinumab (Cosentyx)**—Manual PA criteria now allow use in pediatric patients 6 years of age and older, as well as in adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

3.) **Overactive Bladder Agents**

- **mirabegron (Myrbetriq) tablets and granules**—The manual PA criteria were updated to allow for the new indication for treatment of neurogenic detrusor overactivity (NDO) in patients 3 years of age and older (for the granules) and weighing 35 kg or more (for the tablets) *(note that the granules were reviewed as an innovator at the November 2021 meeting)*

- **fesoterodine (Toviaz)**—Manual PA criteria were updated to allow for the new indication for treatment of neurogenic detrusor overactivity (NDO) in patients 6 years of age and older and weighing more than 25 kg.

4.) **Hepatitis C Agents: Direct Acting Agents— sofosbuvir/velpatasvir (Epclusa) and authorized generic; glecaprevir/pibrentasvir (Mavyret)**—The manual PA criteria now allow use in pediatric patients 3 years of age and older as well as adults for treatment of chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6.

5.) **ADHD Agents: Stimulants – amphetamine sulfate ODT (Evekeo ODT)**—The manual PA criteria now allow use in pediatric patients between the ages of 3 to 17 years for treatment of ADHD.

6.) **Gastrointestinal-2 Agents – obeticholic acid (Ocaliva)** —The manual PA criteria was revised and updated for safety information to narrow the indication for the patient population with primary biliary cholangitis (PBC), based on information from the manufacturer.

XIII. UTILIZATION MANAGEMENT—UPDATED PA CRITERIA FOR NEW FDA-APPROVED INDICATIONS OR EXPANDED AGE RANGES

BAP Comments

A. Updated PA Criteria for expanded uses:

The P&T Committee recommended the updates to the current PA criteria in new users for the following drugs: Ayvakit, Cosentyx, Myrbetriq, Toviaz, Epclusa and authorized generic, Mavyret, Evekeo ODT, and Ocaliva as outlined above.

BAP Comment: ☐ Concur ☐ Non-concur

B. Updated PA Criteria for Expanded Uses Implementation Plan

The updated PA criteria will become effective the first Wednesday 60 days after the signing of the minutes.

BAP Comment: ☐ Concur ☐ Non-concur

XIV. COPAYMENT CHANGE – TIER 1 for the PULMONARY 3 AGENTS: COMBINATIONS SUBCLASS—BREZTRI INHALER COPAYMENT CHANGE

P&T Comments

A. Tier 1 Copayment and Implementation Plan:

The fixed-dose triple combination inhalers containing an inhaled corticosteroid, long-acting muscarinic antagonist, and long-acting beta agonist (ICS/LAMA/LABA) were reviewed for formulary status at the February 2021 Committee meeting. Both budesonide/glycopyrrolate/formoterol (Breztri) and fluticasone/umeclidinium/vilanterol (Trelegy) were recommended to remain on the UF.

Following the meeting, more favorable pricing for Breztri became available, making it the most cost effective triple combination inhaler. As a result the Tier 1 copay was recommended for Breztri at this (August 2021) meeting. (Note that Committee recommendations from February 2021 had not yet been implemented at the time of the August 2021 P&T Committee meeting, due to the BAP zero-based review.)

Applying the Tier 1 copay at both Retail and Mail will also encourage use of the most cost-effective triple fixed-dose combination inhaler. Additionally, lowering the copay for this agent is consistent with 32 CFR 199.21(e)(3) from the Final Rule published June 3, 2020, in that the P&T Committee "will not only evaluate drugs for exclusion from coverage, but will also include identifying branded drugs that may be moved to Tier 1 status with a lower copayment for beneficiaries."

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) changing the copay for Breztri inhaler from Tier 2 (brand) to the Tier 1 (generic) copay at the purchased care points of service (Retail and Mail). Implementation will occur on signing of the minutes.

XV. TIER 1 COPAYMENT CHANGE for the PULMONARY 3 AGENTS: COMBINATIONS SUBCLASS— BUDESONIDE/GLYCOPYRROLATE/FORMOTEROL (BREZTRI INHALER) COPAYMENT CHANGE

BAP Comments

A. Breztri Inhaler Tier 1 Copayment and Implementation Plan

The Committee recommended the Tier 1 Copay change for Breztri inhaler, as outlined above, with implementation occurring upon signing of the minutes.

BAP Comment: □ Concur □ Non-concur

XVI. BRAND OVER GENERIC AUTHORIZATION and TIER 1 (GENERIC) COPAYMENT PULMONARY ARTERIAL HYPERTENSION (PAH) AGENTS: AMBRISENTAN (LETAIRIS)

P&T Comments

B. Ambrisentan (Letairis) brand over generic authorization and Tier 1 Copayment and Implementation Plan

The PAH drugs including the endothelin receptor antagonist subclass were most recently reviewed for formulary placement in May 2019. The Committee originally recommended brand over generic authorization and Tier 1 status for

branded ambrisentan (Letairis). However, multiple cost effective generic formulations were subsequently available prior to the implementation date of October 2019, so this requirement was removed at the August 2019 meeting.

At the August 2021 DoD P&T Committee meeting, the Committee reviewed overall trends in utilization and expenditures since implementation of the formulary recommendations in October 2019. The post-implementation review did reveal that supply of cost effective generic ambrisentan was unreliable. As a result, branded Letairis is currently more cost-effective than generic ambrisentan products. Due to these supply and cost issues, the Committee recommended implementing the brand over generic requirements for ambrisentan, requiring use of the branded Letairis formulation prior to a generic formulation, and applying the Tier 1(generic) copay to the branded Letairis product.

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 1 absent) requiring brand Letairis over generic ambrisentan in all new and current users, based on cost effectiveness. The prescriber will provide patient-specific justification as to why branded Letairis cannot be used. The Tier 1 (generic) copayment will apply to brand Letairis. The effective date will be upon signing of the minutes in all points of service. The "brand over generic" requirement will be removed administratively when it is no longer cost-effective compared to the AB-rated generics.

The authority for the Tier 1 copayment is codified in 32 CFR 199.21(j)(3): [W]hen a blanket purchase agreement, incentive price agreement, Government contract, or other circumstances results in a brand pharmaceutical agent being the most cost effective agent for purchase by the Government, the P&T Committee may also designate that the drug be cost-shared at the generic rate.

XVII. BRAND OVER GENERIC AUTHORIZATION and TIER 1 COPAYMENT PULMONARY ARTERIAL HYPERTENSION (PAH) AGENTS: — AMBRISENTAN (LETAIRIS)

BAP Comments

A. Brand over generic authorization for ambrisentan (Letairis) and Tier 1 Copayment and Implementation Plan

The P&T Committee recommended the Letairis brand over generic authorization, PA criteria, Tier 1 (generic) copay and implementation upon signing of the minutes, as outlined above.

BAP Comment: ☐ Concur ☐ Non-concur

XVIII. INFORMATION ITEM—SUMMARY OF RECOMMENDATIONS AND BENEFICIARY IMPACT (AUGUST 2021 DOD P&T COMMITTEE MEETING)

Table of implementation Status of UF Recommendations/Decisions Summary

DoD PEC Drug Class	UF Drugs	NF Drugs	Tier 4/Not Covered Drugs	Implement Date	Notes and Unique Users Affected
Leukemia and Lymphoma Agents: Bruton Tyrosine Kinase (BTK) Inhibitors	▪ acalabrutinib (Calquence) ▪ ibrutinib (Imbruvica) ▪ zanubrutinib (Brukinsa)	▪ None	▪ None	Pending signing of the minutes: 2 weeks	▪ Existing PAs in place for all 3 drugs ▪ Minor updates to the Ibrance tablets PA, requiring use of the capsules first ▪ UUs affected – not applicable; no NF drugs, no new PAs
Laxatives-Cathartics-Stool Softeners: Bowel Preparations	▪ PEG 3350, sodium sulfate, sodium bicarbonate, sodium chloride and potassium chloride powder for oral solution **(Colyte, GoLYTELY, Galvilyte-A, Galvilyte-C, GalviLyte-G, generics**) ▪ PEG 3350 sodium bicarbonate, sodium chloride and potassium chloride powder for oral solution **(NuLYTELY, TriLyte, generics)** ▪ PEG sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, and sodium ascorbate powder for oral solution **(Moviprep)** ▪ PEG sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, and sodium ascorbate powder for solution **(Plenvu)** ▪ sodium picosulfate, magnesium oxide, and anhydrous citric acid oral solution **(Clenpiq)**	▪ sodium sulfate, potassium sulfate, and magnesium sulfate concentrated oral solution **(Suprep)** ▪ sodium sulfate, potassium chloride and magnesium sulfate tablets **(Sutab)** ▪ sodium phosphate tablets **(Osmoprep)** ▪ sodium picosulfate, magnesium oxide, and anhydrous citric acid power packets **(Prepopik)**	▪ None	Pending signing of the minutes: 2 weeks	▪ No PAs for any of the drugs ▪ UUs affected – not applicable – drugs are used acutely once for bowel prep ▪ Current utilization for the drugs moving to NF: ▪ Suprep: 83,000 patients in calendar year 2020 ▪ Osmoprep: 600 patients ▪ Prepopik: 0 patients

Table of Newly Approved New Drugs Designated Tier 4—Unique Utilizers Affected

Drug	Total
rosuvastatin/ezetimibe (Roszet)	3

Drugs with New Prior Authorization Criteria—Unique Utilizers Affected

Drug	MTF	Mail Order	Retail	Total
Miscellaneous Insulin Devices: Omnipod	1	95	64	160
Miscellaneous Insulin Devices: Omnipod DASH	80	4	2,284	2,368

Armstead, Carolyn D CIV (USA)

From: Frank Lopez <drfrank1@mac.com>
Sent: Thursday, January 20, 2022 9:33 PM
To: DHA NCR J-6 Mailbox BAPREQUESTS
Subject: [Non-DoD Source] Viloxzine
Attachments: 2021 - Nasser, Lopez- Ped NNT.pdf; 2021 - Nasser , Lopez- Ped Functional Impairment.pdf

January 19th, 2022

Uniform Formulary BeneficiaryAdvisoryPanel
DFO
7700Arlington Blvd suite 5101
Falls Church, VA 22042-5101
Dha.ncr.j-6mbx.baprequests@mail.mil
Re: Viloxazine (Qelbree)

Esteemed Panel Members:
My name is Frank A. Lopez, M.D. and I am a Neuro-developmental Pediatrician in private practice in Winter Park, Florida. By way of transparency and disclosure I have been involved in clinical trials for over 20 years and have served on various panels as a consultant and investigator for ADHD medications and have over 30 papers and posters regarding the results of research in the field. More importantly neither I or any family members own stock in any of the companies where I have served as a clinical investigator or consultant.
It has been my distinct honor and pleasure to provide care for many military families over the 30 years of practice, during which I have treated hundreds of children adolescents and young adults with ADHD.
As you are all aware the FDA does not dole out the classification "a new chemical entity" lightly especially when it comes to ADHD medication. The latter is the case for Viloxazine(Qelbree).
Since its approval and launch I have provided it to dozens of affected children.
The experience has been multidimensional one from its MOA which offers a distinct advantage of a more rapid onset than the other non stimulants (based on our clinical observation), and second families, patients, as well as teachers have remarked on the positive changes the children have experienced.
As examples I can cite improved attention, decreased excessive non-purposeful activity, and decreased impulsivity (core symptoms of the disorder). There are also other physical benefits ie appetite is not as suppressed as we see with stimulants, duration of effect is much better than with the other nonstimulants (as I have been involved with their research and am published with them) and have used them all in our practice I believe my observations have merit.
Parents have reported changes as quickly as 1 week with sustained benefits with continued use.
One can argue that we can see this with stimulants and other nonstimulants, however, there can be significant side effects and risks with stimulants and yes, less with nonstimulants in contrast to the stimulants.
Measuring the response with standardized scales, we have seen significant decrease to levels that are typically seen with stimulants. The same cannot be said of the other nonstimulants in our experience with the same speed of onset for benefit.
Yet another very tangible point are parental fears regarding the use of medication for their child ie stimulant versus non stimulants. Hence when a medication as this is not easily available the
January 19th, 2022
Viloxazine (Qelbree)

difficulty in its acquisition leads to parents trying alternative medications that do not have the “data” as to real life benefits and risks, not to understate loss of time in gaining improved quality of life for their child.
Statistically and clinically, there is yet another benefit and that is the “number needed to treat vs number needed to harm” the former is a strong positive for this medication (I have taken the liberty to include a couple of recently published papers in which I participated as a coauthor regarding the benefits).
This medication based on its clinical benefits witnessed in our patients does not have a prolonged period of “non-treatment” ie waiting for weeks before seeing improvement as with the other nonstimulants, during which these patients are often unstable and sensitive to failure. The fact that this mechanism of action is unique and offers a shorter time to effectiveness offers improved quality of life for those children and adolescents who because of their diagnosis often lack the attentional and emotional control required to have success on a daily basis.
I ask that you consider adding this medication to your formulary without having a “step edit” as this only delays the care and positive changes that are essential to these youngsters.

Frank A Lopez, M.D.

Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

The Effect of Viloxazine Extended-Release Capsules on Functional Impairments Associated with Attention-Deficit/Hyperactivity Disorder (ADHD) in Children and Adolescents in Four Phase 3 Placebo-Controlled Trials

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Tesfaye Liranso[2]
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Purpose: The ADHD Rating Scale (ADHD-RS) assesses 18 symptoms of inattention and hyperactivity/impulsivity and has been used in many clinical trials to evaluate the treatment effect of drugs on ADHD. The fifth edition of this scale (ADHD-RS-5) also assesses the impact of inattention and hyperactivity/impulsivity symptoms on six domains of functional impairment (FI): family relationships, peer relationships, completing/returning homework, academic performance at school, controlling behavior at school, and self-esteem. Here, we report the effect of viloxazine extended-release capsules (viloxazine ER), a novel nonstimulant treatment for ADHD in children and adolescents (ages 6–17 years), on FI from a post hoc analysis of four randomized, double-blind, placebo-controlled Phase 3 clinical trials (N=1354).

Patients and Methods: ADHD-RS-5 investigator ratings of ADHD symptoms and FIs were conducted at baseline and weekly post-baseline for 6–8 weeks in the four trials. Change from baseline (CFB) in ADHD-RS-5 FI scores (Total score [sum of 12 FI items] and Inattention and Hyperactivity/Impulsivity subscale scores [sum of 6 corresponding FI items]) and the 30% and 50% Responder Rates (ADHD-RS-5 FI Total score) were compared between viloxazine ER and placebo.

Results: The reduction (improvement) in ADHD-RS-5 FI scores (Total and subscale scores) and the percentage of responders (30% and 50%) at Week 6 were significantly greater in each viloxazine ER dose group vs placebo. In the 100–400 mg/day viloxazine ER groups, improvements were found as early as Week 1 (100-mg/day) or Week 2 (200-, 400-mg/day) of treatment. Analysis of individual items of ADHD-related FIs demonstrated that the effect of viloxazine ER was observed across all domains of impairment.

Conclusion: Significant improvements observed in ADHD-related FIs are consistent with the reduction in inattention and hyperactivity/impulsivity symptoms demonstrated in the viloxazine ER Phase 3 pediatric trials. Therefore, viloxazine ER provides clinically meaningful improvement of ADHD symptoms and functioning in children and adolescents with ADHD, starting as early as Week 1–2 of treatment.

Keywords: impairment domains, academic performance, behavior, self-esteem

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood. It is characterized by inattention, hyperactivity,

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and impulsivity symptoms and is associated with emotional dysregulation reflected in academic, social, and family impairments.[1] Although multiple stimulant and nonstimulant treatment options have demonstrated efficacy in the treatment of ADHD, there is a significant proportion of individuals with ADHD who do not or only partially benefit from these medications and/or have contraindications, tolerability, or preference issues.[2,3]

Historically, the assessment of treatment response in individuals with ADHD has focused on measures of ADHD symptoms. However, functional impairments (FIs) across familial, social, emotional, and academic/occupational domains are frequently the reason for seeking treatment for ADHD.[4] Therefore, current diagnosis of ADHD is based not only on the inattentive and hyperactive/impulsive symptoms, but also the evidence that symptoms cause functional impairments.[5] The assessment and monitoring of the extent to which symptoms interfere with the quality of social, school, or work functioning of the individual is an important part of ADHD diagnosis and treatment.[6]

When evaluating treatment effects in individuals with ADHD, different degrees of improvement are found for symptomatic and functional outcomes. An 11-week open-label study of 200 children and adolescents with ADHD treated with extended-release methylphenidate demonstrated that only 57% of individuals showed functional improvement, even though 94% of individuals exhibited significant improvements in ADHD symptoms.[7] Similar results were obtained using a reliable change index (RCI classifies individuals into three categories based on the direction and the magnitude of change [improvers, no-changers, and deteriorators] regardless of return to the normal range of functioning) in a study of children with ADHD who were enrolled in a school-based mental health program (N=64). In this study, up to 40% of children achieved reliable symptom improvement without reliable change in functioning, and up to 16% achieved reliable improvement in functioning without reliable change in symptoms.[8] High numbers of individuals with incomplete ADHD symptom control and residual disabilities in cognitive functions have been reported in other population-based studies.[9,10] A prospective blind longitudinal study followed up 110 children with ADHD and 105 non-ADHD controls for 10 years. While only 35% of children with ADHD met the full diagnostic criteria for ADHD in their adult years, an additional 43% had functional impairments associated with ADHD, continued to struggle with subthreshold symptoms of ADHD, or had medication-associated remission of their ADHD symptoms.[11,12] These data highlighted the need for routinely including measures of functional outcomes in the assessment of treatment response.[7,13]

Many approaches have been used to assess impairments related to ADHD, including administering a single measure of global impairment (eg, Columbia Impairment Scale), multiple measures to assess a range of impairments such as academic performance and behavior problems, or a single measure to assess multiple domains of impairment (eg, Impairment Rating Scale or Weiss Functional Impairment Rating Scale [WFIRS]).[14–16] These approaches have been frequently criticized for not assessing impairments specifically related to ADHD symptoms as opposed to other conditions, which may occur concomitantly or mimic ADHD, leading to potential problems with scale specificity.[14,17]

The ADHD Rating Scale (ADHD-RS) has been validated and used to assess treatment benefits of drugs in many clinical trials. It is an 18-item rating scale reflecting the 18 symptoms of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM). There are nine items that assess Inattention symptoms and nine items that assess Hyperactivity/Impulsivity symptoms.[6] The earlier version of this scale (ie, ADHD-RS-IV), however, measured ADHD symptoms without assessing ADHD-related FIs. To address this unmet need in assessment of treatment response in ADHD, following the publication of DSM-5,[6] the ADHD-RS has been updated. The fifth edition, ADHD-RS-5, also assesses the extent to which current ADHD symptoms affect functioning of children and adolescents across six domains of impairment.[13] After completing the ratings of the nine items for each ADHD-RS-5 subscale, the clinician/investigator is asked to assess (using a 4-point Likert-scale) how much those nine items cause problems for the child/teenager in each of the six FI domains. Therefore, the ADHD-RS-5 addressed the limitations of previous measures by integrating the assessment of symptoms and impairments in the same measure, focusing on impairments specifically related to ADHD symptoms, and differentiating impairments related to each ADHD symptom dimension (Inattention and Hyperactivity/Impulsivity).[14]

Viloxazine extended-release capsules (viloxazine ER; Qelbree™) is a novel nonstimulant medication which has been approved by the US Food and Drug Administration (FDA) for the treatment of ADHD in children and

adolescents (ages 6–17 years). The objective of this post hoc analysis was to evaluate the effect of viloxazine ER on ADHD-RS-5 derived FI scores assessed in children and adolescents with ADHD during four Phase 3 clinical trials (the primary data from these clinical trials have been reported elsewhere).[18–21]

Methods

Phase 3 Trials Providing Data

The ADHD-RS-5 data collected during four Phase 3, randomized, placebo-controlled, double-blind, 3-arm clinical trials of viloxazine ER in children and adolescents (6–17 years of age) with ADHD were integrated in this analysis (Table 1).[18–21] ADHD-RS-5, Home Version: Child (6–11 years of age) or ADHD-RS-5, Home Version: Adolescent (12–17 years of age) was administered at each study visit.

In each study, the parent(s) or legal guardian(s) of each subject provided written informed consent to allow their child's participation prior to any study-related procedures. Assent was also obtained from the subject, if applicable, according to local requirements. The study protocols were approved by Advarra Institutional Review Board (IRB) and conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation Note for Guidance on Good Clinical Practice. All versions of the informed consent form were reviewed and approved by IRB.

Eligibility in these studies was determined using predefined inclusion/exclusion criteria.[18–21] Subjects with a diagnosis of ADHD based on DSM-5[6] criteria and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), ADHD-RS-5 Total score of ≥28, and Clinical Global Impression-Severity of Illness (CGI-S)[22] scale score of ≥4 were eligible to participate. Key exclusion criteria were as follows: major psychiatric disorder or neurological disorder (excluding oppositional defiant disorder, or major depressive disorder if the individual was free of major depressive episodes within the 6 months prior to screening), a history of allergic reaction to viloxazine or its excipients, any food allergy/intolerance that contraindicated trial participation, suicidal ideation, history of seizures, or significant systemic disease. Subjects had to weigh ≥20 kg (children) or ≥35 kg (adolescents) and have a body mass index ≤95th percentile for the appropriate age and gender.

After a screening period (≤28 days), eligible subjects were randomized (1:1:1 ratio) to receive one of the two viloxazine ER doses or placebo (the treatment groups, treatment duration, and titration periods are summarized in Table 1).[18–21] Subjects were instructed to take the study medication once daily by mouth in the morning, with or without food, throughout the treatment period. The viloxazine ER and placebo capsules were identical in appearance. If necessary, the subject's parent(s) or legal guardian(s) could open the capsules and sprinkle the contents over a spoon of soft food (eg, apple sauce). Subjects were required to refrain from taking medications prohibited by the study protocol, including FDA-approved ADHD medications, starting at least 1 week prior to randomization until the end of study. Baseline ADHD-RS-5 and safety assessments were conducted on the day, but prior to, randomization and the administration of the first

Table 1 Overview of Phase 3 Randomized Controlled Trials Providing Data

Age Group	Children (6–11 Years of Age)		Adolescents (12–17 Years of Age)	
Study	812P301	812P303	812P302	812P304
CT.gov identifier	NCT03247530	NCT03247543	NCT03247517	NCT03247556
Viloxazine ER doses	100 mg/200 mg	200 mg/400 mg	200 mg/400 mg	400 mg/600 mg
Weeks, T + M	6 (1+5)	8 (3+5)	6 (1+5)	7 (2+5)
Randomized (N)	477	313	310	297
Safety population (N)	474	310	308	296
ITT population (N)	460	301	301	292
Viloxazine ER/Placebo[a]	305/155	204/97	197/104	196/96

Note: [a]N based on ITT population.
Abbreviations: ITT, intent-to-treat; M, maintenance; T, titration; viloxazine ER, viloxazine extended-release capsules.

dose of study medication. They were then repeated weekly during post-baseline study visits until the end of study or early termination.[18–21] The ADHD-RS-5 was administered by a trained clinician/investigator.

ADHD-RS-5 FI Analysis

After completing the ratings of the nine items for each ADHD-RS-5 subscale, the clinician/investigator rated the child/teenager on a 4-point Likert-scale (0–3; where 0=No Problem; 1=Minor Problem; 2=Moderate Problem; 3=Severe Problem) on "How much do the nine behaviors in the previous question cause problems for the child/teenager?" in the following six FI domains:

1. Getting along with family members
2. Getting along with other children/teenagers
3. Completing or returning homework
4. Performing academically in school
5. Controlling behavior at school
6. Feeling good about himself/herself

The change from baseline (CFB) in the ADHD-RS-5 FI scores by study visit (Total and for the Inattention and Hyperactivity/Impulsivity subscales) and the 30% and 50% Responder Rates were evaluated. The ADHD-RS-5 Inattention FI score was the sum of six impairment items assessed for the Inattention subscale. The ADHD-RS-5 Hyperactivity/Impulsivity FI score was the sum of six impairment items for the Hyperactivity/Impulsivity subscale. The ADHD-RS-5 Total FI score was the sum of all 12 impairment items. The 30% and 50% Responder Rates represent proportions of subjects who achieved 30% or 50% improvement in the ADHD-RS-5 Total FI score. The 30% response threshold was selected as it is among the most commonly cited thresholds in ADHD studies,[23–25] while the 50% response threshold was selected as it has been shown to be statistically linked with the Clinical Global Impression-Improvement (CGI-I) score of 2 (much improved),[26,27] commonly used as the minimum threshold for clinically meaningful change.[28,29] The data were analyzed using mixed model for repeated measures (MMRM), which included fixed effect terms for baseline, age group, treatment (dose 100-mg /day, 200-mg/day, 400-mg/day, and 600-mg/day), visit, and treatment-by-visit interaction as independent variables. The least square (LS) means ± standard error (SE) compared to placebo and *p* values were determined for all measures. Data from four trials over 6 weeks of treatment with viloxazine ER were analyzed and presented by dose (100-mg/day, 200-mg/day, 400-mg/day, and 600-mg/day). The 30% and 50% Responder Rates were analyzed using the Pearson's Chi-square test. Numbers needed to treat (NNT) were calculated based on 30% and 50% Responder Rates. Statistical analyses were performed using SAS® system software, version 9.2 or higher.

Results

A total of 1354 subjects with ADHD (intent-to-treat population) were included in the four Phase 3 trials of viloxazine ER (subjects treated with placebo: 452; subjects treated with 100-mg/day viloxazine ER: 147; subjects treated with 200-mg/day viloxazine ER: 359; subjects treated with 400-mg/day viloxazine ER: 299; and subjects treated with 600-mg/day viloxazine ER: 97). Of these subjects, 761 were children 6–11 years of age and 593 were adolescents 12–17 years of age; a majority were male (n=873) and either White (n=759) or African American (n=529). Seven subjects (five from the placebo group and two from the 200-mg/day viloxazine ER group) were excluded from the current analysis because they had no impairment item data at baseline.

CFB ADHD-RS-5 FI Score

Statistically significant improvement vs placebo was observed in the CFB ADHD-RS-5 Total FI scores: with 100-mg/day viloxazine ER, starting at Week 1 of treatment (p=0.0041) through Week 6 (p=0.0026); with 200- or 400-mg/day viloxazine ER starting at Week 2 of treatment (p=0.0018 and p=0.0003, respectively) through Week 6 (p<0.0001 and p<0.0001, respectively); and with 600-mg/day viloxazine ER, at Week 6 (p=0.0208) (Figure 1).

Statistically significant improvement vs placebo was observed in the CFB ADHD-RS-5 Inattention FI scores: with 100-mg/day viloxazine ER, starting at Week 1 of treatment (p=0.0040) through Week 6 (p=0.0085); with 200- or 400-mg/day viloxazine ER, starting at Week 2 of treatment (p=0.0088 and p=0.0020, respectively) through Week 6 (p<0.0001 and p<0.0001), and with 600-mg/day viloxazine ER, at Week 6 (p=0.0183) (Figure 2).

Statistically significant improvement vs placebo was observed in the CFB ADHD-RS-5 Hyperactivity/Impulsivity FI scores: with 100-mg/day viloxazine ER, starting at Week 1 of treatment (p=0.0187) through

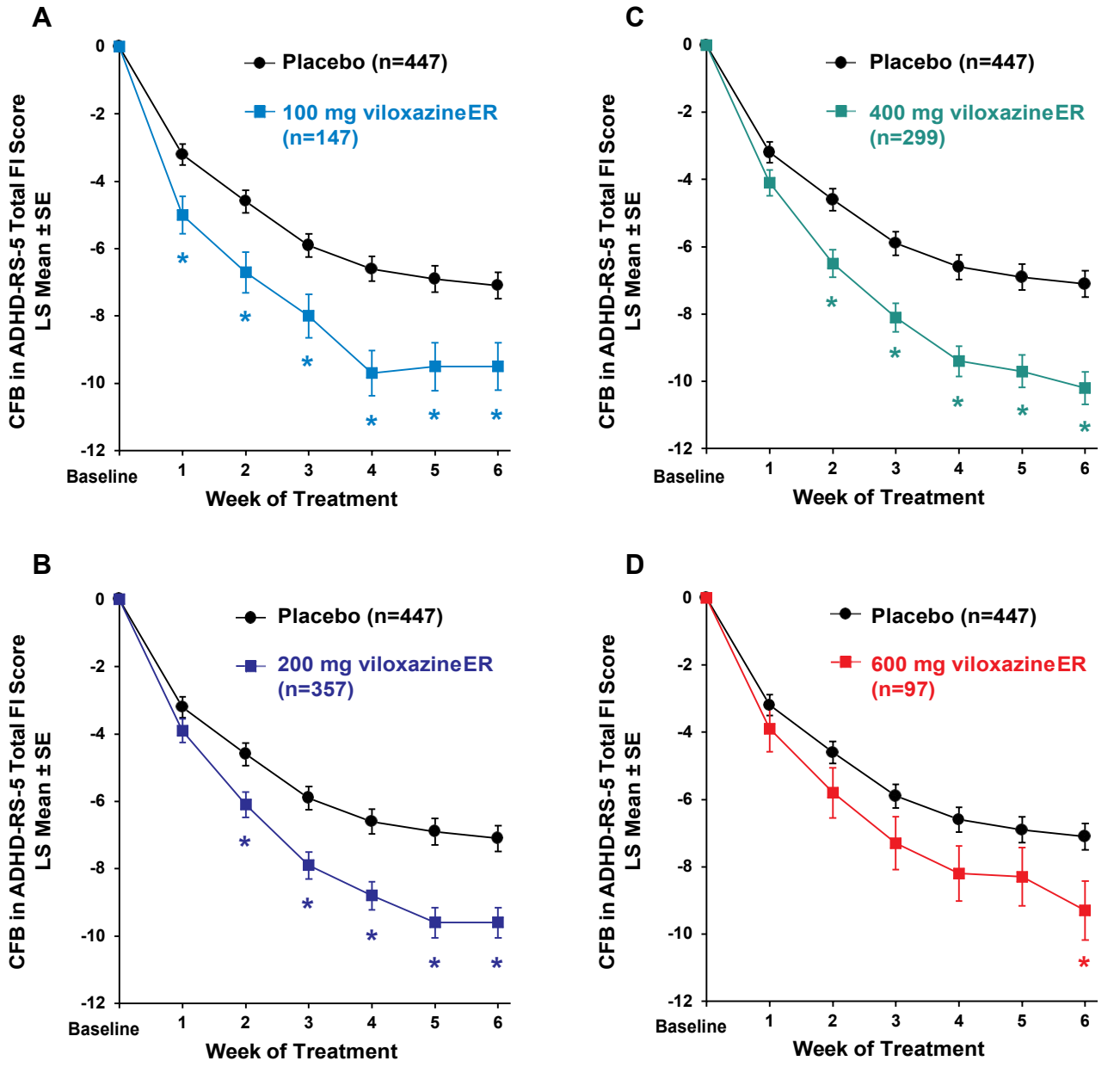

Figure 1 CFB in the ADHD-RS-5 Total FI Score by Week. (**A**) 100 mg viloxazine ER vs placebo; (**B**) 200 mg viloxazine ER vs placebo; (**C**) 400 mg viloxazine ER vs placebo; (**D**) 600 mg viloxazine ER vs placebo.

Notes: *$P<0.05$, placebo vs viloxazine ER. *P* values were obtained from MMRM modeling change from baseline in ADHD-RS-5 Total FI Score as function of fixed effect terms for baseline ADHD-RS-5 Total FI Score, age group, treatment, visit, and treatment-by-visit interaction, as fixed independent variables.

Abbreviations: ADHD-RS-5, ADHD rating scale fifth edition; CFB, change from baseline; FI, functional impairments; SE, standard error; viloxazine ER, viloxazine extended-release capsules.

Week 6 (p=0.0020); with 200- or 400-mg/day viloxazine ER, starting at Week 2 of treatment (p=0.0012 and p=0.0001, respectively), through Week 6 (p<0.0001 and p<0.0001); and with 600-mg/day viloxazine ER, at Week 4 (p=0.0428) and Week 6 (p=0.0208) (Figure 3).

CFB ADHD-RS-5 scores for each Inattention and Hyperactivity/Impulsivity FI item by week of treatment and by dose are shown in Figure 4. These descriptive statistics curves demonstrate that, overall, the effect of viloxazine ER was observed across all FI items for both the Inattention and Hyperactivity/Impulsivity subscales.

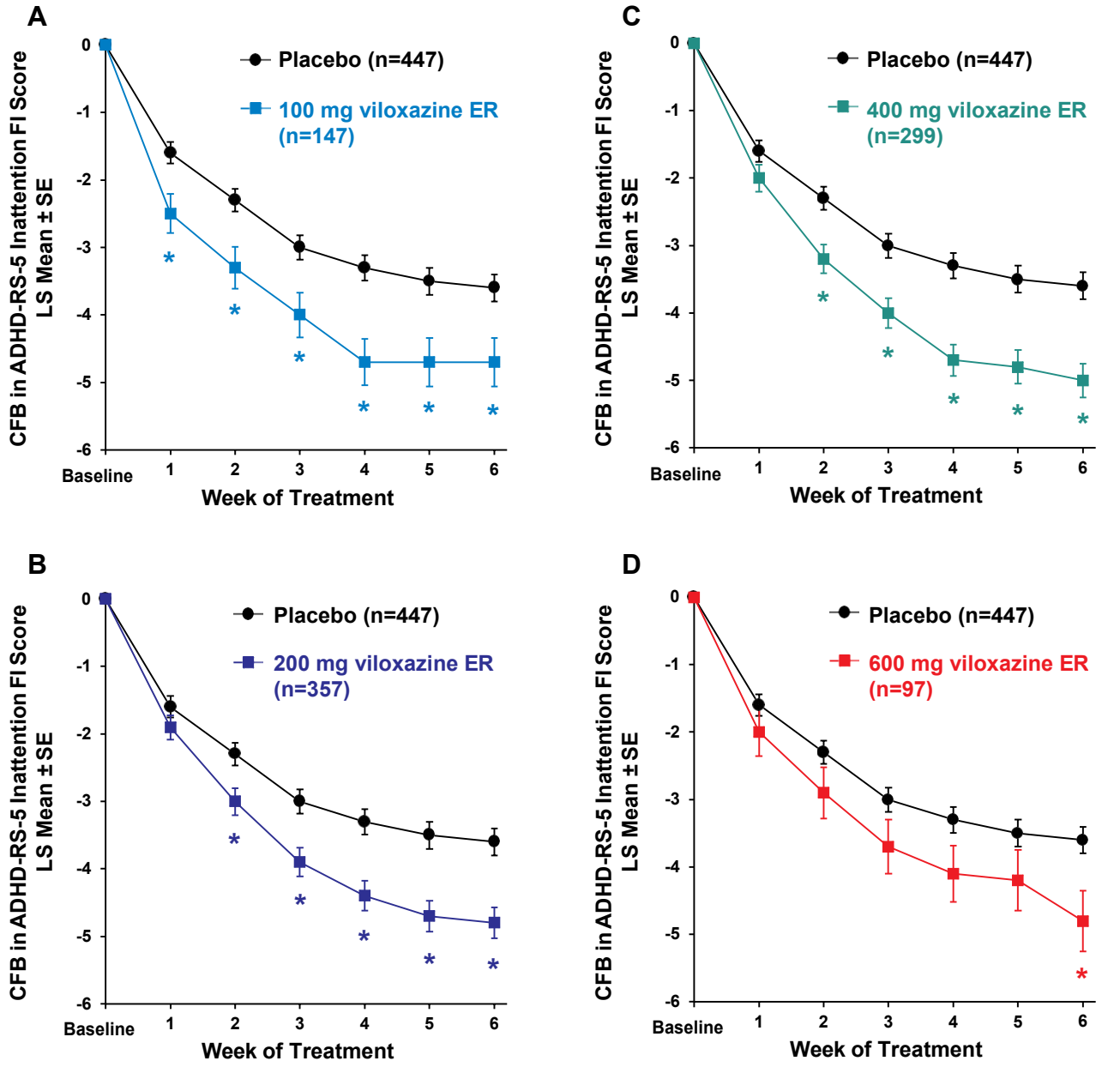

Figure 2 CFB in the ADHD-RS-5 Inattention FI Score by Week. (**A**) 100 mg viloxazine ER vs placebo; (**B**) 200 mg viloxazine ER vs placebo; (**C**) 400 mg viloxazine ER vs placebo; (**D**) 600 mg viloxazine ER vs placebo.

Notes: *$P<0.05$, placebo vs viloxazine ER. *P* values were obtained from MMRM modeling change from baseline in ADHD-RS-5 Inattention FI Score as function of fixed effect terms for baseline ADHD-RS-5 Inattention FI Score, age group, treatment, visit, and treatment-by-visit interaction, as fixed independent variables.

Abbreviations: ADHD-RS-5, ADHD rating scale fifth edition; CFB, change from baseline; FI, functional impairments; SE, standard error; viloxazine ER, viloxazine extended-release capsules.

30% and 50% Responders for ADHD-RS-5 Total FI Score

A significantly higher percentage of viloxazine ER treated subjects achieved a ≥30% reduction (improvement) in the CFB ADHD-RS-5 Total FI score (30% Responders) compared to placebo-treated subjects at Week 1, 4, 5, and 6 with 100-mg/day viloxazine ER; Weeks 2 through 6 with 200- or 400-mg/day viloxazine ER; and at Week 3, 4, and 6 with 600-mg/day viloxazine ER (Table 2).

The 30% Responder Rate at Week 6 was as follows: 53.4 % for placebo; 64.0% for 100-mg/day viloxazine ER (p=0.0293); 65.1% for 200-mg/day viloxazine ER (p=0.0015); 74.3% for 400-mg/day viloxazine ER (p<0.0001); and 70.4% for 600-mg/day viloxazine ER (p=0.0049) (Table 2). The NNTs for 100-, 200-, 400-,

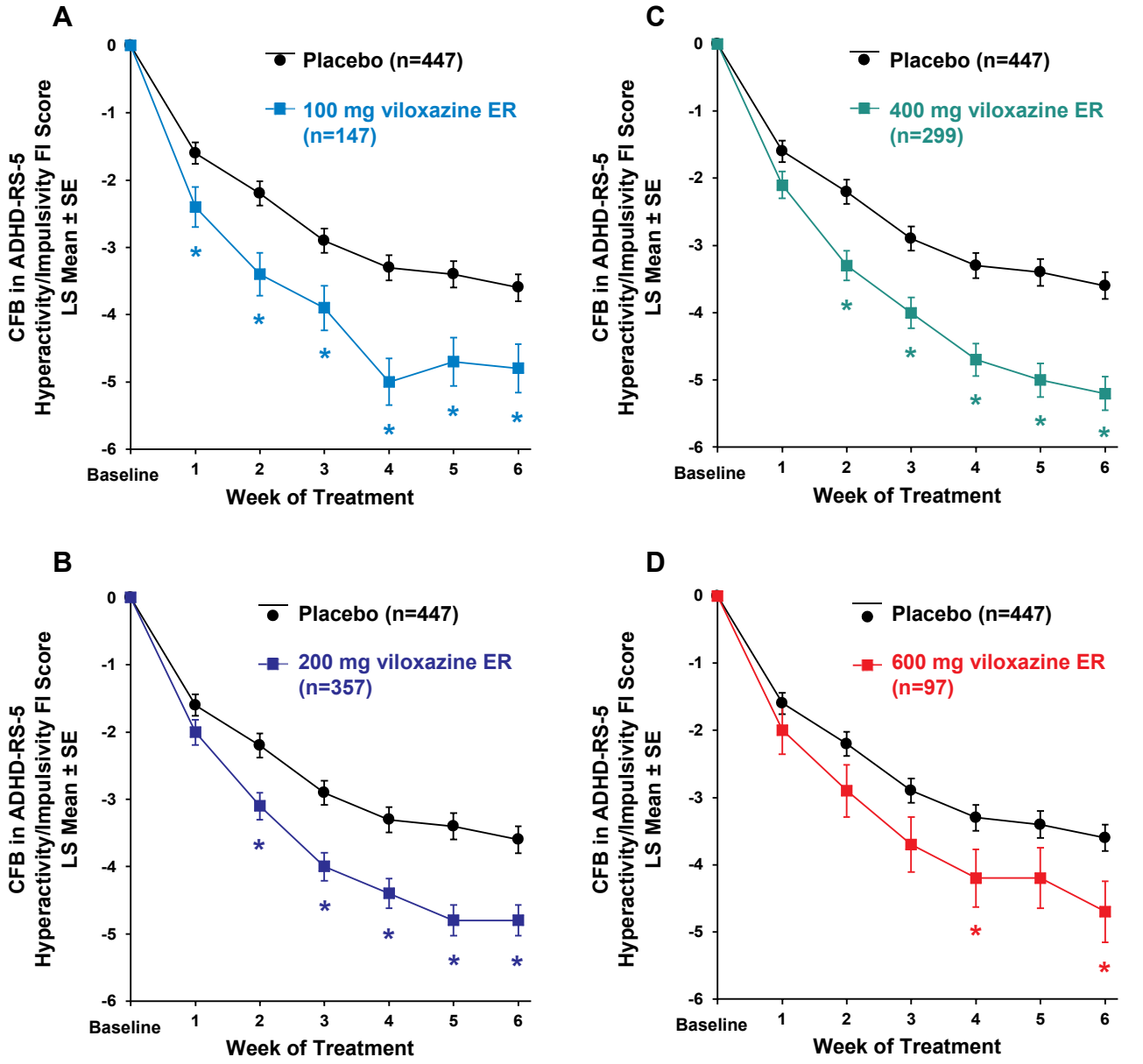

Figure 3 CFB in the ADHD-RS-5 Hyperactivity/Impulsivity FI Score by Week. (**A**) 100 mg viloxazine ER vs placebo; (**B**) 200 mg viloxazine ER vs placebo; (**C**) 400 mg viloxazine ER vs placebo; (**D**) 600 mg viloxazine ER vs placebo.

Notes: *P<0.05, placebo vs viloxazine ER. P values were obtained from MMRM modeling change from baseline in ADHD-RS-5 Hyperactivity/Impulsivity FI Score as function of fixed effect terms for baseline ADHD-RS-5 Hyperactivity/Impulsivity FI Score, age group, treatment, visit, and treatment-by-visit interaction, as fixed independent variables.

Abbreviations: ADHD-RS-5, ADHD rating scale fifth edition; CFB, change from baseline; FI, functional impairments; SE, standard error; viloxazine ER, viloxazine extended-release capsules.

and 600-mg/day, based on 30% Responder Rates at Week 6, were 9.4, 8.6, 4.8, and 5.9, respectively.

A significantly higher percentage of viloxazine ER treated subjects achieved a ≥50% reduction (improvement) in the CFB ADHD-RS-5 Total FI score (50% Responders) compared to placebo-treated subjects at Week 1, 3, 4, 5, and 6 with 100-mg/day viloxazine ER; Weeks 2 through 6 with either 200- or 400-mg/day viloxazine ER; and Week 2, 3, 4, and 6 with 600-mg/day viloxazine ER (Table 3).

The 50% Responder Rate at Week 6 was as follows: 37.8% for placebo; 53.2% for 100-mg/day viloxazine ER (p=0.0014); 50.3% for 200-mg/day viloxazine ER (p=0.0007); 56.2% for 400-mg/day viloxazine ER (p<0.0001); and 53.1% for 600-mg/day viloxazine ER

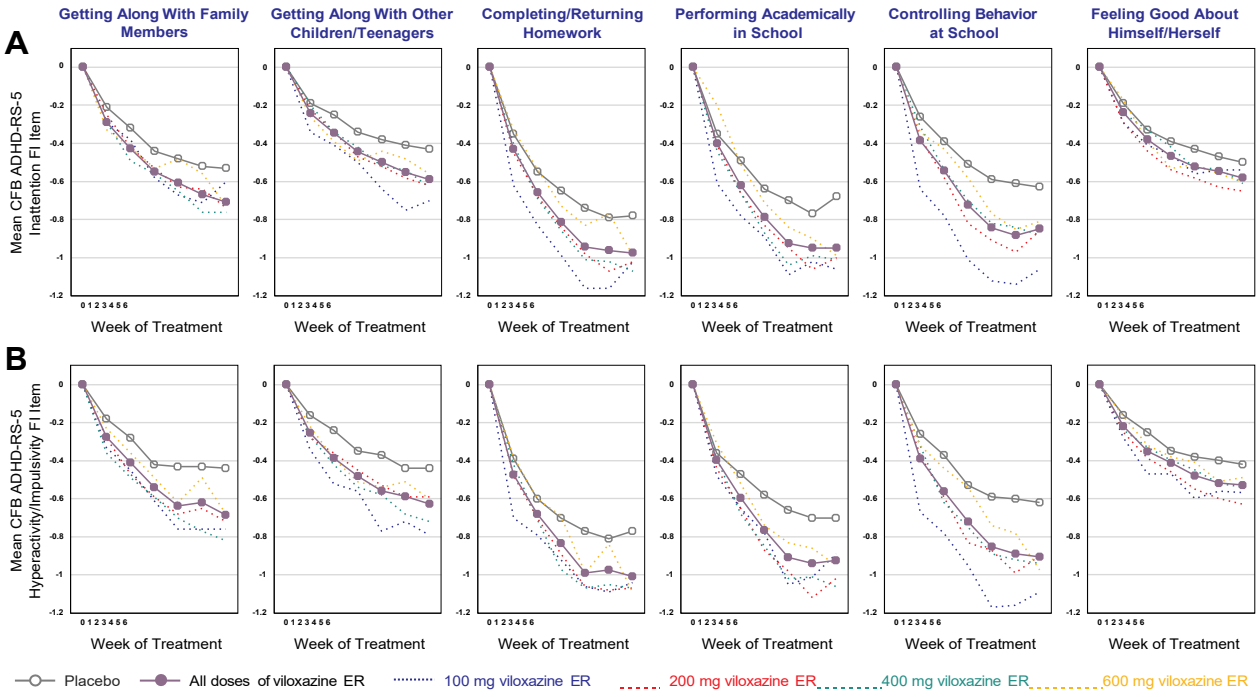

Figure 4 Mean CFB in the ADHD-RS-5 Inattention (**A**) and Hyperactivity/Impulsivity (**B**) FI Score by Item by Week (Descriptive Statistics).
Abbreviations: ADHD-RS-5, ADHD rating scale fifth edition; CFB, change from baseline; FI, functional impairments; viloxazine ER, viloxazine extended-release capsules.

(p=0.0104) (Table 3). The NNTs for 100-, 200-, 400-, and 600-mg/day, based on 50% Responder Rates at Week 6, were 6.5, 8, 5.4, and 6.5, respectively.

Discussion

To the best of our knowledge, this is the first study to evaluate a change in the ADHD-RS-5 impairment scores following a treatment with an approved or investigational medication for ADHD using a large sample of children and adolescents. The larger sample size was achieved by pooling data from multiple studies, which increased the statistical power of the analysis and allowed for integrated evaluation of each dose group across the studies. This analysis has demonstrated significant improvements in the CFB ADHD-RS-5 Total, Inattention, and Hyperactivity/Impulsivity FI scores compared to placebo. The analysis of CFB ADHD-RS-5 scores (Figures 1–3) by week found that with 100- to 400-mg/day viloxazine ER, the separation from placebo started at Week 1–2 of treatment. With 600-mg/day viloxazine ER, the statistically significant improvements vs placebo for Total and Inattention FI scores were only observed at Week 6 and for Hyperactivity/Impulsivity FI scores at Week 4 and Week 6. The responder analysis demonstrated that at Week 6, 50% to 56% of subjects treated with 100- to 600-mg/day viloxazine ER had 50% improvement in FI (Table 3), while 64% to 74% of subjects displayed a 30% improvement in FI at the same time point (Table 2). The NNTs for most of the dose groups at Week 6 were around 5 and 6 (ranging from 4.8 to 9.4), which is consistent with the effect sizes evaluated based on the primary data reported for viloxazine ER.[30]

These results are consistent with the primary data of viloxazine ER, which have demonstrated statistically significant improvements in ADHD symptoms vs placebo for 100-, 200-, and 400-mg/day viloxazine ER (as measured with ADHD-RS-5 and CGI-I scales) across three of four pivotal trials.[18–20] In the fourth clinical trial, the primary efficacy endpoint was not achieved; one of the active arms (400-mg/day) separated from placebo but the other active arm (600-mg/day) did not. Thus, the trial was considered negative due to step-down statistical analysis.[21] The placebo response in the fourth study was higher than in the three other studies and may have contributed to the 600-mg/day dose failure.[21]

Interestingly, a statistically significant increase in the 50% Responder Rate for ADHD-RS-5 Total FI score was demonstrated between all doses of viloxazine ER (including 600-mg/day) compared to placebo at nearly every

Table 2 30% Responder Rate Based on ADHD-RS-5-Derived Total Functional Impairment Score by Week

Week	Statistic	Placebo	Viloxazine ER 100 mg	Viloxazine ER 200 mg	Viloxazine ER 400 mg	Viloxazine ER 600 mg
1	% (n/N)	27.7 (123/444)	42.0 (60/143)	31.3 (109/348)	33.2 (98/295)	31.9 (30/94)
	P value		0.0014	0.2667	0.1086	0.4109
2	% (n/N)	38.9 (165/424)	44.9 (62/138)	48.2 (164/340)	51.1 (145/284)	45.6 (41/90)
	P value		0.2112	0.0097	0.0014	0.2430
3	% (n/N)	47.4 (195/411)	57.3 (75/131)	60.9 (204/335)	61.5 (168/273)	60.0 (51/85)
	P value		0.0506	0.0002	0.0003	0.0351
4	% (n/N)	49.8 (203/408)	69.8 (90/129)	63.4 (203/320)	66.2 (178/269)	65.9 (54/82)
	P value		<0.0001	0.0002	<0.0001	0.0077
5	% (n/N)	52.4 (210/401)	65.4 (83/127)	68.8 (216/314)	68.3 (179/262)	61.7 (50/81)
	P value		0.0103	<0.0001	<0.0001	0.1232
6	% (n/N)	53.4 (219/410)	64.0 (89/139)	65.1 (207/318)	74.3 (197/265)	70.4 (57/81)
	P value		0.0293	0.0015	<0.0001	0.0049

Notes: n/N represents a proportion of subjects who achieved 30% improvement in the ADHD-RS-5-derived Total Functional Impairment Score; shaded boxes indicate $p<0.05$; *p* value is from Pearson's Chi-square test.
Abbreviation: Viloxazine ER, viloxazine extended-release capsules.

weekly post-baseline assessment from Week 1 (100-mg /day) or 2 (200-, 400-, and 600-mg/day) through Week 6 (shaded cells in Table 3). The 30% Responder Rate results showed a similar pattern, except an increase with 600-mg /day viloxazine ER was not observed until Week 3 (shaded cells in Table 2). In the primary analysis of the Phase 3 trials, the 50% Responder Rate for the ADHD-RS-5 symptoms was also increased for all doses of viloxazine ER, but the difference vs placebo for 600-mg/day of viloxazine ER was not statistically significant.

In the clinical trials of viloxazine ER, changes in subjects' functioning were also evaluated by parents using WFIRS–Parent (WFIRS–P). Similar to the ADHD-RS-5 FI items, which assess to what degree ADHD symptoms affect an individual's ability to accomplish daily tasks and interactions, the WFIRS–P assesses to what degree an individual's behavior and emotional problems affect their ability to accomplish daily tasks and interactions (without taking into account the ADHD symptoms).[15,31] The 50 items included in this scale are grouped into six domains (family, school, life skills, self-concept, social activities, and risky activities) that are scored using a 4-point Likert scale.

While none of the viloxazine ER Phase 3 trials were powered to detect changes vs placebo in CFB at end of study using the WFIRS–P, the Phase 3 trial with the highest sample size (Table 1) that evaluated 100- and 200-mg/day viloxazine ER vs placebo was able to detect a statistically significant improvement in the WFIRS–P Total average score.[18] Statistically significant improvements were also observed in several individual WFIRS–P domains in the three studies (evaluating 100- and 200-mg/day viloxazine ER vs placebo in children and 200- and 400-mg/day viloxazine ER vs placebo in children and adolescents), including the domains of family, school, social activities, and risky activities.[18–20] Therefore, WFIRS–P data support findings presented in the current study. Multi-informant assessment in ADHD has been

Table 3 50% Responder Rate Based on ADHD-RS-5-Derived Total Functional Impairment Score by Week

Week	Statistic	Placebo	Viloxazine ER 100 mg	Viloxazine ER 200 mg	Viloxazine ER 400 mg	Viloxazine ER 600 mg
1	% (n/N)	14.9 (66/444)	27.3 (39/143)	19.3 (67/348)	17.3 (51/295)	20.2 (19/94)
	P value		0.0008	0.1011	0.3768	0.1966
2	% (n/N)	22.9 (97/424)	31.2 (43/138)	30.9 (105/340)	32.0 (91/284)	33.3 (30/90)
	P value		0.0507	0.0127	0.0068	0.0367
3	% (n/N)	29.9 (123/411)	42.7 (56/131)	39.7 (133/335)	43.2 (118/273)	42.4 (36/85)
	P value		0.0066	0.0052	0.0004	0.0254
4	% (n/N)	36.0 (147/408)	51.2 (66/129)	47.2 (151/320)	49.4 (133/269)	50.0 (41/82)
	P value		0.0022	0.0024	0.0005	0.0176
5	% (n/N)	38.2 (153/401)	55.1 (70/127)	51.9 (163/314)	54.6 (143/262)	45.7 (37/81)
	P value		0.0007	0.0002	<0.0001	0.2062
6	% (n/N)	37.8 (155/410)	53.2 (74/139)	50.3 (160/318)	56.2 (149/265)	53.1 (43/81)
	P value		0.0014	0.0007	<0.0001	0.0104

Notes: n/N represents a proportion of subjects who achieved 50% improvement in the ADHD-RS-5-derived Total Functional Impairment Score; *p* value is from Pearson's Chi-square test; shaded boxes indicate $p<0.05$.
Abbreviation: Viloxazine ER, viloxazine extended-release capsules.

suggested as an important approach to comprehensive evaluation of individual's functional outcomes.[14] Therefore, the use of two types of assessments provided by different informants (ie, clinicians and parents) for viloxazine ER can provide a more comprehensive understanding of how much the individual's functionality improves in response to treatment in different domains of the individual's life.

The descriptive statistics in the present post hoc analysis revealed improvements in both ADHD-RS-5 Inattention and Hyperactivity/Impulsivity FI scores across all impairment domains with all doses of viloxazine ER (100- to 600-mg/day), with somewhat greater effects seen in the academic performance and behavioral functioning at school and at home, followed by family and peer relationship domains, and a relatively smaller effect seen in the self-esteem domain (Figure 4, solid lines). Interestingly, the individual dose curves showed that while the improvements in all FI domains reached a plateau at approximately Week 3 with 100-mg/day dose of viloxazine ER, there was still a trend for improvement after Week 3 with higher doses (Figure 4, dotted lines).

One of the potential limitations of this study is that the data collected here were based on investigator-rated scales, and no parent or teacher ratings were included in this analysis. Parent-rated scales were used in individual trials of viloxazine ER and are described in their respective publications.[18–21] Another potential limitation is the length of follow-up. In the future, studies with longer duration may provide further insights into functional outcomes with viloxazine ER treatment. Finally, the current findings cannot be directly compared to those for other medications, given the differences in how response rates are reported across studies. To summarize, the statistically significant improve- ments vs placebo in the CFB ADHD-RS-5 FI scores and 30% and 50% Responder Rates observed in this post hoc analysis extend the primary efficacy data reported in the Phase 3 clinical trials of viloxazine ER demonstrating early and sustained improvement in inattention and hyperactivity/impulsivity symptoms. Furthermore, a recently

published analysis using a machine learning approach has demonstrated that early response to viloxazine ER treatment at Week 2 can be predictive of efficacy outcome at Week 6.[32] Together, these results demonstrate that viloxazine ER (viloxazine extended-release capsules) can be considered an effective and well-tolerated treatment option that provides clinically meaningful improvement in ADHD symptoms and functioning in children and adolescents starting as early as Week 1–2 of treatment.

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Evaluating the likelihood to be helped or harmed after treatment with viloxazine extended-release in children and adolescents with attention-deficit/hyperactivity disorder

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Abstract

Aims: When clinicians evaluate potential medications for their patients, they must weigh the probability of a treatment's benefits against the possible risks. To this end, the present analyses evaluate the novel nonstimulant viloxazine extended-release (viloxazine ER) using measures of effect size to describe the potential benefits of its treatment in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) as well as the risk of discontinuation because of intolerable adverse events.

Methods: These post hoc analyses use pooled data from four pivotal Phase 3 trials in paediatric patients treated with viloxazine ER. The Likelihood to be Helped or Harmed (LHH) effect size measure was calculated to describe the probability of patients benefiting from treatment vs discontinuing. The Number Needed to Treat (NNT) was calculated from frequently used thresholds of response. The Number Needed to Harm (NNH) was calculated using discontinuations because of adverse events.

Results: LHH values for viloxazine ER ranged from 5 to 13, suggesting that subjects were 5-13 times more likely to benefit from, rather than discontinue, viloxazine ER treatment. Specifically, NNT values for viloxazine ER treatment ranged from 6 to 7. NNH values for viloxazine ER treatment ranged from 31 to 74. By convention, single-digit NNTs (<10) suggest the intervention is potentially useful, while NNH values ≥10 for adverse events suggest it is potentially safe or tolerable.

Conclusions: These results indicate that patients with ADHD are likely to benefit from treatment with viloxazine ER, and are unlikely to discontinue, as viloxazine ER treatment was associated with favourable LHH, NNT, and NNH values. Clinicaltrials.gov: NCT03247530, NCT03247543, NCT03247517, NCT03247556.

What's known

Viloxazine extended-release (viloxazine ER) is a novel nonstimulant recently FDA-approved for the treatment of ADHD. Viloxazine ER has been shown to be effective in reducing symptoms

of ADHD in children and adolescents by the first week of treatment. Viloxazine ER has a favourable safety and adverse event profile.

What's new

This analysis describes the clinical relevance of four pivotal Phase 3 trials in paediatric patients with ADHD treated with viloxazine ER, using measures of treatment effect that quantify both the benefits of treatment as well as its risks (defined as discontinuation because of adverse events).

Message for the Clinic

When considering ADHD treatments for their patients, clinicians must weigh the probability of a treatment's benefits against the potential risks. Ultimately, medications that are effective but poorly tolerated are likely to result in premature treatment cessation and are thus ineffective for the patient in the long term. Based on the results reported here, viloxazine ER may be a viable candidate for the treatment of ADHD because of its favourable efficacy, safety, and tolerability profiles.

1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioural disorder characterised by a pattern of age-inappropriate inattentiveness, hyperactivity, and/or impulsivity that occurs across multiple settings (eg, school, home) and leads to various degrees of impairment.[1,2] Diagnosed in approximately 6.1 million (9.4%) US children and adolescents[3] and 2.5%-4.4% of adults,[4-6] ADHD often persists into adulthood as a chronic, life-long disorder that requires continuous, flexible treatment approaches across the lifespan.[7,8]

Current guidelines for pharmacotherapy recommend stimulants (eg, lisdexamfetamine, methylphenidate) as first-line therapy because of their greater efficacy in improving ADHD symptoms than nonstimulants (for a comprehensive review, see Cortese 2020).[9-12] However, stimulants must be used with caution, or may be contraindicated in patients with marked anxiety or agitation,[13] substance use disorders,[14,15] and bipolar disorder,[16] and are associated with weight loss, decreased appetite, and insomnia.[17,18] Stimulants also carry some risks of serious cardiovascular events[13,16] and have a risk for abuse, misuse, and diversion.[19-21] In children and adolescents for whom stimulant therapy is an option, 20%-30% have an inadequate response.[22] Nonstimulants, while generally less effective and with slower onset of effect than stimulants,[23] tend to have fewer limitations, no significant risk of abuse, misuse, or diversion, and generally lower risk of cardiovascular events in patients with pre-existing risk factors.[24,25]

When considering treatment with any medication, treating clinicians must weigh the potential benefits (ie, response to treatment) against the potential risks (ie, issues with safety and/or tolerability). Functionally, a medication that patients cannot tolerate and will eventually discontinue is of limited utility, even if patients find it beneficial in reducing ADHD symptoms. Likewise, patients, their caregivers, and physicians will have limited utility for a medication that is well tolerated but does not provide benefit in reducing ADHD symptoms.

To quantify the potential benefits of ADHD treatments, clinical trials in ADHD are increasingly reporting efficacy results as the proportion of subjects having achieved pre-specified criteria of response, commonly based on the ADHD Rating Scale (ADHD-RS) or the Clinical Global Impressions - Improvement scale (CGI-I). Most commonly, the CGI-I (a quick, clinician-friendly assessment of overall change in illness) is used to convey the clinical relevance of a given treatment by reporting the percentage of subjects achieving a CGI-I level of 2 (*much improved*) or 1 (*very much improved*) after treatment, as a CGI-I assessment of *much improved* is conventionally thought to be the threshold indicative of clinically meaningful improvement.[26,27] These analyses can also define responder rates in terms of symptom scales such as the ADHD-RS, using response criteria ranging from 20%[28] to 70%[29] improvement, with 30% being amongst the most frequent percentage cited in the literature.[30-32] Conversely, risks can be quantified in a variety of ways depending on the event of interest (eg, headaches, fatigue, syncope, cardiovascular events, death), or their frequency, intensity, or duration. Ultimately, study discontinuation because of adverse events (AEs) has been proposed and is frequently used as a practical measure of overall tolerability.[33]

Viloxazine extended-release (viloxazine ER) is a bicyclic structurally distinct molecule with demonstrated in vitro activity as a moderate norepinephrine reuptake inhibitor (IC_{50} = 0.269 μM).[34] In a preclinical rodent model (microdialysis), viloxazine has also been shown to increase norepinephrine, serotonin, and dopamine levels in the prefrontal cortex, a region implicated in ADHD pathophysiology.[34] However, interspecies differences and limitations of this animal model preclude the functional translation of these data into humans. As such, additional research is needed to fully elucidate the mechanism of action of viloxazine ER beyond its noradrenergic activity.[34]

Viloxazine ER has recently been FDA-approved for the treatment of ADHD in children and adolescents under the trade name Qelbree.™ The present post hoc analyses quantify and report the benefits and tolerability of viloxazine ER using data from four Phase 3 studies in children[35,36] and adolescents.[37,38] To this end, we use Likelihood to be Helped or Harmed (LHH) as an overall measure of treatment effects, which succinctly measures the benefit-risk ratio that clinicians, parents/caregivers, and patients must consider when selecting a treatment plan, and its component measures Number Needed to Treat (NNT), which describes the beneficial effect of treatment, and Number Needed to Harm (NNH), a measure of risk, such as discontinuations because of AEs. Unlike traditional measures of effect size such as Cohen's d, which are used to report the benefits of treatment, LHH also describes the risks associated with treatment and was thus selected because of its clinically relevant interpretation.

2 | METHODS

2.1 | Data sources

These analyses were conducted using pooled data from four pivotal Phase 3 trials assessing the efficacy and safety of viloxazine ER for the treatment of ADHD in children 6-11 years (study P301, NCT03247530[35] and study P303, NCT03247543[36]) and adolescents 12-17 years (study P302, NCT03247517[37] and study P304, NCT03247556[38]) (Table 1). All four trials were randomised, double-blind, placebo-controlled, multicentre, three-arm, parallel-group studies evaluating efficacy and safety of viloxazine ER (a novel non-stimulant with effects on norepinephrine and serotonin[34]) in paediatric patients with ADHD. In each study, symptoms of ADHD were measured according to the diagnostic criteria of the Diagnostic and Statistical Manual, Fifth Edition, and the diagnosis of ADHD was confirmed with the Mini International Neuropsychiatric Interview for Children and Adolescents. All participants were required to have a minimum ADHD-RS (Fifth Edition; ADHD-RS-5) Total score of 28 at screening and baseline, and a minimum CGI-Severity (CGI-S) score of 4 (ie, *moderately ill*) at screening. Subjects were required to refrain from taking any ADHD medication (other than the study medication) starting at least 1 week prior to randomisation and continuing through end-of-study (EOS) or early termination. A trained investigator/clinician administered the CGI-S at screening only, the ADHD-RS-5 at screening, baseline, and each post-baseline study visit, and the CGI-I at each post-baseline study visit.

Exclusion criteria included a current diagnosis of any major psychiatric disorders (a diagnosis of major depressive disorder was allowed if the subject was free of episodes at the time of screening and for six months prior), major neurological disorders or history of seizure disorder within the immediate family, current evidence of significant systemic disease, and/or evidence of suicidality within 6 months. Other exclusion criteria included a body mass index greater than 95th percentile for age and gender, history of receiving any investigational drug within the longer of 30 days or 5 half-lives prior to Day 1 dosing of viloxazine ER, or any other reason which might have prevented the subject from participating in the study (as determined by the Investigator).

Eligible participants were randomised at baseline in a 1:1:1 ratio to either placebo or one of the two doses of once-daily viloxazine ER as follows: children (6 to 11 years of age) received either 100 or 200 mg in study P301 and either 200 or 400 mg in study P303; adolescents (12 to 17 years of age) received either 200 or 400 mg in study P302 and either 400 or 600 mg in study P304 (Table 1). In P301, all subjects randomised to active treatment took an initial dose of 100 mg viloxazine ER on Week 1. Those subjects that were randomised to the 200 mg viloxazine ER arm were subsequently titrated up to 200 mg on Week 2. In P303, all subjects randomised to active treatment took an initial dose of 100 mg viloxazine ER on Week 1, and then were titrated up to 200 mg on Week 2. Those subjects that were randomised to the 400 mg viloxazine ER arm were subsequently titrated up to 300 mg on Week 3, and then 400 mg on Week 4. In P302, all subjects randomised to active treatment took an initial dose of 200 mg viloxazine ER on Week 1. Those subjects that were randomised to the 400 mg viloxazine ER arm were subsequently titrated up to 400 mg on Week 2. In P304, all subjects randomised to active treatment took an initial dose of 200 mg viloxazine ER on Week 1, and then titrated up to 400 mg on Week 2. Those subjects that were randomised to the 600 mg viloxazine ER arm were subsequently titrated up to 600 mg on Week 3. Regardless of the varied titration periods, subjects in all four studies maintained fixed-target, once-daily dosing for 5 weeks until EOS. The primary endpoint was the change from baseline at EOS in the ADHD-RS-5 Total score, and a key secondary endpoint was the mean CGI-I score at EOS.

TABLE 1 Summary of Phase 3 clinical trials evaluating viloxazine ER in paediatric populations

Age group	Children 6-11 years		Adolescents 12-17 years	
Study number	P301[35]	P303[36]	P302[37]	P304[38]
N[a] (randomized/completed)	477 / 399	310 / 266	313 / 281	297 / 276
Viloxazine ER doses (per day)	100 mg, 200 mg	200 mg, 400 mg	200 mg, 400 mg	400 mg, 600 mg
Weeks (t + m)	6 (1 + 5)	8 (3 + 5)	6 (1 + 5)	7 (2 + 5)
End of study assessment	Week 6 (Day 42)	Week 8 (Day 56)	Week 6 (Day 42)	Week 7 (Day 49)

Abbreviations: ER, extended-release; m, maintenance dosing; t, titration dosing.

[a]N = total number of participants randomized to the study/who completed the study.

The study protocols were approved by Advarra Institutional Review Board (IRB) and conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation Note for Guidance on Good Clinical Practice. Parents or legal guardians provided written informed consent for all study procedures including protocol amendments. All versions of the informed consent were reviewed and approved by the IRB.

2.2 | Assessments

2.2.1 | ADHD rating scale, Fifth Edition

The ADHD-RS[39,40] is an ADHD-specific rating scale designed and validated to assess current ADHD symptomatology as described in the Diagnostic and Statistical Manual, Fifth edition (DSM-5), currently in its Fifth Edition (ADHD-RS-5), and is a frequently used assessment in ADHD clinical trials. The scale consists of 18 items that directly correspond to the 18 DSM-5 ADHD symptoms, which are further subdivided into two subscales (nine symptoms/items per subscale): Inattention and Hyperactivity/Impulsivity. On the ADHD-RS-5 scale, the individual or caregiver rates the frequency of each symptom or behaviour over the preceding week on a 4-point Likert scale ranging from 0 (no or rare symptoms) to 3 (severe or frequent symptoms). The sum of scores for the 18 items provides the total score (ranging from 0 to 54). In the four Phase 3 trials, a trained investigator/clinician administered and scored the ADHD-RS-5 Home Version Child (P301/P303) or Adolescent (P302/P304) instrument at screening, baseline, and at each weekly post-baseline study visit through to EOS. The present analyses used the ADHD-RS-5 Total score change from baseline, expressed as a percent reduction (ie, improvement) of baseline scores.

2.2.2 | Clinical global impressions – improvement

The CGI-I scale is a single-item, stand-alone assessment of a clinician's view of a patient's overall functioning relative to an established baseline. Although the CGI-I is non-specific to any one disease, it is often used to measure the improvement/exacerbation of dysfunction as a result of a psychiatric disorder.[26,41] The CGI-I is rated on a 7-point Likert scale from 1 (*very much improved*) to 7 (*very much worse*), with each score described as *very much improved*, *much improved*, *minimally improved*, *no change*, *minimally worse*, *much worse*, and *very much worse*. After an initial clinical evaluation, considering a patient's symptoms, behaviour, and circumstances, an experienced rater can complete the CGI-I in typically less than a minute. Successful therapy is indicated by a lower overall score in subsequent testing. In each of the four pivotal Phase 3 trials of viloxazine ER, the CGI-I was administered at each weekly post-baseline study visit to EOS (inclusive) to assess ADHD-specific clinical improvement.

2.3 | Statistical analyses

The risk-benefit balance of treatment is described by LHH (the ratio of NNH to NNT), which quantifies how much more likely a patient is to encounter a benefit vs harm from treatment, eg, if Drug A has an LHH value of 5, a patient taking Drug A is five times more likely to experience a benefit from treatment rather than harm.[42-44] Thus, larger LHH values are considered more favourable, though specific rubrics for what constitutes a favourable, acceptable, or poor LHH value depends on the specific events in question (ie, an acceptable value describing a side effect of dry mouth will be smaller than that describing death).[42-44] The components of LHH – NNT (which describes clinical treatment benefits) and NNH (which describes risks) – each quantify the likelihood of a response in a given patient by indicating how many patients would need to be treated with Drug A vs Drug B (eg, active vs placebo) in order to achieve one additional outcome of interest, such as a response to treatment (via NNT) or an adverse outcome (via NNH).[42-44]

NNT and NNH values were calculated by first computing the frequency of each event (ie, responses, discontinuations), then calculating the Attributable Risk Reduction (ARR; the difference in rates between the experimental group and the placebo group), and finally taking the inverse of the ARR[42-44]; ie, NNT or NNH = 1/ARR, where ARR = $f_a - f_b$, where f_a = the frequency of events for viloxazine ER, and f_b = the frequency of events for placebo:

$$\frac{1}{f_a - f_b} \quad (1)$$

Confidence intervals were calculated by taking the reciprocals of the values defining the confidence intervals for the ARR.[45] LHH values were calculated as the ratio of NNH over NNT (ie, LHH = NNH/NNT). When calculations resulted in a value other than a whole number, values were rounded to minimise bias and facilitate translation into clinical practice (ie, numbers of whole patients): NNT values were rounded up to the nearest whole number, and NNH and LHH values were rounded down.[45] NNT, NNH, and LHH calculations of values and confidence intervals were performed in SAS (version 9.4). When interpreting NNT, smaller values are more desirable, suggesting a bigger difference between Drug A and Drug B.[42-44] Similarly, when comparing across multiple NNT values, smaller values indicate fewer patients need to be treated before one patient responds to treatment.[42-44] Conversely, larger values are desirable for NNH,[42-44] eg, an NNH = 50 would mean that fifty patients need to be treated in order for one patient to experience an adverse outcome (relative to the comparator treatment, eg, placebo). Similarly, larger values are desirable for LHH, indicating a more favourable risk-to-benefit ratio. By convention, single-digit NNTs (< 10) suggest the intervention is potentially useful, while NNH values ≥ 10 for adverse, unfavourable outcomes suggest it is potentially safe or tolerable.[42-44] These measures can provide a clinical context to traditional statistical hypothesis testing (which conveys the probability that a treatment effect is not the results of chance, yet says nothing of the clinical significance) by describing the magnitude of the treatment effect.

NNT values were calculated based on the intent-to-treat population (defined as any subject with at least one post-randomisation score), and based on percent responders as defined by four criteria: (a) 30% improvement (ie, reduction from baseline) on the ADHD-RS-5 alone, (b) 50% improvement on the ADHD-RS-5 alone, (c) 30% improvement on the ADHD-RS-5 *or* response on the CGI-I (score of 1 or 2, *very much improved* or *much improved*, respectively), and (d) 50% improvement on the ADHD-RS-5 *or* response on the CGI-I (score of 1 or 2). The 30% response threshold was selected as it is amongst the most commonly cited threshold in ADHD studies,[29,46-49] while the 50% response threshold was selected as it has been shown to be statistically linked with the CGI-I level *much improved* (CGI-I = 2),[50,51] commonly used as the minimum threshold for clinically meaningful change.[26,27] Response data were computed as the percent of subjects (treated with viloxazine ER vs receiving placebo) meeting the threshold for each criterion. NNH values were based on the safety population (defined as any subject having received at least one dose of study medication) using study discontinuation because of AEs, selected as a practical measure of overall tolerability.[33]

3 | RESULTS

Demographic characteristics are shown in Table 2.

3.1 | Likelihood to be helped or harmed

When using only the ADHD-RS-5 criteria to define treatment responders, the overall LHH value for viloxazine ER was 8 at the 30% improvement level (children = 13, adolescents = 5), and 7 at the 50% improvement level (children = 11, adolescents = 5) (Figure 1A). When response was defined by either the ADHD-RS-5 *or* CGI-I ≤ 2 criteria, the overall LHH value for viloxazine ER was 8 (children = 13, adolescents = 5), regardless of whether 30% or 50% improvement thresholds were used (Figure 1B). Table 3 shows the n's associated with these values and NNT/NNH values used to calculate LHH based on only ADHD-RS-5 criteria, and Table 4 shows these values for response defined by either the ADHD-RS-5 or CGI-I.

TABLE 2 Demographic data and baseline characteristics

N	761	593
BMI		
Mean ± SD (range)	17.2 ± 2.3 (12.5-26.3)	21.3 ± 3.4 (13.5-32.6)
Race, n(%)		
White	395 (51.9%)	364 (61.4%)
Black or African American	326 (42.8%)	203 (34.2%)
Other	40 (5.3%)	26 (4.4%)

Note: Based on the intent-to-treat population.

Abbreviations: BMI, body mass index; n, number of subjects with that observation; N, total number of subjects; SD, standard deviation.

3.2 | Number needed to treat using ADHD-RS-5 criteria

When using only the ADHD-RS-5 criteria to define treatment responders, more subjects treated with viloxazine ER achieved response vs subjects receiving placebo. At the 30% ADHD-RS-5 improvement level, 58.6% of viloxazine ER-treated subjects met the definition of responders, vs 40.7% from the placebo group. When examined by age group, 55.4% of children treated with viloxazine ER responded, vs 37.7% receiving placebo, while 62.8% of adolescents treated with viloxazine ER responded, vs 44.5% receiving placebo. At the 30% response level, the NNT value for viloxazine ER for all groups was 6, regardless of age.

At the 50% ADHD-RS-5 improvement level, 40.7% of viloxazine ER-treated subjects met the definition of responders, vs 24.8% from the placebo group. When examined by age group, 37.3% of children

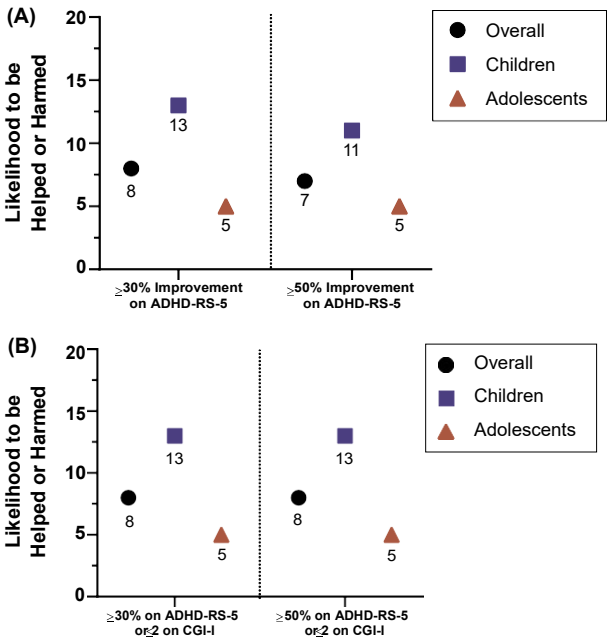

FIGURE 1 Likelihood to be helped or harmed. Likelihood to be Helped or Harmed (LHH) based on the rate of discontinuations because of adverse events and (A) ADHD-RS-5 criteria only or (B) either ADHD-RS-5 criteria *or* CGI-I criteria. LHH values under each symbol represent the likelihood of responding to treatment vs discontinuing treatment because of adverse events. ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale, Fifth Edition; CGI-I, Clinical Global Impressions – Improvement

TABLE 3 NNT (based only on ADHD-RS-5 criteria), NNH (based on discontinuations because of adverse events), and LHH

Subjects	NNT (95% CI)	N for NNT (viloxazine ER, Placebo)	NNH (95% CI)	N for NNH (viloxazine ER, Placebo)	LHH	Studies
30% Improvement on ADHD-RS-5						
All subjects (6-17 y)	6 (5 to 9)	902, 452	46 (26 to 167)	925, 463	8	P301, P302, P303, P304
Children (6-11 y)	6 (4 to 10)	509, 252	74 (−inf to −110) & (+27 to +inf)[a]	522, 262	13	P301 & P303
Adolescents (12-17 y)	6 (4 to 10)	393, 200	31 (18 to 88)	403, 201	5	P302 & P304
50% Improvement on ADHD-RS-5						
All subjects (6-17 y)	7 (5 to 10)	902, 452	46 (26 to 167)	925, 463	7	P301, P302, P303, P304
Children (6-11 y)	7 (5 to 11)	509, 252	74 (−inf to −110) & (+27 to +inf)[a]	522, 262	11	P301 & P303
Adolescents (12-17 y)	7 (5 to 13)	393, 200	31 (18 to 88)	403, 201	5	P302 & P304

Note: Abbreviations: ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale, Fifth Edition; CI, confidence interval; ER, extended-release; inf, infinity; LHH, likelihood to be helped or harmed; N, number of subjects; NNH, number needed to harm; NNT, number needed to treat.

[a]The ARR value and CI for children is 1.35 (−0.90 to 3.59). When the ARR CI includes zero, this results in an NNT CI that contains two ranges of numbers: a negative value to negative infinity, and a positive value to positive infinity,[45,52,53] and suggests there exists no difference in event rates between patients treated with viloxazine ER and placebo.

TABLE 4 NNT (based on either ADHD-RS-5 *or* CGI-I criteria), NNH (based on discontinuations because of adverse events), and LHH

Subjects	NNT (95% CI)	N for NNT (viloxazine ER, placebo)	NNH (95% CI)	N for NNH (viloxazine ER, placebo)	LHH	Studies
30% Improvement on ADHD-RS-5 *or* CGI-I ≤ 2						
All Subjects (6-17 y)	6 (5 to 8)	902, 452	46 (26 to 167)	925, 463	8	P301, P302, P303, P304
Children (6-11 y)	6 (4 to 9)	509, 252	74 (−inf to −110) & (+27 to +inf)[a]	522, 262	13	P301 & P303
Adolescents (12-17 y)	6 (4 to 10)	393, 200	31 (18 to 88)	403, 201	5	P302 & P304
50% Improvement on ADHD-RS-5 *or* CGI-I ≤ 2						
All Subjects (6-17 y)	6 (5 to 8)	902, 452	46 (26 to 167)	925, 463	8	P301, P302, P303, P304
Children (6-11 y)	6 (4 to 9)	509, 252	74 (−inf to −110) & (+27 to +inf)[a]	522, 262	13	P301 & P303
Adolescents (12-17 y)	6 (4 to 10)	393, 200	31 (18 to 88)	403, 201	5	P302 & P304

Abbreviations: ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale, Fifth Edition; CGI-I, Clinical Global Impressions – Improvement scale; CI, confidence interval; ER, extended-release; inf, infinity; LHH, likelihood to be helped or harmed; N, number of subjects with that observation; NNH, number needed to harm; NNT, number needed to treat.

[a]The ARR value and CI for children is 1.35 (−0.90 to 3.59). When the ARR CI includes zero, this results in an NNT CI that contains two ranges of numbers: a negative value to negative infinity, and a positive value to positive infinity,[45,52,53] and suggests there exists no difference in event rates between patients treated with viloxazine ER and placebo.

treated with viloxazine ER responded, vs 21.4% receiving placebo, while 45.0% of adolescents treated with viloxazine ER responded, vs 29.0% receiving placebo. At the 50% response level, the NNT value for viloxazine ER for all groups was 7, regardless of age. These NNT values and the 95% confidence intervals based only on ADHD-RS-5 criteria are shown in Figure 2A and Table 3.

3.3 | Number needed to treat using either ADHD-RS-5 or CGI-I criteria

When using either ADHD-RS-5 or CGI-I ≤ 2 response criteria at EOS, more subjects treated with viloxazine ER achieved response vs subjects receiving placebo. Using 30% ADHD-RS-5 improvement or CGI-I ≤ 2 response criteria, 61.9% of viloxazine ER subjects met the definition of responders, vs 43.1% from the placebo group. When examined by age group, 59.5% of children treated with viloxazine ER responded, vs 40.9% receiving placebo, while 64.9% of adolescents treated with viloxazine ER responded, vs 46.0% receiving placebo. At this response level, the overall NNT value for viloxazine ER was 6 (regardless of age).

Using 50% ADHD-RS-5 improvement or CGI-I ≤ 2 response criteria at EOS, 53.3% of viloxazine ER subjects met the definition of responders, vs 34.7% from the placebo group. When examined by age, 51.9% of children treated with viloxazine ER responded, vs 33.3% receiving placebo, while 55.2% of adolescents treated

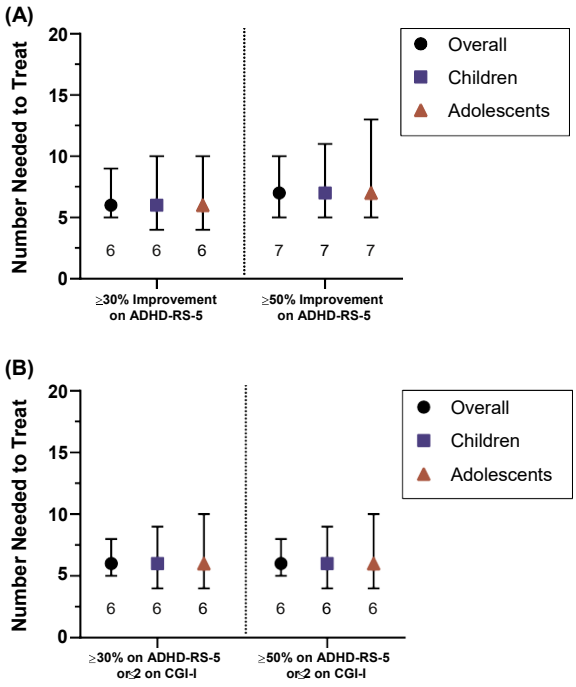

FIGURE 2 Number needed to treat. Number Needed to Treat (NNT; ± 95% confidence intervals) based on (A) ADHD-RS-5 criteria only or (B) either ADHD-RS-5 criteria *or* CGI-I criteria. NNT values under each symbol represent the number of patients who need to be treated before one patient responds. ADHD-RS-5, Attention-Deficit Hyperactivity Disorder Rating Scale, Fifth Edition; CGI-I, Clinical Global Impressions – Improvement

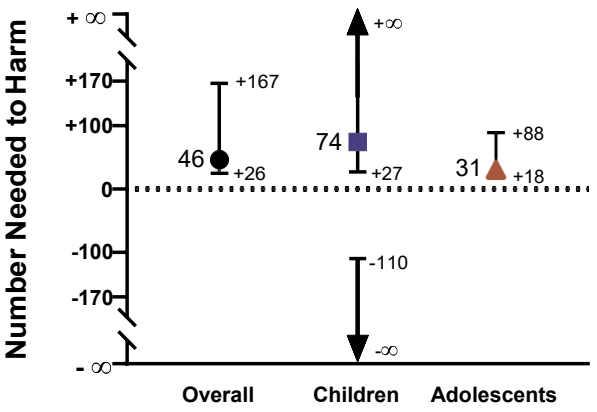

FIGURE 3 Number needed to harm. Number Needed to Harm (NNH; ± 95% confidence intervals) based on the rate of discontinuations because of adverse events. NHH values represent the number of patients who need to be treated before one patient discontinues treatment because of adverse events. Confidence intervals for NNH values that are not statistically significant (ie, Children, blue square) contain two ranges of numbers: negative infinity to a negative value (ie, −infinity to −110), and a positive value to positive infinity (ie, +27 to +infinity), and suggest that there exists no difference in event rates between patients treated with viloxazine ER and placebo. NNH values are to the left of each symbol, 95% upper- and lower-bound confidence intervals are to the right

with viloxazine ER responded, vs 36.5% receiving placebo. At this response level, the overall NNT value for viloxazine ER was also 6 (regardless of age). These NNT values and the 95% confidence intervals based on either ADHD-RS-5 or CGI-I criteria are shown in Figure 2B and Table4.

3.4 | Number needed to harm using discontinuations because of adverse events

Averaging across all four studies, discontinuations because of AEs occurred in 3.5% of subjects treated with viloxazine ER, and 1.3% of subjects receiving placebo. When examined by age group, discontinuations because of AEs were reported by 3.3% of children treated with viloxazine ER, and 1.9% of children receiving placebo. Similarly, discontinuations because of AEs were reported by 3.7% of adolescents treated with viloxazine ER, and 0.5% of adolescents receiving placebo. The overall NNH value for viloxazine ER was 46 (children = 74, adolescents = 31). The NNH values and 95% confidence intervals are shown in Figure 3 and Tables 3 and 4.

4 | DISCUSSION

The present post hoc analyses describe the results of four piv- otal Phase 3 trials using the standardised measures LHH, NNT, and NNH. Across these Phase 3 studies (randomised N = 1,397), three of the four trials resulted in statistically significant improvements (vs placebo) on the primary endpoint (the change from baseline in ADHD-RS-5 Total score), as quickly as within one week of treatment.[35-37] When analysed by response rates, ie, the percentage of subjects achieving 50% or more improvement on the ADHD-RS-5 (a key secondary endpoint), significantly more subjects treated with viloxazine ER improved (relative to participants receiving placebo).[35-37]

Based on response rates from these studies and the low rate of dropouts because of AEs (3.5% in the viloxazine ER group, vs 1.3% in the placebo group, averaged across all four studies), the present analyses report favourable LHH values that support the use of viloxazine ER in reducing ADHD symptoms, with a relatively low risk of discontinuing the drug. The large LHH values reported here (Figure 1) suggest patients are 5 to 13 times more likely to benefit from viloxazine ER than discontinue because of AEs (a common proxy for tolerability[33]). Specifically, the NNT values (Figure 2) for viloxazine ER (ranging from 6 to 7) fall well within the convention of NNT <10 for a potentially useful intervention.[43,44] This was true for all analysis pools, ie, both age groups had NNT values indicative of potentially useful treatment.

When interpreting NNT or NNH, the ARR value (the inverse of which is taken to compute NNT/NNH, see Equation 1, *Methods*) of the drug is considered statistically significant from the comparator (in this analysis, placebo) if both ends of the 95% confidence interval are positive or both ends are negative; if the ARR confidence interval includes zero, the value is not considered statistically significant

from its comparator.[45,52,53] For all groups analysed (children, adolescents, and overall), all NNT 95% confidence intervals were positive (Figure 2), suggesting that the NNT values were statistically significant; in other words, the rates of response for participants treated with viloxazine ER were significantly different from those receiving placebo, consistent with reports from these data using traditional statistical hypothesis testing.[35-37]

Similarly, NNH values (ranging from 31 to 74; Figure 3) measuring overall tolerability are well beyond the conventional threshold of NNH ≥10 for a potentially tolerable intervention.[43,44] Using the overall data (overall NNH = 46, with a confidence interval spanning 26 to 167), this suggests that a clinician will have to treat 46 patients on average before one patient discontinues because of an AE, indicating that this treatment is likely to be very well tolerated.[43,44] On this measure, modest differences between age groups were detected, as fewer discontinuations because of AEs were reported by children treated with viloxazine ER (3.3%, vs placebo = 1.9%) than by adolescents (3.7%, vs placebo = 0.5%). These differences—with the children's NNH value double that of the adolescents—are not likely to be clinically significant given the large overlap described by the 95% confidence intervals.

Interestingly, amongst children, the ARR value for discontinuations because of AEs was 1.35, with a confidence interval spanning −0.90 to 3.59. As described above, when the confidence interval for the ARR value includes zero, the value is not considered statistically significant from its comparator. Because NNT and NNH values are the inverse of the ARR (see Equation 1, *Methods*), when converting a confidence interval which includes zero to confidence intervals for NNT or NNH values, this results in a confidence interval with two ranges: a positive value to positive infinity and a negative value to negative infinity.[45,52,53] As such, the NNH value for the children in the present analysis includes two ranges: +27 to +infinity, and −110 to −infinity (Figure 3), suggesting that the event rate of the drug is not considered statistically significant from its comparator (here, placebo).[45,52,53] The confidence interval describing the range for the children's NNH value, therefore, can be interpreted to mean that the rate of AE-driven discontinuations between children treated with viloxazine ER and those receiving placebo was not significantly different.

The use of LHH to guide treatment decisions is likely to be more informative to clinicians than traditional measures of effect size, such as Cohen's d, odds ratios, or even NNT alone; as a measure of a treatment's *overall* effect, LHH quantifies the potential benefits *and* risks associated with a treatment, whereas traditional measures of effect size generally describe only the potential benefits. If exclusively considering a treatment's efficacy, clinicians may not fully consider the event rates of risks such as adverse events, safety considerations, or tolerability implications. The analyses here describe, in clinically relevant terms, how treatment with viloxazine ER is likely to affect individuals with ADHD with regard to clinical benefits *and* tolerability, which may help clinicians select a therapy that is both effective and unlikely to be prematurely discontinued.

Accordingly, data from randomised clinical trials (like those reported here) can be complemented by real-world data from observational studies, providing clinicians with additional information on a medication's impact on patients. Such data can provide evidence of a medication's efficacy or safety on additional measures not easily captured during short-term treatment (eg, infrequent events not likely to occur in short time frames, such as a reduction of risk of injuries[54]). Importantly, the LHH, NNT, and NNH values reported here were relatively consistent—regardless of how the response was defined, or which age group was analysed—suggesting that these data are likely to accurately represent the true effect in the population.

4.1 | Identifying clinically relevant improvement

Previous reports[35-37] from three of these Phase 3 trials have demonstrated that treatment with viloxazine ER significantly reduces ADHD symptoms and improves overall functioning vs placebo in children and adolescents. Like all statistical hypothesis testing, these significant results demonstrate the low likelihood of these effects occurring by chance, yet do not fully describe the clinical relevance or the potential clinical impact on patients. To identify which response thresholds might be most indicative of meaningful clinical improvement, recent analyses linking the ADHD-RS with the CGI-I scale[50,51] found that the commonly used 30% criteria threshold[29,46-49] was linked with *minimally improved* on the CGI-I (associated with no clinically meaningful reduction of symptoms and very little change in functioning[26,27]), while an improvement of 50% on the ADHD-RS was linked with *much improved*, which is typically assumed to be the threshold for clinically meaningful change.

Binary responder/non-responder efficacy results based on these or similar criteria lend themselves well to the measures NNT and NNH, clinically meaningful effect size measures which describe the results of a clinical trial in terms of the numbers of patients a clinician can expect to treat before one patient experiences the event of interest (eg, responds to therapy, drops out of treatment) vs a comparator treatment such as placebo. Regardless of which response criteria were used (ie, 30% or 50% improvement on the ADHD-RS-5 or CGI-I ≤ 2), all viloxazine ER NNT values for children and adolescents were smaller than 10 (Figure 2), the conventional threshold for a potentially beneficial intervention.[43]

4.2 | Medication discontinuation as an impediment to treatment

ADHD is a potentially lifelong disorder that is known to persist into adulthood,[7,8] yet several studies have reported medication discontinuation rates that are significantly higher than the relative rates ofreported ADHD symptoms and diagnosis,[55-57] suggesting that many patients may be terminating treatment prematurely. While a variety of factors can cause a patient to discontinue treatment, intolerable AEs are consistently amongst the most cited reasons,[58] and present significant challenges to therapy. Although treatment

discontinuation rates in clinical trials tend to be lower than those in population-based studies (likely because clinical trials carefully select, monitor, and support patients throughout the study),[59] low early trial terminations as a result of AEs can indicate the likelihood that patients will continue treatment over the long term vs discontinuing prematurely.

The present analyses describe the likelihood of AE-induced treatment terminations using the effect size measure NNH. Using this measure, viloxazine ER had an overall NNH value of 46 (Figure 3), which exceeded the conventional NNH ≥10 threshold (indicating a potentially favourable tolerability profile), suggesting that a clinician would have to treat 46 patients with viloxazine ER before one patient found the medication intolerable. Because retrospective or longitudinal analyses tend to find higher rates of medication cessation than clinical trials,[59] these discontinuation rates—which are exclusively from randomised clinical trials—are likely to be an underestimation of the true frequency in clinical practice. This likely underestimation further emphasises the need to consider discontinuations as a barrier to treatment.

4.3 | Conclusions

Amongst children and adolescents with ADHD, treatment with viloxazine ER was associated with favourable LHH values, describing a medication that is likely to be clinically effective in treating ADHD symptoms and unlikely to result in premature medication cessation because of intolerability. Further, these analyses describe, in clinically relevant terms, how treatment with viloxazine ER is likely to affect patients and may help guide clinicians in understanding the potential impact of viloxazine ER treatment in patients (6-17 years of age) with ADHD. Although LHH is relatively simple to calculate from dichotomous data, an overwhelming majority of clinical trials fail to report it. In fact, many published NNT values are calculated during secondary meta-analyses (such as these analyses of stimulants[60] and atomoxetine[61]), rather than the original clinical trial reports. We believe reporting the LHH value resulting from clinical trials would increase the translational value of such studies and the clinical relevance for physicians, researchers, and patients alike, and we encourage authors to do so in their future studies.

DISCLOSURES

A Nasser, AR Kosheleff, T Liranso, P Qin, JT Hull, GD Busse, and J Rubin are employees of Supernus Pharmaceuticals, Inc For a list of M Fava's lifetime disclosures, please see this link. V Maletic is an employee of the University of South Carolina School of Medicine. He is a consultant for ACADIA Pharmaceuticals Inc; Alfasigma USA, Inc; Alkermes, Inc; Allergan; Eisai-Purdue; Intra-Cellular Therapies; Janssen; H. Lundbeck A/S; Otsuka America Pharmaceutical, Inc; Sage Pharmaceuticals; Sunovion Pharmaceuticals Inc; Supernus Pharmaceuticals, Inc; and Takeda Pharmaceutical Company Limited. He serves on the speakers' bureau of ACADIA Pharmaceuticals Inc; Alkermes, Inc; Allergan; Ironshore; Intra-Cellular; Janssen; H. Lundbeck A/S; Otsuka America Pharmaceutical, Inc; Sunovion Pharmaceuticals Inc; and Takeda Pharmaceutical Company Limited; and his spouse serves on the speakers' bureau of Otsuka America Pharmaceutical, Inc F Lopez has served as a consultant to and received speaker fees and/or research support from Eli Lilly, GSK, Ironshore, Neos, Novartis, Noven, Pfizer, Shire, Sunovion, Supernus, and Tris.

DATA AVAIL ABILIT Y STATEMENT

The data are not available in a repository, but reasonable requests can be directed to anasser@supernus.com.

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January 17, 2022

Dear Tricare Uniform Formulary Beneficiary Advisory Panel members:

We understand that your group has reviewed our product Qelbree™ (viloxazine-extended release capsules) and based on our analysis of your review we would like to share some differences between Qelbree and other nonstimulants including Strattera based on indirect comparisons of clinical and scientific data. We believe these differences are important in highlighting areas where Qelbree's safety profile and onset of action in reducing ADHD symptoms differentiates from Strattera.

Qelbree™ (viloxazine extended-release capsules)

Refer to complete Prescribing Information: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aedf408d-0f84-418d-9416-7c39ddb0d29a

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS In clinical studies, higher rates of suicidal thoughts and behaviors were reported in pediatric patients with ADHD treated with Qelbree than in patients treated with placebo. Closely monitor all Qelbree-treated patients for clinical worsening and for emergence of suicidal thoughts and behaviors.

- **There have been no head-to-head studies comparing Qelbree and other nonstimulants including Strattera.**
- While there are (31) drugs approved for the treatment of ADHD, all but 3 are formulations of just 2 stimulant molecules, methylphenidate and amphetamine.[1]

- The diagnosis of ADHD in children is complex, and patients require more than just new stimulant delivery systems. Moreover, there are only 3 other FDA approved nonscheduled options, two of which have similar mechanisms of action. What is needed are additional nonscheduled options such as Qelbree.[2]

- Whether for considerations of stimulant abuse and diversion, patient intolerance to stimulants or nonstimulants, or inability to swallow pills, Qelbree offers an important option for the treatment of ADHD.[2-5] Data support that treating ADHD with medication is a protective factor against the development of substance use disorders (SUD).[6] We recognize that data showing reduction of SUD is primarily from evaluation of stimulants. Qelbree, as a nonscheduled option, reduces ADHD symptoms and may act as a protective factor against development of SUD. Lastly, we know that 52% of pediatric and adolescent patients have engaged in one of three forms of diversion of stimulants, which may be an additional consideration for adding another nonscheduled option to the category.[7]

- Qelbree is a new chemical entity (NCE), nonscheduled, once-daily medication approved by the FDA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6-17 years of age.[2]
- This new molecular entity (NME) is the first NME approved for ADHD in over 10 years.[2,8]

- The mechanism of action of viloxazine in the treatment of ADHD is unclear; however, it is thought to be through inhibiting the reuptake of norepinephrine. Additional data from animal models and *in vitro* research suggests that viloxazine increases dopamine, norepinephrine, and serotonin in the prefrontal cortex. The increase in serotonin is not through reuptake inhibition, but through other mechanisms under furthered investigation. Data from animal studies may not be predictive of a mechanism for treating ADHD in humans. This combined pharmacology makes viloxazine distinct from any FDA approved medication used to treat ADHD.[2,8]
- Patients receiving certain dosages of Qelbree demonstrated statistically significant improvement (ADHD-RS-5 scale) in ADHD symptoms occurring as early as week 1 that continued to the end of the clinical studies. Clinical Global Impression-Improvement scores also showed statistically significant early improvement that continued through end of clinical studies. Other ADHD nonscheduled medicines such as Strattera may take a median time to improvement of 4 weeks after treatment initiation; at least 12 weeks to full response; and 14.3 weeks to remission.[2,8,9-11, 14-20]
- The most common adverse reactions (≥ 5% and at least twice the rate of placebo for any dose) were somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.[2]
- Qelbree is contraindicated with monoamine oxidase inhibitors and sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.[2]
- Warnings and Precautions with Qelbree: possible effect on blood pressure and heart rate; activation of mania or hypomania; potential somnolence and fatigue.[2]
- <u>Additional clinical data that indirectly highlight areas unique to Qelbree that differentiate it from Strattera</u>:
    - No evidence of hepatic injury as evidenced by minimal AST and ALT elevations in liver enzymes across all trials. No Drug-Induced Liver Injury (DILI). [2,10] There is a warning/precaution for severe liver injury with Strattera.[13]
    - Qelbree has multiple metabolic routes of elimination and is unlikely to have an interaction with other drugs metabolized by CYP2D6.[2] Strattera has a warning/precaution for concomitant use with potent CYP2D6 inhibitors.[13]
    - ~10% of the patient population has a polymorphism at the CYP2D6 enzyme. Phenotypic CYP2D6 metabolizer status appears to have only a minimal impact on Qelbree metabolism with only a 1.5-fold increase in poor metabolizers vs. extensive metabolizers.[2,10] Poor metabolizers using Strattera may have a 10-fold higher AUC and a 5-fold higher Cmax, which could place them at high risk for experiencing adverse events.[13]
    - Qelbree has minimal impact on the cardiovascular system, with supratherapeutic doses producing no clinically significant effects on cardiac repolarization or other ECG parameters in healthy adults, suggesting that it is not associated with a risk for cardiac arrhythmias.[2,10, 12] Assess heart rate and blood pressure prior to initiating treatment with Qelbree, following dosage increases and periodically while on treatment.[2] In comparison, there is a warning/precaution for serious cardiovascular events with Strattera. Strattera has a post marketing report of QT prolongation and syncope. Sudden

death, stroke, and myocardial infarction have been reported in association with Strattera treatment.[13]

- Medication adherence can also be negatively impacted due to pill swallowing difficulties. Qelbree has convenient, once-daily dosing providing full-day medicine coverage; capsules can be opened and sprinkled on a spoonful of applesauce, yogurt, or pudding within 2 hours.[2,10] About one-third of adolescents and about 50% percent of children between the ages of 6 and 11 have reported some level of difficulty with pill swallowing without an intervention. After education, using pill cup or regular cup, ~10% of patients 6-11 years old can't swallow pills. [21-22] Strattera does not provide the option to be sprinkled.[13]
- No clinically significant impact on growth or weight effects were observed in Qelbree trials. Advise patients and their caregivers that Qelbree can affect weight and should be monitored while using Qelbree.[2,10] Strattera has a warning/precaution for growth (height and weight should be monitored).[13]
- Lastly, Number Needed to Treat (NNT) and Number Needed to Harm (NNH) are calculations that provide an assessment on the effect size and overall tolerability, respectively. The ratio of these two calculations provides the Likelihood to be Helped or Harmed (LHH). These calculations provide context on the clinical meaningfulness of the Qelbree data. The NNT for Qelbree is 7, NNH is 46 and LHH is 7. By contrast, for the Strattera, the NNT is 8, NNH is 29 and the LHH is 3.6. For Intuniv, the NNT is 4, NNH is 15 and LHH is 3.8. NNH values greater than 10 denote a potentially tolerable intervention so the NNH of 46 for Qelbree and 29 for Strattera and 15 for Intuniv indirectly highlight another differentiating area in which Qelbree may be a more safe and tolerable intervention in ADHD patients. NNH values are calculated based on dropout rates due to adverse events. The LHH ratios suggest that the benefit to risk ratio for Qelbree is more than double that of Strattera and Intuniv.[10,23]

- **Based on these data we feel that Qelbree has a safety, tolerability and scientific profile that differentiates it from Strattera. Therefore, we do not believe Strattera should be a step edit to Qelbree.**

Respectfully,

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There have been <u>no</u> head-to-head studies comparing Qelbree and other nonstimulants.

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January 20, 2022

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Braintree appreciates the opportunity to provide comments on the Pharmacy and Therapeutics (P&T) Committee's recommendations to Department of Defense's Beneficiary Advisory Panel (BAP). As an innovator in the field of gastroenterology for over 40 years, and a manufacturer of several products in the bowel preparation class under review at the August 2021 meeting, we would like to clarify several positions put forth by the P&T Committee.

Section IV. UF Drug Class Reviews – Laxatives-Cathartics-Stool Softeners: Bowel Preparations Subclass

Section A – Bullet 1, Sub-bullets 1 & 2

- *Several different dosage formulations are available, including powders for reconstitution, oral solutions, and tablets. The bowel preparations vary in the amount of liquid that is required for consumption, ranging from 2 to 4 liters.*
    - *Full-volume (standard volume) preparations require consumption of 4 liters (L) of total volume and include Colyte, GoLYTELY, NuLYTELY, and TriLyte and their generics.*
    - *Low-volume preparations range from 2 to 3.5 liters of total volume consumed and include Osmoprep (2 L), Plenvu (2 L), Clenpiq (2.2 L), Suprep (3 L), Sutab (3 L), and Moviprep (3 L). Although the tablet formulations (Osmoprep and Sutab) do not require mixing of solutions, significant additional water consumption is still required.*

Braintree comment: The P&T Committee's description of required liquids does not differentiate medicinal liquid preparation volumes from the water/clear liquids included in labeling to avoid dehydration.

Lower volume preparations are preferred by patients because their hypertonic formulations result in a lower requirement of medicinal fluid. Since an effective bowel preparation produces 2.5 liters or more of liquid stool output (Patel, et al[1]), the fluid deficit is made up for by water or clear liquids.

While both referenced as 3 liter preparations, SUPREP requires 1 liter of medicinal solution while MoviPrep requires 2 liters. PLENVU is referenced as a 2 liter prep, however the approved labeling notes that "additional clear liquids must be consumed after each dose of PLENVU in both dosing regimens". SUTAB and Osmoprep require no medicinal fluid, with only water or clear liquid needed to avoid dehydration.

Section A – Bullet 2

- *There do not appear to be clinically relevant differences in efficacy, based on indirect evidence.*

Braintree comment: Direct evidence exists demonstrating the superior cleansing efficacy of SUPREP compared to sodium picosulfate, magnesium oxide, anhydrous citric acid (Prepopik). In a large, randomized, investigator-blinded trial, Rex et al[2] demonstrated significant differences favoring SUPREP for overall success (95% vs 86% for Prepopik), "excellent" preparations (54% vs 26% for Prepopik), and volume of washing needed to achieve a clinically adequate exam (significantly more water was needed to irrigate with Prepopik).

Although Clenpiq was not included as a comparator in this study, it contains the same active ingredients in the same amounts as Prepopik, except in a prediluted form.

This difference in efficacy was confirmed and explained further in a recent ACG abstract by Walker, et al[3], which describes Phase 1 studies in which stool output was assessed following the administration of several FDA-approved bowel preparations. Stool output is an important marker as it reflects the true impact of the bowel preparation without the influence of the endoscopist. The results demonstrated that sulfate-based preparations (SUPREP = 2.9L, SUTAB = 2.8L) produced greater than a liter more of stool than sodium picosulfate, magnesium oxide preparations (Prepopik = 1.3L, Clenpiq = 1.6L).

Section A – Bullet 5, Sub-bullets 5 & 6

- Specific clinical considerations for the products are as follows:

    - ***Sodium sulfate, potassium sulfate, magnesium sulfate, concentrated oral solution (Suprep)*** *is a low volume (3 L) product indicated for patients 12 years of age and older. Safety concerns include a higher risk of nausea, vomiting and abdominal distension compared to other products. Overall Suprep offers no compelling clinical advantages relative to the other bowel prep agents.*

Braintree comment: As noted above, SUPREP has been demonstrated to have superior cleansing efficacy to Prepopik and produce significantly higher stool output compared to Prepopik and Clenpiq. The safety concerns listed by the P&T Committee are expected symptoms for bowel preparations and have been shown to be transient. The rates of these symptoms included in SUPREP label are disproportionately high compared to other bowel preparation labels due to the solicited data collection methods required by FDA for those studies.

    - ***Sodium sulfate, potassium chloride, magnesium sulfate tablets (Sutab):*** *Although Sutab provides the convenience of a tablet, it requires consumption of 28 tablets and 3 L of extra volume. Overall Sutab offers no compelling clinical advantages relative to the other bowel prep agents.*

Braintree comment: The tablet count for SUTAB is incorrectly stated as 28 tablets, instead of the FDA approved dose of 24 tablets. As stated previously, the 3L of extra volume is necessary water (not medicinal liquid) to counterbalance the 2.7L of stool output to avoid dehydration. SUTAB offers a clinical safety advantage as the only tablet-based preparation without a black box warning (Osmoprep has a black box warning for acute phosphate nephropathy). As a recently FDA approved, safe and effective tablet preparation, SUTAB represents an important option for

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patients with anxiety over the taste/volume of liquid bowel preparations or who have previously had a negative preparation experience. As an example, 91% of patients in one clinical trial found SUTAB "tolerable and very easy to consume" (Dipalma, et al, 2021[4]). Patient fear of the colonoscopy preparation and compliance with the preparation is well established as a barrier to colon cancer screening (Harewood, et al, 2002[5]). The inclusion of low volume and tablet-based preparations is an important tool for physicians to use in their screening procedures.

Based on the differentiating efficacy and safety factors outlined above, we believe that SUPREP and SUTAB merit inclusion in the Uniform Formulary. SUPREP has been the #1 prescribed prescription bowel preparation over the last 10 years in a landscape of parity coverage, confirming its preference by prescribers and patients. SUTAB which launched in January 2021 has grown to become the second most prescribed branded bowel prep[6]. In addition, with the recent extended supply chain disruptions of the generic 4L PEG preparations, it is critical that patients be allowed access to SUPREP and SUTAB.

In conclusion, Braintree asks that these comments be added an addendum to the Tricare P&T minutes from the August 2021 Meeting where Bowel Prep Formulations were reviewed.

If you have any questions about my comments, I welcome the opportunity to discuss them live with yourself or the Tricare P&T committee.

John McGowan

John McGowan
Head of R&D
Braintree Laboratories, Inc.

CC: Julia Trang, PharmD, Rob Raleigh, COO and General Counsel; Scott Briggs, CCO; Richard Ferguson, Senior Director, Managed Markets; Bob Stauffer, Director, Managed Markets

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6. IQVIA National Prescription Audit, December 30, 2021

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SUPREP® Bowel Prep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) Oral Solution is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. Most common adverse reactions (> 2%) are overall discomfort, abdominal distention, abdominal pain, nausea, vomiting and headache. Use is contraindicated in the following conditions: gastrointestinal (GI) obstruction, bowel perforation, toxic colitis and toxic megacolon, gastric retention, ileus, known allergies to components of the kit. Use caution when prescribing for patients with a history of seizures, arrhythmias, impaired gag reflex, regurgitation or aspiration, severe active ulcerative colitis, impaired renal function or patients taking medications that may affect renal function or electrolytes. Use can cause temporary elevations in uric acid. Uric acid fluctuations in patients with gout may precipitate an acute flare. Administration of osmotic laxative products may produce mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Patients with impaired water handling who experience severe vomiting should be closely monitored including measurement of electrolytes. Advise all patients to hydrate adequately before, during, and after use. Each bottle must be diluted with water to a final volume of 16 ounces and ingestion of additional water as recommended is important to patient tolerance.

SUTAB® (sodium sulfate, magnesium sulfate, potassium chloride) tablets for oral use is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults. DOSAGE AND ADMINSTRATION: A low residue breakfast may be consumed. After breakfast, only clear liquids may be consumed until after the colonoscopy. Administration of two doses of SUTAB (24 tablets) are required for a complete preparation for colonoscopy. Twelve (12) tablets are equivalent to one dose. Water must be consumed with each dose of SUTAB and additional water must be consumed after each dose. Complete all SUTAB tablets and required water at least 2 hours before colonoscopy. CONTRAINDICATIONS: Use is contraindicated in the following conditions: gastrointestinal obstruction or ileus, bowel perforation, toxic colitis or toxic megacolon, gastric retention. WARNINGS AND PRECAUTIONS: Risk of fluid and electrolyte abnormalities: Encourage adequate hydration, assess concurrent medications and consider laboratory assessments prior to and after each use; Cardiac arrhythmias: Consider pre-dose and post-colonoscopy ECGs in patients at increased risk; Seizures: Use caution in patients with a history of seizures and patients at increased risk of seizures, including medications that lower the seizure threshold; Patients with renal impairment or taking concomitant medications that affect renal function: Use caution, ensure adequate hydration and consider laboratory testing; Suspected GI obstruction or perforation: Rule out the diagnosis before administration. ADVERSE REACTIONS: Most common gastrointestinal adverse reactions are: nausea, abdominal distension, vomiting and upper abdominal pain. DRUG INTERACTIONS: Drugs that increase risk of fluid and electrolyte imbalance. See Full Prescribing Information and Medication Guide.

Armstead, Carolyn D CIV (USA)

From: Davis, William <William.Davis@astrazeneca.com>
Sent: Friday, January 21, 2022 6:03 PM
To: DHA NCR J-6 Mailbox BAPREQUESTS
Cc: Davis, William; Trang, Julia N CIV DHA DHA (USA)
Subject: [Non-DoD Source] ACTION: FDA Label Oversight in Meeting Recommendations - August 2021 - BTK inhibitor
Attachments: Calquence PI 11-2019.pdf; BAP Background Document for the August 2021 PT Committee meeting_508 Compliant.pdf

Dear Sir/Ma'am,

Calling attention to an error in the Meeting Recommendations (BAP Background Document 2021) – **BTK inhibitors CLL-acalabrutinib (Calquence)**:

- On page 5 of 42 (see attached), an approved FDA labeled indication is absent in the BAP Background documentation.
- The PA recommendation section for acalabrutinib should also include 'Frontline Therapy' for CLL/SLL
- The acalabrutinib PA criteria, as currently written in the recommendations, does not include the FDA approved indication for Front Line CLL/SLL (FDA approval November 2019)
- The approved indication for acalabrutinib includes
    - Front Line CLL patients with or without obinutuzumab
    - Relapsed Refractory , Monotherapy
- NCCN Guidelines include acalabrutinib as Preferred and Category 1 for Front Line and Relapse/Refractory treatment. Patients with and without del 17p/TP53 mutations were included in both registrational studies.

Attached is the approved FDA label for acalabrutinib which includes both Front Line and Relapsed/Refractory CLL/SLL. The confirmatory sections are 1.2 and 14.2. 14.2 includes both registrational Front Line and Relapse Refractory studies used for approval.

1.2 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

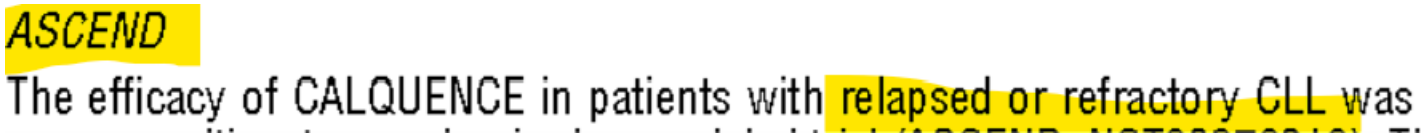
CALQUENCE is indicated for the treatment of adult patients with chronic lymp leukemia (CLL) or small lymphocytic lymphoma (SLL).

FRONT LINE:

ELEVATE-TN

The efficacy of CALQUENCE was evaluated in the ELEVATE-TN trial, a randor multicenter, open-label, actively controlled, 3 arm trial of CALQUEN combination with obinutuzumab, CALQUENCE monotherapy, and obinutuzum combination with chlorambucil in 535 patients with previously untreated cl lymphocytic leukemia (NCT02475681). Patients 65 years of age or older or be

RELAPSED/REFRACTORY:



Please reach out to me with questions or further information.

Regards,
Bill Davis

William C Davis, RPh, JD
National Clinical Account Director
Accounts - VA and Department of Defense

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