HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on February 23, 2024 via MS Teams. The meeting was called to order by Dr. Matthews, representing Dr. Moron as Chair, at 9:32 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Present	Jeffery Matthews, MD	Present
Angela Babin, RPh	Absent	David Moron, MD- Chair	Absent
John Bennett, MD	Present	Teri Newsom, APRN	Present
Giovanna Betancourt, PharmD	Present	Leah Nunez, PharmD	Present
Rakesh Chadalavada, MD	Absent	Brittany Parmentier, PharmD	Present
German Corso, MD	Present	Kasey L. Pena, PharmD- Secretary	Present
Megan Cummings, APRN	Present	Kenda Pittman, PharmD	Present
Brad Fitzwater, MD	Present	Sangeetha Rajan, MD	Absent
Catherine Hall, PharmD	Present	Lesia Trickett, MD	Absent
Dana Hopkins, RN	Present	Ashton Wickramasinghe, MD	Present
Sobia K. Khurram, MD	Present	Patrick Young, MD	Absent

Guests Present: Tonya Barrios, State Hospitals Central Administration; Kristen Neumeister, PharmD, North Texas State Hospital, Wichita Falls; John Fullerton, PharmD, Lufkin State Supported Living Center; Lisa Mican, PharmD, Austin State Hospital

Opening

Introduction and Other Information

Dr. Pena introduced Dr. Sobia Khurram, El Paso Psychiatric Center, as a new state hospital physician member of the committee.

Since our last meeting, Dr. Sawhney left his position as the HHSC Community Behavioral Health Medical Director, this position will remain open until his replacement is in place.

Annual Conflict of Interest Disclosures

A signed disclosure form has been received from most committee members. None of the forms reviewed indicated any issues with conflict of interest.

We will reach out again to request the signed disclosures from those still missing.

Review of Minutes

The minutes from the October 20, 2023 meeting were approved as previously distributed.

Unfinished Business

None.

New Business

New Drug Applications

Progesterone micronized (Prometrium®)- Pend

Ofloxacin otic (Floxin® [DSC])

Presented by Catherine Hall, PharmD. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of ofloxacin otic (Floxin) to the formulary in the Topical Agents- Otics section.

The formulary check list was completed and no issues were detected.

Ofloxacin ophthalmic (Ocuflox®)

Presented by Catherine Hall, PharmD. Please refer to Appendix B for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of ofloxacin ophthalmic (Ocuflox) to the formulary in the Topical Agents- Ophthalmics-Antibiotics section.

The formulary check list was completed and no issues were detected.

Respiratory Synctial Virus Vaccine (Arexvy)

Presented by Kasey Pena, PharmD. Please refer to Appendix C for the monographs that were considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of Respiratory Synctial Virus Vaccine (Arexvy) to the formulary in the Immunological Agents-Viral Vaccines section.

The formulary check lists were completed and no issues were detected.

Respiratory Synctial Virus Vaccine (Abrysvo)

Presented by Kasey Pena, PharmD. Please refer to Appendix D for the monographs that were considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of Respiratory Synctial Virus Vaccine (Abrysvo) to the formulary in the Immunological Agents-Viral Vaccines section.

The formulary check lists were completed and no issues were detected.

Viloxazine extended release (Qelbree®)

Presented by John Fullerton, PharmD. Please refer to Appendix E for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of viloxazine extended release (Qelbree) to the formulary as a Reserve Drug in the Psychotropic Agents-Other ADHD Agents section.

The formulary check list was completed and no issues were detected.

Cefadroxil (Duricef®)

Presented by Lisa Mican, PharmD. Please refer to Appendix F for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of cefadroxil (Duricef) to the formulary in the Infectious Disease Agents- Antibiotics-Cephalosporins section.

The formulary check list was completed and no issues were detected.

Dexmedetomidine (Igalmi®)

Dexmedetomidine (Igalmi) was added to the formulary in April 2023. The PEFC determined that a follow up on usage should be completed after 6 months of formulary status. The following data is from May to January 2024.

Per the records from the wholesaler used by the HHSC State Hospitals (SH) and State Supported Living Centers (SSLC), one SSLC and four SH's have purchased this medication:

- 120mg SL film = 117 packs (10 in each pack), for $117,875
- 180mg SL film = 38 packs (10 in each pack), for $38,284

Per a review of SH medication orders, Igalmi has been ordered for nine unique patients at two facilities. Most orders were either STAT doses or ordered PRN (daily or twice daily-prn). Four patients at one facility had orders for scheduled Igalmi 120mcg with indications of agitation or aggression. All orders have since been discontinued.

A review of SSLC orders showed five individuals at one facility had received Igalmi between April 2023 and January 2024. One of the orders was discontinued due to an increase in behaviors. The other four orders were written for daily dosing, with doses being administered up to three times per day.

After discussion, the committee agreed to update the reserve use criteria to include additional guidelines. The committee determined that an additional follow up on usage should be completed in six months.

Adverse Drug Reaction Reports

ADR: DDAVP/hyponatremia

A 37-year-old male with schizophrenia was admitted to North Texas State Hospital for competency restoration. On 9/29/23, he was found to be hyponatremic with a serum sodium of 121 and transferred to a local hospital for evaluation. At the time of local hospital admission, patient was prescribed benztropine 1mg twice daily, desmopressin nasal spray 10mcg/0.1mL 1 spray at bedtime, divalproex sprinkles 1500mg twice daily, docusate 200mg twice daily, guanfacine ER 1mg at bedtime, haloperidol decanoate 450mg every 4 weeks, metformin 500mg twice daily, methylcellulose powder 1 packet daily, metoprolol XL 50mg daily, polyethylene glycol 17gm daily, risperidone 4mg twice daily, sennosides 17.2mg Daily.

Serum sodium lab results:

- 9/8/23: 140
- 9/29/23: 121
- 9/30/23: 120
- 10/1/23: 128
- 10/2/23: 134
- 10/6/23: 141

A review of this patient's medical record revealed that he was started on desmopressin nasal spray for nocturnal enuresis on 9/12/23. At the time of medication initiation, a serum sodium was ordered for 9/29/23, which is what ultimately caught this lab abnormality. Per review of outside hospital records, this patient's review of system was negative for nausea, vomiting, headache, confusion, muscle weakness or spasms, and seizures. Desmopressin nasal spray was discontinued on 9/30/23 and his hyponatremia was treated with gentle IV normal saline and fluid restriction. He was discharged back to North Texas State Hospital on 10/2/23.

Conclusion: This case demonstrates a correlation between the development of hyponatremia after the initiation of desmopressin nasal spray.

The boxed warning for desmopressin recommends that serum sodium be measured within 7 days after initiating therapy. Additionally, it is recommended that fluid intake be monitored, and potentially restricted, to reduce the risk of hyponatremia with desmopressin.

After discussion, the committee agreed to create an audit criteria for desmopressin. The audit criteria will be presented at the next meeting.

Psychotropic Medication Audit Criteria

The committee reviewed and approved recommended revisions to the following audit criteria documents:

- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Valproic Acid
- Lithium

The updated documents will be posted to the PEFC website.

Psychotropic Monitoring Guidelines Review

The committee reviewed and approved updates to the Psychotropic Monitoring Guidelines that were based on revisions to the audit criteria approved at this meeting.

The updated document will be posted to the PEFC website.

HHSC Psychotropic Medications Consent List Annual Review

The committee reviewed and approved the following changes to the list of psychotropic medications requiring consent:

- Update vortioxetine (Trintellix) to "Reserve"
- Remove "Reserve" from buprenorphine (Subutex)
- Remove "Reserve" from buprenorphine/naloxone (Suboxone)
- Add "dexmedetomidine (Igalmi) Reserve" to Anxiolytics/Sedatives/ Hypnotics
- Add "tasimelteon (Hetlioz) nonformulary" to Anxiolytics/Sedatives/ Hypnotics
- Update amphetamine/dextroamphetamine to "amphetamine mixed salts" to match formulary
- Update Ritalin SR to "XR" to match formulary
- Add "nonformulary" to methylphenidate (Jornay PM)
- DSC added to several discontinued brand names

The updated document will be posted on the PEFC website.

Antipsychotic Tier Schedule Annual Review

The committee reviewed and approved recommended revisions to the Antipsychotic Tier Schedule:

- Add "lauroxil" to aripiprazole LAIs, Aristada and Initio
- Updated references
- Updated Cost Index of several items

The updated 2024 HHSC Antipsychotic Tier Schedule will be posted on the PEFC website.

Drug Formulary Sectional Review

In reviewing the formulary drug listings for Ophthalmics, Otics, Mouth/throat, and Nasal the following changes were approved:

- Ophthalmics-Antibiotics
  - Sulfacetamide Sodium (Bleph-10) – remove ointment, ophthalmic
- Ophthalmics-Mydriatics
  - Atropine Sulfate (Isopto Atropine) – remove ointment, ophthalmic
  - Homatropine - add brand name "Homatropaire"

- Ophthalmics-Decongestant/Antiallergy
  - Olopatadine – add brand name "Pataday"
- Miscellaneous Ophthalmics
  - Mineral Oil-Petrolatum – remove brand name "Akwa Tears"
  - Polyvinyl Alcohol – remove brand name "Akwa Tears"
- Otics
  - Acetic Acid – add brand name "Vosol"
- Add DSC to several discontinued brand name medications
- Updated Cost Index of several items

The updated formulary will be posted on the PEFC website.

Other Formulary Changes

At the previous PEFC meeting, the committee recommended a review of felbamate (Felbatol), a Reserve Drug. Dr. Parmentier presented the review with recommended changes to the Guidelines for Use. The committee approved the recommended changes.

The committee also approved an additional maximum daily dose of olanzapine for treatment resistant schizophrenia in the Psychotropic Dosage Guidelines, Antipsychotics section of the formulary.

The committee discussed and approved the addition of colchicine capsule to the formulary, as the tablet is already formulary.

The updated formulary will be posted on the PEFC website.

Quarterly Non-Formulary Drug Justification Report

For the first quarter of fiscal year 2024 (September 2023 to November 2023), only the state hospitals reported use of non-formulary agents. The state supported living centers (SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the first quarter of fiscal year 2024:

- Torsemide
- NAC
- Zinc gluconate
- Quercetin
- Paxlovid

Updates from the Chief Medical Officer, State Hospitals

Dr. Matthews had nothing new to report.

Updates from the Medical Services Coordinator, SSLCs

Dr. Wickramasinghe stated the SSLCs continue to work very hard to move past the DOJ settlement agreement.

Drug Shortages, Recalls, and FDA Safety Communications

The FDA has issued the following safety communications and recalls that may impact our facilities:

Shortages

The following medications are in shortage:

- Albuterol sulfate inhalation solution
- Amphetamine salt combos
- Amoxicillin oral powder for suspension
- Carbamazepine ER capsule (generic will be discontinued) **(NEW)**
- Clonazepam
- Diazepam rectal gel
- Levemir flexpen and Levemir vial (discontinued by the end of the year) **(NEW)**
- Lidocaine injection and lidocaine solution
- Liraglutide (Victoza)
- Lisdexamfetamine (Vyvanse)
- Lorazepam injection
- Semaglutide (Ozempic, Wegovy)
- Tirzepatide (Mounjaro, Zepbound)
- Sterile water for injection

Recalls

- OTC ophthalmic sterile drops (several brands) due to insanitary conditions in manufacturing facility and bacterial contamination
- Zenzedi (dextroamphetamine) 30mg due to mislabeled packaging

FDA Safety-related Communications and Labeling Changes

- **Promethazine HCl injection products**: labeling updates intended to reduce the risk of severe chemical irritation and damage to tissues from IV administration.
- **Paxlovid:** Paxlovid manufactured and labeled in accordance with EUA (EUA-labeled Paxlovid) will remain authorized for use through March 8, 2024 (or

expiration date if earlier). EUA labeled Paxlovid will no longer be authorized for emergency use after that date.

- **Opioid analgesics:** FDA announced and approved implementation of required labeling changes to address the opioid crisis and encourage HCP to take a patient centered approach when prescribing. Labeling should include language stating: risk of overdose increases as dosage increases, IR opioids should not be used for an extended period of time, many acute pain conditions in outpatient setting require no more than a few days of an opioid pain med, recommend reserving ER/LA opioids for severe and persistent pain that require an extended treatment period. A warning about hyperalgesia or allodynia (increase sensitivity to pain) should also be included.
- **Counterfeit Ozempic (semaglutide):** FDA released lot number and serial number of counterfeit Ozempic and encouraged pharmacies and wholesalers to review their stock.

Open Forum

None.

Next Meeting Date

The next meeting is scheduled for April 19, 2024.

Adjourn

There being no further business, the meeting was adjourned at 3:24 p.m.

Approved: *David Moron*

David Moron, MD, Chairman

Minutes Prepared by:
Tonya Barrios, PhTR
Reviewed by:
Kasey L. Pena, PharmD

Appendix A

Ofloxacin Otic Solution 0.3% (Floxin® [DSC])

Classification

Fluoroquinolone Antibiotic

Pharmacology

Ofloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin exerts its bactericidal activity by inhibiting DNA gyrase, an essential enzyme which assists in DNA replication, repair, deactivation and transcription.

An advantage of topical therapy is the high concentration of antibiotic that can be delivered to the site of infection; prolonged exposure to subtherapeutic antibiotic concentrations can lead to the selection of resistant microorganisms.

Indication

Otitis Externa in adults and pediatric patients, 6 months and older, due to *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus.*

Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes due to *Proteus mirabilis, Pseudomonas aeruginosa,* and *Staphylococcus aureus*.

Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae.*

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	A maximum serum concentration of 10 ng/mL was reported in adults with perforated tympanic membranes. In 2 single-dose (10 drops) studies looking at adults with tympanostomy tubes with and without otorrhea, mean ofloxacin serum concentrations were 4.1 ng/mL and 5.4 ng/mL.
Distribution	After oral administration, ofloxacin has been detected in lung tissue, blister fluid, cervix, ovary, prostatic fluid, prostatic tissue, sputum, and skin.
Metabolism	Minimally metabolized in the liver when ofloxacin is taken orally with doses of 100 to 600 mg.

Pharmacokinetic Parameter	Details
Excretion	Oral ofloxacin is cleared renally with a half-life of 5-7.5 hours. Approximately 72% - 98.5% of ofloxacin remains unchanged in urine within 48 hours.

Dosage/Administration

Pediatric Dosing

Indication	Dosing
Otitis Externa	From 6 months to 13 years old: 5 drops (0.25 mL/0.75 mg ofloxacin) instilled into the affected ear once daily for 7 days
Acute Otitis Media with tympanostomy tubes	From 1 – 12 years old: 5 drops (0.25 mL/0.75 mg ofloxacin) instilled into the affected ear twice daily for 10 days

Adult Dosing

Indication	Dosing
Otitis Externa	From 13 years and older: Instill 10 drops into affected ear(s) once daily for 7 days; may extend an additional 7 days if symptoms are improving but not yet resolved
Chronic Suppurative Otitis media	Instill 10 drops into affected ear(s) twice daily for 14 days

The bottle should be held in hand for 1-2 minutes to warm up and avoid dizziness from instilling cold solution into ear. Patient should lie down with affected ear pointing upward, then solution drops should be instilled after. Remain in lying down position for five minutes to ensure penetration of the solution into the ear canal.

Use in Special Populations

Pregnancy: Category C. Adverse events have been observed in some animal reproduction studies. There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended clinical doses. Ofloxacin otic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: Unlike the oral formulation, it is unknown if ofloxacin otic solution is excreted into breast milk. The manufacturer recommends patient-provider decision making to weigh benefits and risk, such as potentially serious adverse events in infants.

Pediatric Use: Safety and efficacy have been demonstrated in pediatric patients of the following ages for the listed indications. Safety and efficacy in pediatric patients below these ages have not been established.

- Six months and older: otitis externa with intact tympanic membranes
- One year and older: acute otitis media with tympanostomy tubes
- Twelve years and older: chronic suppurative otitis media with perforated tympanic membranes

Geriatric Use: No dosage adjustment necessary.

Hepatic Impairment: No dosage adjustment necessary in hepatic impairment.

Renal Impairment: No dosage adjustment necessary in renal impairment.

Contraindication

History of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

Precautions

- NOT FOR OPHTHALMIC USE
- NOT FOR INJECTION
- Prolong use of ofloxacin may lead to fungal or bacterial superinfection. Discontinue therapy and switch to alternative if this occurs if there are no improvements after one week. Cultures should be collected to decide next steps. If otorrhea continues after a full treatment course, or if $\geq$2 episodes of otorrhea occur within six months, further evaluation is recommended to exclude other conditions such as cholesteatoma, foreign body, or a tumor.
- The systemic administration of quinolones, including ofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution showed no systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of arthropathy. No drug-related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guinea pig following otic administration of 0.3% ofloxacin for one month.
- Hypersensitivity reactions, such as anaphylactic shock and anaphylaxis, can occur with systemic quinolones. Some were accompanied by airway obstruction, loss of consciousness, or edema. Discontinue treatment if an allergic reaction occurs.

Adverse Effects

Subjects with Otitis Externa

Phase III clinical trials studied once-daily dosing for ofloxacin otic solution in 799 patients with otitis externa and intact tympanic membranes. That studies which are the basis for approval were study 020 (pediatric, adolescents, and adults), 016 (adolescents and adults) and 017 (pediatric). The chart below displays treatment-related adverse events that occurred in two or more patients.

Adverse Events of Subjects with Otitis Externa

Adverse Events	Incidence Rate Studies 002/003 BID (N=229) [a]	Incidence Rate Studies 016/017 QD (N= 310) [a]	Incidence Rate Study 020 QD (N=489) [a]
Application Site Reaction	3%	16.8% [b]	0.6%
Pruritus	4%	1.2%	1.0%
Earache	1%	0.6%	0.8%
Dizziness	1%	0.0%	0.6%
Headache	0%	0.3%	0.2%
Vertigo	1%	0.0%	0.0%

[a] Studies 002/003 (BID) and 016/017 (QD) were active-controlled and comparative. Study 020 (QD) was open and non-comparative.

[b] The increased incidence might be the result of specific questioning towards the patients, since both drug and active control displayed similar incidence rates.

Subjects with Acute Otitis Media with Tympanostomy Tubes (AOM TT) & Subjects with Chronic Suppurative Otitis Media (CSOM) with Perforated Tympanic Membranes

In phase III clinical trials, the treatment-related adverse events listed below occurred in >1% in the 656 patients with non-intact tympanic membranes in AOM TT or CSOM with twice daily dosing of ofloxacin otic solution.

Adverse Events	Incidence (N=656)
Taste Perversion	7%
Earache	1%
Pruritus	1%
Paresthesia	1%
Rash	1%

Adverse Events	Incidence (N=656)
Dizziness	1%

Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous post-marketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

Monitoring

- Toxicity: Signs and symptoms of ofloxacin toxicity, such as hot and cold flushes, drowsiness, nausea, and slurring of speech
- Efficacy: Sign and Symptom of improvement

Interactions

Specific drug interactions have not been studied with ofloxacin otic solution. There are also no known significant interactions.

Efficacy

Jones and colleagues

In a randomized, evaluator-blind, multi-center trial, the safety and efficacy of ofloxacin otic solution (0.3%) was compared to that of Cortisporin otic solution (neomycin sulfate, polymyxin B sulfate, and hydrocortisone) in adults (n = 247) and children (n = 227) with otitis externa (OE). Inclusion criteria included clinically diagnosed, unilateral or bilateral OE of $\leq$ two weeks' duration with purulent or mucopurulent otorrhea. Patients with perforated tympanic membranes within previous six months were excluded. If randomized to ofloxacin 0.3%, adults and children received 0.5 ml (10 drops) and 0.25 ml (5 drops), respectively, twice daily for 10 days. If randomized to Cortisporin otic solution, adults and children received 0.2 ml (4 drops) and 0.15 ml (3 drops), respectively, four times daily for 10 days.

The overall response was cure in 97% of ofloxacin-treated children vs 95% of Cortisporin-treated children ($p = 0.48$) and 82% of ofloxacin-treated adults vs 84% of Cortisporin-treated adults ($p = 0.56$). There were no statistically significant differences in microbiological cure or AE's between the two treatment groups.

Torun and colleagues

In a multicenter, open-label, Phase III study, Torun and colleagues evaluated efficacy and safety profile of seven days of once-daily ofloxacin otic 0.3% solution in the treatment of otitis externa. Inclusion criteria included age $\geq$ 6 months, symptom duration of < two weeks, moderate to severe edema and tenderness involving 1 or both ears, an intact tympanic membrane, and sufficient exudate for

microbiologic culture. Children aged 6 months to < 13 years received 5 drops once daily for 7 days; adolescents and adults received 10 drops once daily for 7 days.

Study subjects were examined at baseline, end of therapy (EOT, day 7), and test-of-cure (TOC, day 14-17). The primary efficacy end point was success (complete resolution of all signs and symptoms) or failure (all other responses). A culture was taken at baseline and if secretion was still present at the EOT visit, another specimen was collected for microbiologic analysis. Compliance/adherence was assessed at the EOT visit (patient diary). Researchers evaluated patients (n = 439) who did not use prohibited treatment and received $\geq$ 6 doses of ofloxacin otic solution and returned for the EOT and TOC visits. Also included were patients whose symptoms did not improve after $\geq$ 3 days of treatment with the study drug (clinical failures).

The clinical cure rate was 91%--68% of patients were cured by the EOT visit, 23% were cured within 7 to 10 days thereafter (TOC visit). Fifty-eight (58%) of patients were microbiologically evaluable (n = 253) and the microbiologic eradication rate was 96%. P aeruginosa was isolated from 158 (62%) patients and was eradicated in 153 (97%) of them; of patients infected with P aeruginosa, 143 (91%) were clinically cured. S aureus was isolated from 32 (13%) patients and eradicated in 31 (97%) of them; 24 (75%) patients infected with S aureus were cured. 98% of patients were compliant.

The authors concluded that the efficacy and safety profile of ofloxacin otic 0.3% solution were not compromised by being administered once daily for 7 days rather than twice daily for 10 days as in earlier OE trials. This reduced treatment course may contribute to increased patient adherence and greater rates of treatment completion.

Name	Dosing Frequency	Form	Price (GoodRx)
Ofloxacin 0.3%	Once daily	Otic solution	$42.54, 5 ml
Ciprofloxacin-dexamethasone (Ciprodex)	BID	Otic suspension	$75.95, 7.5 ml
Ciprofloxacin-hydrocortisone (non-sterile)	BID	Otic suspension	$336.29, 10 ml
Ciprofloxacin 0.2%	BID	Otic solution	$55.71 per carton (14 containers)

Safety Considerations

- Look Alike-Sound Alike: Floxin may be confused with Flexeril. Floxin is currently discontinued in the United States, but generic is available.

Summary/Conclusion

In a strong recommendation, Rosenfeld RM et al (2014) state that clinicians should not prescribe systemic antimicrobials as initial therapy for diffuse, uncomplicated AOE unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. FDA approved topical agents for the treatment of AOE include the following: acetic acid solution (q 4-6 h); acetic acid/hydrocortisone (q 4-6 h); ciprofloxacin/hydrocortisone (non-sterile, BID); ciprofloxacin/dexamethasone (BID); neomycin, polymyxin B, hydrocortisone (TID-QID); ofloxacin 0.3% (once daily) and ciprofloxacin 6%.

According to Rosenfeld RM et al (2014), there are no meaningful differences in clinical outcomes based on class of therapy (antibiotic vs antiseptic), use of a quinolone versus a non-quinolone, or monotherapy versus combination drugs with or without a concurrent steroid. For the treatment of otitis externa, Sanford (2023) recommends the following: (1) ciprofloxacin + (dexamethasone or hydrocortisone) bid x 7 days; (2) ofloxacin qd x 7 days; (3) ciprofloxacin single dose. Ciprofloxacin plus hydrocortisone is a non-sterile formulation and needs to be avoided in patients who do not have an intact ear drum because of increased infection risk. Compared to ciprofloxacin + dexamethasone, ofloxacin is less expensive and has the advantage of once-daily dosing.

Recommendation

Ofloxacin 0.3% otic should be added to the formulary.

References

1. Rosenfeld RM, Schwartz SR, Cannon CR, et al. Clinical Practice Guideline: Acute Otitis Externa. Otolaryngology—Head and Neck Surgery 2014, Vol 150(IS) S1-S24
2. Gilbert DN, Chambers HF, Saag MS, et al. The Sanford Guide to Antimicrobial Therapy 2023. 53th edition.
3. Clinical Resource, Prevention and Treatment of Swimmer's Ear. Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber's Letter. June 2023.
4. Torum B, Block SL, Avila H, et al. Efficacy of Ofloxacin Otic Solution Once Daily for 7 Days in the Treatment of Otitis Externa: A Multicenter, Open-Label, Phase III Trial. Clin Ther 2004;26:1046-54.
5. Jones RN, Milazzo J, Seidlin M. Ofloxacin Otic Solution for Treatment of Otitis Externa in Children and Adults. Arch Otolaryngol Head Neck Surg. 1997;123:1193-1200.

6. Ofloxacin Otic solution 0.3% prescribing information. Apotex Corp. Revised 11/2022.

Date: January 12, 2024
Prepared by: Nathalie Nguyen, University of Texas College of Pharmacy P4 student
Reviewed by: Catherine Hall, PharmD, BCPP, BCACP

Appendix B

Ofloxacin Ophthalmic Solution 0.3% (Ocuflox®)

Classification

Antibiotic, Fluoroquinolone

Pharmacology

Ofloxacin has invitro activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin exerts its bactericidal activity by inhibiting DNA gyrase, an essential enzyme which assists in DNA replication, repair, deactivation and transcription.

Indication

Treatment of Bacterial Conjunctivitis caused by:

Gram-Positive	Gram-Negative	
Staphylococcus aureus *Staphylococcus epidermidis* *Streptococcus pneumoniae*	*Enterobacter cloacae* *Proteus mirabilis*	*Haemophilus influenzae* *Pseudomonas aeruginosa*

Treatment of Corneal Ulcer caused by:

Gram-Positive	Gram-Negative	Anaerobic
Staphylococcus aureus *Staphylococcus epidermidis* *Streptococcus pneumoniae*	*Pseudomonas aeruginosa* *Serratia marcescens** *Efficacy for this organism was studied in >10 infection.	*Propionibacterium acnes*

Introduction

Acute conjunctivitis can be categorized as infectious (bacterial or viral) or noninfectious (allergic, toxic, non-specific). Children are more prone to the bacterial variety while viral infection is more common in adults. Bacterial conjunctivitis is characterized by thick purulent discharge that is yellow, white or green and continues throughout the day. The most common causative pathogens are *Staphylococcus* aureus, *Streptococcus pneumonia, Haemophilus influenza,* and *Moraxella catarrhalis.* Most cases of bacterial conjunctivitis are self-limited; however, the use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission compared to placebo. Topical antibiotics are recommended to deliver high levels of medication directly to the site of infection. Mild disease is treated empirically.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Minimal systemic absorption. Max serum concentrations after 10 days of topical ophthalmic dosing were more than 1000 times lower than those reported after standard po doses.
Distribution	Upon ophthalmic administration of ofloxacin 0.3% solution, tear film ofloxacin concentrations ranged from 5.7 – 31 mg/g with a mean value of 9.2 mg/g four hours after administration. This shows ofloxacin maintains clinically effective concentrations in tear film for up to 240 minutes after administration.
Metabolism	Minimally metabolized in the liver when ofloxacin is taken orally with doses of 100 to 600 mg.
Excretion	Ofloxacin is excreted in the urine primarily unmodified (renally excreted).

Dosage/Administration

Bacterial Conjunctivitis:

Days	Dosage
Day 1 -2	Instill 1-2 drops every 2-4 hours in the affected eye(s)
Day 3-7	Instill 1-2 drops four times daily in the affected eye(s)

Bacterial Corneal Ulcer:

Days	Dosage
Day 1 and 2	Instill 1-2 drops into the affected eye every 30 minutes, while awake. Awaken at approximately 4-6 hours after retiring and instill 1-2 drops.
Day 3 through 7-9	Instill 1-2 drops hourly, while awake
Days 7-9 through treatment completion	Instill 1-2 drops, four times daily until clinical cure

Use in Special Populations

Pregnancy: Adverse events have been observed in some animal reproduction studies, but there are no well-controlled studies in pregnant women. Oral formulation of ofloxacin can cross the placenta, but the amount of ofloxacin ophthalmic solution that would cross is significantly less than oral. If benefits outweigh the risk for pregnant patient and fetus, the minimum effective dose

should be used in addition with punctal occlusion for 3-5 minutes after application to decrease exposure to the fetus.

Lactation: Unlike the oral formulation, it is unknown if ofloxacin ophthalmic solution is excreted into breast milk. The manufacturer recommends patient-provider decision making to weigh benefits and risk, such as potentially serious adverse events in infants.

Pediatric Use: No dosage adjustment necessary possibly due to low systemic absorption.

Geriatric Use: No dosage adjustment necessary.

Hepatic Impairment: No dosage adjustment necessary in hepatic impairment.

Renal Impairment: No dosage adjustment necessary in renal impairment.

Contraindication

History of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

Precautions

- Not for injection—should not be injected subconjunctivally nor introduced directly into the anterior chamber of the eye.
- Prolong use of ofloxacin may lead to fungal or bacterial superinfection. Discontinue therapy and switch to alternative if this occurs.
- Hypersensitivity reactions, such as anaphylactic shock and anaphylaxis, can occur with systemic quinolones. Some were accompanied by airway obstruction, loss of consciousness, or edema. Discontinue treatment if an allergic reaction occurs.
- Tendon inflammation and rupture can occur with systemic quinolone antibiotics. Although ophthalmic administration has a lower exposure than systemic therapy, discontinue at first sign of tendon inflammation/pain.

Adverse Effects

Ophthalmic Use

- Ocular burning and discomfort were the most frequently reported drug-related adverse reactions. Other reported reactions include stinging, redness, itching, chemical conjunctivitis/keratitis, ocular/periocular/facial edema, foreign body sensation, photophobia, blurred vision, tearing, dryness, and eye pains.
- Dizziness and nausea were also reported but rare.

Monitoring

- Toxicity: Signs and symptoms of ofloxacin toxicity, such as hot and cold flushes, drowsiness, nausea, and slurring of speech
- Efficacy: Sign and Symptom improvement

Interactions

Specific drug interaction studies have not been conducted with ofloxacin ophthalmic solution.

Efficacy

Data Sets #1-2: The following data was provided by the manufacturer. The two studies were randomized, double-masked, multicenter clinical trials. While the studies do not appear published, clinical success was stated with ofloxacin.

Data Set #	Clinical Trial	Intervention	Outcomes	Results
1	Conjunctivitis	1: Ofloxacin 0.3% 2: Placebo	1: CIR: 86% ER: 65% 2: CIR: 72% ER: 25%	Ofloxacin ophthalmic solution 0.3% was superior to its placebo (vehicle of drug only) after 2 days of treatment in patients with conjunctivitis and positive conjunctival cultures.
2	Corneal Ulcers	1: Ofloxacin 0.3% 2: 1.5% tobramycin and 10% cefazolin	1: CSR: 82% 2: CSR: 80%	Ofloxacin ophthalmic solution 0.3% compared to combination of tobramycin and cefazolin showed better clinical success rates.

CIR: Clinical Improvement Rate; ER: microbiologic eradication rate; CSR: Clinical Success Rate (measured by complete re-epithelialization and no progression of the infiltrate for two consecutive visits)

Dosage Forms/Cost (AWP)

Name	Form	Indication	Dosing Schedule	AWP
Ofloxacin (**Ocuflox)** 0.3%	Ophthalmic Solution	Bacterial conjunctivitis Corneal ulcers	BC: 1-2 drops q 2-4 h in affected eye(s) for Day 1-2 1-2 drops QID for Day 3-7	5 ml = $148.85
Ofloxacin 0.3%	Ophthalmic Solution	Bacterial conjunctivitis Corneal ulcers	BC: 1-2 drops q 2-4 h in affected eye(s) for Day 1-2 1-2 drops QID for Day 3-7	5-10 ml range from $6.09-$70.35

Name	Form	Indication	Dosing Schedule	AWP
Ciprofloxacin (Ciloxan) 0.3%	Ophthalmic ointment	Bacterial conjunctivitis	BC: ½ inch ribbon into conjunctival sac TID for Day 1-2 BID next 5 d	3.5 g = $296.83 (brand)
Ciprofloxacin 0.3%	Ophthalmic solution	Bacterial conjunctivitis Corneal ulcer	BC: 1-2 drops into conjunctival sac q 2 h (while awake) for Day 1-2 1-2 drops q 4 h next 5 d	2.5 ml = $12.60, 5 ml = $ 16.80, 10 ml = $26.40 (g)
Moxifloxacin (Moxeza, Vigamox) 0.5%	Ophthalmic solution	Bacterial conjunctivitis	BC: 1 drop into affected eye BID x 7 d (Moxeza) 1 drop into affected eye TID x 7 d (Vigamox)	Generic 3 ml= $167.35 (g)

Safety Considerations

Look Alike-Sound Alike: Occlusal-HP, Ocufen

Summary/Conclusion

Bacterial conjunctivitis is usually self-limited but topical antibiotics can shorten the clinical course if given early. Head to head trials evaluating the efficacy of ophthalmic antibiotics for the treatment of bacterial conjunctivitis have shown that no one medication was inferior to another. Ophthalmic antibiotics are required for patients who wear contact lenses and in cases of adult inclusion conjunctivitis or hyperacute bacterial conjunctivitis. For noncontact lens wearers, preferred treatment options are erythromycin ophthalmic ointment or trimethoprim-polymyxin B drops. Systemic antibiotic therapy is necessary to treat conjunctivitis due to *Neisseria gonorrhoeae* (hyperacute bacterial conjunctivitis) and *Chlamydia trachomatis* (adult inclusion conjunctivitis).

Because of the increased incidence of *Pseudomonas*, fluoroquinolones are first-line in contact lens wearers who develop bacterial conjunctivitis and are also the therapy of choice for corneal ulcers. They are generally considered equally effective but the fourth generation fluoroquinolones gatifloxacin ophthalmic solution (Zymaxid) and moxifloxacin ophthalmic (Moxeza, Vigamox) have better activity against resistant gram-positive cocci than do second generation agents (ciprofloxacin and ofloxacin ophthalmic).

Currently, ciprofloxacin ophthalmic ointment and solution and moxifloxacin ophthalmic solution are the only two ophthalmic quinolones available on the Texas Health and Human Services Psychiatric Drug Formulary. The use of moxifloxacin (Moxeza, Vigamox) is reserved for cases of bacterial conjunctivitis where MRSA or gram-negative microorganisms are identified or suspected. Of these two, only ciprofloxacin is indicated for the treatment of corneal ulcer. Ofloxacin ophthalmic

solution is indicated for the treatment of bacterial conjunctivitis and corneal ulcer and its prices are similar to those of ciprofloxacin ophthalmic solution.

Recommendation

It is recommended to add ofloxacin ophthalmic solution to the Texas HHS Psychiatric Drug Formulary.

References

1. U.S. National Library of Medicine. Daily Med. OCUFLOX – ofloxacin solution/drops Package Insert. [Online] April 23, 2017. [Cited: Sept 22, 2023.] https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=8db221b1-32f3-f6ca-e404-71f56a860d08
2. Ofloxacin. In: Merative™ Micromedex® DRUGDEX® (electronic version). Merative, Ann Arbor, Michigan, USA. 2022. Available at: https://www-micromedexsolutions-com.ezproxy.lib.utexas.edu [Cited: Sept 22, 2023]
3. Jacobs DS. Conjunctivitis. UpToDate. Accessed 1/3/24.
4. Therapeutic Class Overview. Ophthalmic Fluoroquinolones. University of Massachusetts Medical School, 9/5/2014.

Date: January 12, 2024
Prepared by: Nathalie Nguyen, University of Texas College of Pharmacy P4 student
Reviewed by: Catherine Hall, PharmD, BCPP, BCACP

Appendix C

RSVPreF3 (Arexvy®)[3]

Classification

RSV Vaccine

Pharmacology

Induces an immune response against RSVpreF3 that protects against LRTD caused by RSV.

Indication

Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in individuals 60 years of age and older.

Dosage/Administration

A single 0.5 mL intramuscular injection. There are currently no recommendations for repeat vaccination.

Supplied as two vials, a lyophilized antigen component (a sterile white powder) that is to be reconstituted and an accompanying adjuvant suspension component (an opalescent, colorless to pale brownish sterile liquid) that will be used to reconstitute the lyophilized antigen component.

Use in Special Populations

Pregnancy: Not approved for use in patients <60 years of age. Clinical trial data found an increase in preterm births with the RSVPreF3 antigen.

Lactation: It is Unknown whether Arexvy is secreted in human milk, no data is available to assess the effects of Arexvy on breastfed infants or on milk production/excretion. Provider discretion should be used when evaluating the decision to breastfeed post-vaccination.

Pediatric Use: Not approved for use in patients <60 years of age. Evidence from an animal model strongly suggests that AREXVY would be unsafe in individuals younger than 2 years of age because of an increased risk of enhanced respiratory disease. It was not studied for safety and effectiveness in individuals 2-17 years of age.

Geriatric Use: Approved for use in individuals 60 years of age and older.

Contraindication

Do not administer AREXVY to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of AREXVY.

Component list:

- RSVPreF3 antigen
- MPL
- QS-21
- Trehalose
- Sodium Chloride
- Potassium dihydrogen phosphate
- Dipotassium phosphate
- Polysorbate
- Disodium phosphate anhydrous
- DOPC
- Cholesterol

Precautions

Preventing and managing allergic vaccine reactions: It is recommended that appropriate medical supervision and treatment be available to manage possible anaphylactic reactions following administration of Arexvy.

Syncope: It is recommended to take appropriate measures to avoid injury from fainting due to possible risk of Syncope in association with the administration of injectable vaccines.

Altered immunocompetence: In immunocompromised persons, Arexvy may produce a diminished immune response.

Adverse Effects

The most common adverse effects were identified as injection site pain (60.9%), fatigue (33.6%), myalgia (28.9%), headache (27.2%), and arthralgia (18.1%).

In study 1, serious adverse events with onset within 6 months following vaccination were reported at similar rates in participants who received AREXVY (4.2%) or placebo (4.0%). Serious events of atrial fibrillation were reported in 13 participants who received AREXVY and 15 participants who received placebo within 6 months after vaccination. The currently available information on the atrial fibrillation is insufficient to determine a causal relationship to the vaccine.

Serious adverse events were reported in 3 patients in study 2 and study 3; Guillain-Barré syndrome beginning 9 days after AREXVY vaccination was reported in a participant enrolled in a study site in Japan; Acute disseminated encephalomyelitis was reported in 2 participants enrolled in a study site in South Africa; the onset of the symptoms was 7- and 22-days post vaccination, respectively. One event was fatal and the other non-fatal. These participants received AREXVY concomitantly with FLUARIX QUADRIVALENT.

Monitoring

Immediate supervision after administration of the vaccination is recommended due to potential risk of allergic vaccine reactions and syncope. Any adverse events believed

to have resulted from Arexvy should be reported to the Vaccine Adverse Event Reporting System.

Interactions

Immunosuppressant agents: Immunosuppressant agents may diminish the immunological response to Arexvy. Immunocompromised participants were excluded from the study.

No evidence was found to indicate reduced efficacy when given in combination with Fluarix quadrivalent. In Study 3, an open-label, Phase 3, clinical study conducted in New Zealand, Panama, and South Africa, participants 60 years of age and older received 1 dose of AREXVY and FLUARIX QUADRIVALENT at Month 0 (n = 442) or 1 dose of FLUARIX QUADRIVALENT at Month 0 followed by a dose of AREXVY at Month 1 (n = 443).

There was no evidence for interference in the immune response to any of the antigens contained in both concomitantly administered vaccines. The criteria for non-inferiority of the immune responses in the control versus "co-administration" group were met as the 2-sided 95% confidence interval upper limits on the group geometric mean titer ratios were below 1.5 for the RSV-A neutralizing antibodies and haemagglutinin inhibition antibodies against the strains Flu A/Hong Kong/H3N2, Flu A/Victoria/H1N1, Flu B/Phuket/Yamagata, and Flu B/Washington/Victoria.

There is no data available on the concomitant administration with other vaccines.

Efficacy

Compared with placebo, Arexvy significantly reduced the risk of developing RSV-associated LRTD by 82.6% (96.95% CI [57.9, 94.1]) in participants 60 years of age and older, which met the pre-specified success criterion for the primary study objective. The median duration of efficacy follow-up was 6.7 months.

Table 2. Efficacy Analysis: First Respiratory Syncytial Virus-associated Lower Respiratory Tract Disease Overall, by Age and Co-morbidity Subgroups in Study 1[a] (Modified Exposed Set)

	AREXVY			Placebo			
Subgroup	N	n	Incidence Rate per 1,000 Person-Years	N	n	Incidence Rate per 1,000 Person-Years	% Efficacy (CI)[b]
Overall (≥60 years)	12,466	7	1.0	12,494	40	5.8	82.6 (57.9, 94.1)
60 to 69 years	6,963	4	1.0	6,979	21	5.5	81.0 (43.6, 95.3)
70 to 79 years	4,487	1	0.4	4,487	16	6.5	93.8 (60.2, 99.9)
Participants with at least 1 comorbidity of interest	4,937	1	0.4	4,861	18	6.6	94.6 (65.9, 99.9)

(The above table is from the Arexvy Package insert)

One case of severe RSV-associated LRTD in the group that received Arexvy and 17 cases in the group that received placebo were reported, amongst which 2 cases required supportive therapy. Compared with placebo, Arexvy significantly reduced the risk of developing severe RSV-associated LRTD by 94.1% (95% CI [62.4, 99.9]) in participants 60 years of age and older.

Dosage Forms/Cost (AWP)[1]

IM, Single dose vial to be reconstituted with supplied diluent. Packaged in carton of 10 doses.

Pricing from Morris and Dickson: **$**336.00/dose, $3360.00/box of 10 doses

Safety Considerations

Look Alike-Sound Alike: Abrysvo (RSVpreF)

Summary/Conclusion

Arexvy is FDA approved for prevention of RSV-LRTD in adults ≥ 60-year-old. The data from the clinical trials is robust and targets an appropriate population for RSV-LRTD and would be applicable to numerous state hospital patients. The side effect profile is favorable and is one of two new novel vaccinations against RSV-LRTD.

Recommendation

Add both Arexvy and Abrysvo to the formulary. The prevention of RSV-LRTD in the State Hospital system would prove majorly beneficial. Despite Arexvy's more limited target population it would still be beneficial to have a secondary, cheaper, option

should Abrysvo encounter supply issues or the additional indication of vaccination in pregnant individuals at 32-36 weeks gestational age is not needed.

Arexvy vs Abrysvo at a Glance

Medication	Arexvy (RSVPreF3)	Abrysvo (RSVpreF)
Cost	$336.00/dose[1]	$354.00/dose[2]
Population	≥ 60-year-old[3]	≥ 60-year-old and pregnant individuals at 32-36 weeks gestational age[4]
Route and form	IM, single dose vial to be reconstituted[3]	IM, single dose vial to be reconstituted[4]
Storage	2-8°C[3]	2-8°C[4]
Effectiveness	82.6% efficacy in reducing the risk of developing RSV-LRTD in patients ≥ 60-year-old.[3]	76.5% Vaccine Efficacy against severe RSV-LRTED in Infants from birth through 6 months of age.[4] 85.7% vaccine effectiveness in preventing RSV-LRTD with ≥3 symptoms in patients ≥ 60-year-old.[4]

References

1. Morris & Dickson. (12/18/2023) Arexvy product information. https://www.mdwebportal.net/mdwp/ProductInfo.aspx?id=%20J5eMCrNe8yLXTHzzCMKFwwXYXrRzJneHeUdXauNfCsw=&item=296996
2. Morris & Dickson. (12/18/2023) Abrysvo product information. https://www.mdwebportal.net/mdwp/ProductInfo.aspx?id=%20J5eMCrNe8yLXTHzzCMKFwwXYXrRzJneHeUdXauNfCsw=&item=296566
3. Arexvy (RSVpreF3) [package insert]. Durham, NC: GlaxoSmithKline Biologicals; 2023
4. Abrysvo (RSVPreF) [package insert]. New York, NY: Pfizer Inc; 2023

Date: 12/18/2023
Prepared by: Tyler Stromberg PharmD
Reviewed by: Kasey Leggette Peña, PharmD, BCPP

Appendix D

RSVpreF (Abrysvo®)[4]

Classification

RSV Vaccine

Pharmacology

Active Immunization: ABRYSVO induces an immune response against RSVpreF that protects against lower respiratory tract disease caused by RSV.

Passive Immunization: Antibodies to RSV antigens from individuals vaccinated in pregnancy are transferred transplacentally to protect infants younger than 6 months of age against LRTD and severe LRTD caused by RSV.

Indication

Immunization of pregnant individuals: Immunization of pregnant individuals at 32-36 weeks gestational age for the prevention of RSV-LRTD and severe RSV-LRTD in infants from birth through 6 months of age.

Immunization of individuals ≥ 60-year-old: Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in individuals 60 years of age and older.

Dosage/Administration

A single 0.5 mL intramuscular injection. There are currently no recommendations for repeat vaccination.

Supplied as two vials, a lyophilized antigen component (a sterile white powder) that is to be reconstituted and an accompanying prefilled syringe containing sterile water diluent component. A Vial adapter is included to assist with reconstitution.

Use in Special Populations

Pregnancy: A voluntary pregnancy exposure registry has been established that collects data from either patients or providers for patients that have been exposed to Abrysvo while pregnant. 1-800-616-3791 to enroll in or obtain information about the registry.

Study 1 enrolled 7,358 pregnant individuals who were randomized 1:1 and received Abrysvo or placebo. This revealed no evidence for vaccine-associated increase in the risk of congenital anomalies or fetal deaths.

Study 2 evaluated 115 pregnant individuals who received Abrysvo and 117 who received placebo. A numerical imbalance in preterm births in Abrysvo recipients was observed compared to placebo recipients in these two clinical studies.

Abrysvo has not been studied in pregnant individuals less than 24 weeks gestational age, and those at increased risk for preterm birth.

Lactation: It is unknown whether Abrysvo is secreted in human milk, no data is available to assess the effects of Abrysvo on breastfed infants or on milk production/excretion. Provider discretion should be used when evaluating the decision to breastfeed post-vaccination.

Pediatric Use: The safety and effectiveness of Abrysvo to prevent RSV LRTD and severe RSV LRTD in infants born to individuals vaccinated at younger than 10 years of age have not been established.

The safety and effectiveness of Abrysvo to prevent RSV LRTD in non-pregnant individuals younger than 18 years of age via active immunization have not been established.

Geriatric Use: Approved for use in individuals 60 years of age and older.

Contraindication

Do not administer ABRYSVO to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of ABRYSVO.

Component list:

- RSV stabilized prefusion F proteins
- Tromethamine
- Tromethamine hydrochloride
- Sucrose
- Mannitol
- Polysorbate 80
- Sodium chloride

Precautions

Potential risk of preterm birth: There is currently insufficient evidence to establish or exclude a causal relationship between preterm birth and Abrysvo administration. There was an observed numerical imbalance of preterm births towards Abrysvo when compared to placebo. To avoid any potential risk of preterm birth, administration of Abrysvo is limited to individuals at 32 and through 36 weeks gestational age.

Preventing and managing allergic vaccine reactions: It is recommended that appropriate medical supervision and treatment be available to manage possible anaphylactic reactions following administration of Abrysvo.

Syncope: It is recommended to take appropriate measures to avoid injury from fainting due to possible risk of Syncope in association with the administration of injectable vaccines.

Altered immunocompetence: In immunocompromised persons Abrysvo may produce a diminished immune response.

Limitations of vaccine effectiveness: After vaccination, Abrysvo may not protect all vaccine recipients.

Adverse Effects

In pregnant individuals, the most commonly reported (≥10%) adverse reactions were pain at the injection site (40.6%), headache (31.0%), muscle pain (26.5%), and nausea (20.0%). Most of the serious adverse events in maternal participants were related to pregnancy complications and occurred after the 1-month period following vaccination.

In Study 1, 3,682 pregnant individuals received Abrysvo and 3,676 received placebo at 24 through 36 weeks' gestation. The infant safety population included 3,568 and 3,558 infants born to individuals in the Abrysvo or placebo group, respectively. Among the infants born to individuals in the Abrysvo group and in the placebo group, 202 (5.7%) and 169 (4.7%), respectively, had adverse events of preterm birth and 180 (5.0%) and 220 (6.2%), respectively, had reported congenital malformations or anomalies. There were 10 (0.3%) fetal deaths in the Abrysvo group and 8 (0.2%) in the placebo group.

Table 3 Select Pregnancy-related Serious Adverse Events in Study 1 in Pregnant Individuals Occurring at any Time Following Vaccination[a]

Serious Adverse Reaction	ABRYSVO N=3,682 n (%)	95% CI	Placebo N=3,675 n (%)	95% CI
All Maternal SAEs	598 (16.2)	(15.1, 17.5)	558 (15.2)	(14.0, 16.4)
Pre-eclampsia	68 (1.8)	(1.4, 2.3)	53 (1.4)	(1.1, 1.9)
Gestational hypertension	41 (1.1)	(0.8, 1.5)	38 (1.0)	(0.7, 1.4)
Premature rupture of membranes	15 (0.4)	(0.2, 0.7)	16 (0.4)	(0.2, 0.7)
Preterm premature rupture of membranes	15 (0.4)	(0.2, 0.7)	10 (0.3)	(0.1, 0.5)
Hypertension	13 (0.4)	(0.2, 0.6)	6 (0.2)	(0.1, 0.4)
Maternal death[b]	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Fetal Death[c]	10 (0.3)	(0.1, 0.5)	8 (0.2)	(0.1, 0.4)

[a] Includes all SAEs from vaccination to 6 months post-delivery (up to approximately 10 months, depending on the gestational age at the time of vaccination). In Study 1, eclampsia occurred in 5 participants (3 in the ABRYSVO group and 2 in the placebo group) and HELLP syndrome occurred in 5 participants (2 in the ABRYSVO group and 3 in the placebo group).

[b] There was one maternal death in the ABRYSVO group due to postpartum hemorrhage that was not likely to be associated with vaccination.

[c] A total of 18 intrauterine deaths were reported for the index pregnancy: 10 intrauterine deaths in the ABRYSVO group (0.3%) and 8 intrauterine deaths in the placebo group (0.2%). The intrauterine deaths represented various clinical conditions and presentations resulting in fetal demise without clear evidence of a common pathophysiology.

(The above table is from the Abrysvo package insert)

In individuals 60 years of age and older, the most commonly reported (≥10%) adverse reactions were fatigue (15.5%), headache (12.8%), pain at the injection site

(10.5%), and muscle pain (10.1%). Within 30 days after vaccination, atrial fibrillation was reported in 10 vaccine recipients and 4 placebo recipients (of which 4 in the Abrysvo group and 3 in the placebo group were serious adverse events); the onset of symptoms was 18 to 30 days post vaccination. The currently available information on atrial fibrillation is insufficient to determine a causal relationship to the vaccine. In Study 3, Severe Adverse Events were reported by 2.3% of participants in both the Abrysvo and placebo groups. Three participants in the Abrysvo group had SAEs which were assessed as possibly related to study vaccination: Guillain-Barre Syndrome reported 7 days after vaccination, Miller Fisher Syndrome reported 8 days after vaccination, and hypersensitivity reported 8 hours after vaccination.

Monitoring

Immediate supervision after administration of the vaccination is recommended due to potential risk of allergic vaccine reactions and syncope. Any adverse events believed to have resulted from Abrysvo should be reported to the Vaccine Adverse Event Reporting System.

Interactions

Immunosuppressant agents: Immunosuppressant agents may diminish the immunological response to Abrysvo.

Tdap: Abrysvo may diminish the therapeutic effect of Tdap vaccination when administered together. Specifically, concentrations of acellular pertussis antigens (pertussis toxin [PT], filamentous hemagglutinin (FHA), and pertactin [PRN]) were lower when Abrysvo was administered concomitantly with Tdap compared to Tdap alone.

Efficacy

In pregnant individuals 32-36 weeks of gestational age: It was found that Vaccine Efficacy results met the statistical criterion for success which was defined as a lower bound confidence interval >20% for reducing severe RSV-LRTD. This result held true through all points assessed to 180 days. Statistical criterion for success were not met for reducing RSV-LRTD but clinically meaningful efficacy was observed after 90 days.

Table 6 Vaccine Efficacy of ABRYSVO Against Severe LRTD Caused by RSV - Infants From Birth Through 6 Months of Age by Active Immunization of Pregnant Individuals (Study 1)[a]

Time Period	ABRYSVO Number of Cases N=3,495[b]	PLACEBO Number of Cases N=3,480[b]	VE (%) (CI)[c]
90 days	6	33	81.8 (40.6, 96.3)
120 days	12	46	73.9 (45.6, 88.8)
150 days	16	55	70.9 (44.5, 85.9)
180 days	19	62	69.4 (44.3, 84.1)

CI - confidence interval; N – number of participants; RSV – respiratory syncytial virus; VE - vaccine efficacy
[a] The prespecified success criterion was met for this endpoint evaluation
[b] Evaluable efficacy population
[c] 99.5% CI at 90 days; 97.58% CI at later intervals

Table 7 Vaccine Efficacy of ABRYSVO Against LRTD Caused by RSV - Infants From Birth Through 6 Months of Age by Active Immunization of Pregnant Individuals (Study 1)[a]

Time Period	ABRYSVO Number of Cases N=3,495[b]	PLACEBO Number of Cases N=3,480[b]	VE (%) (CI)[c]
90 days	24	56	57.1 (14.7, 79.8)
120 days	35	81	56.8 (31.2, 73.5)
150 days	47	99	52.5 (28.7, 68.9)
180 days	57	117	51.3 (29.4, 66.8)

CI - confidence interval; N – number of participants; RSV – respiratory syncytial virus; VE - vaccine efficacy
[a] The prespecified success criterion (a CI lower bound >20%) was not met for this endpoint evaluation at 90 days
[b] Evaluable efficacy population
[c] 99.5% CI at 90 days; 97.58% CI at later intervals

(The above table is from the Abrysvo package insert)

In individuals ≥ 60-year-old: Participants were randomized (1:1) to receive Abrysvo (n=17,197) or placebo (n=17,186). Randomization was stratified by age, 60-69 years (n=21,499, 63%), 70-79 years (n=10,948, 32%), and ≥80 years (n=1,934, 6%). Healthy adults and adults with stable chronic diseases were included. Among enrolled participants 15% had stable chronic cardiopulmonary conditions such as chronic obstructive pulmonary disease (COPD), asthma, or congestive heart failure (CHF).

Vaccine efficacy (VE), against RSV-LRTD, defined as the relative risk reduction of first episode of RSV-LRTD in the Abrysvo group compared to the placebo group in the first RSV season, was assessed. Pre-specified success criteria were met for prevention of RSV-LRTD with ≥2 symptoms and prevention of RSV-LRTD with ≥3 symptoms.

The median duration of follow-up for efficacy was 7 months. Participants are planned to be followed for up to two RSV seasons, approximately 25 months.

Table 11 Vaccine Efficacy of ABRYSVO Against RSV-LRTD - Individuals 60 years of Age and Older (Study 3)[a]

Efficacy Endpoint	ABRYSVO N=16,306[b] n	Placebo N=16,308[b] n	VE (%) (96.66% CI)
First episode of RSV-associated lower respiratory tract disease with ≥2 symptoms	11	33	66.7 (28.8, 85.8)
First episode of RSV-associated lower respiratory tract disease with ≥3 symptoms	2	14	85.7 (32.0, 98.7)

CI – confidence interval; N – number of participants; n = number of cases; RSV – respiratory syncytial virus; VE – vaccine efficacy (VE based on case count ratio is calculated as 1-(P/[1-P]), where P is the number of RSVpreF cases divided by the total number of cases)

[a] NCT05035212

[b] Evaluable efficacy population

(The above table is from the Abrysvo package insert)

Dosage Forms/Cost (AWP)

IM, Single dose vial to be reconstituted with supplied diluent and vial adapter as a kit. Supplied in cartons of 1, 5, and 10 kits.

Pricing from Morris and Dickson: $354.00/dose

Safety Considerations

Look Alike-Sound Alike: Arexvy (RSVPreF3)

Summary/Conclusion

Abrysvo is FDA approved for prevention of RSV-LRTD in adults ≥ 60-year-old and immunization of pregnant individuals for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age. The data from the clinical trials is robust and targets an appropriate population for RSV-LRTD and would be applicable to numerous state hospital patients with the indication for adults ≥ 60-year-old as well as a potentially useful extra indication of immunization of pregnant individuals in the 32-36 week gestational period. The side effect profile is favorable and is one of two new novel vaccinations against RSV-LRTD. A potential downside is the increased price when compared to Arexvy.

Recommendation

Add both Arexvy and Abrysvo to the formulary. The prevention of RSV-LRTD in the State Hospital system would prove majorly beneficial. Despite Arexvy's more limited target population it would still be beneficial to have a secondary, cheaper, option should Abrysvo encounter supply issues or the additional indication of vaccination in pregnant individuals at 32-36 weeks gestational age is not needed.

Arexvy vs Abrysvo at a Glance

Medication	Arexvy (RSVPreF3)	Abrysvo (RSVpreF)
Cost	$336.00/dose[1]	$354.00/dose[2]
Population	≥ 60-year-old[3]	≥ 60-year-old and pregnant individuals at 32-36 weeks gestational age[4]
Route and form	IM, single dose vial to be reconstituted[3]	IM, single dose vial to be reconstituted[4]
Storage	2-8°C[3]	2-8°C[4]
Effectiveness	82.6% efficacy in reducing the risk of developing RSV-LRTD in patients ≥ 60-year-old.[3]	76.5% Vaccine Efficacy against severe RSV-LRTED in Infants from birth through 6 months of age.[4] 85.7% vaccine effectiveness in preventing RSV-LRTD with ≥3 symptoms in patients ≥ 60-year-old.[4]

References

1. Morris & Dickson. (12/18/2023) Arexvy product information. https://www.mdwebportal.net/mdwp/ProductInfo.aspx?id=%20J5eMCrNe8yLXTHzzCMKFwwXYXrRzJneHeUdXauNfCsw=&item=296996
2. Morris & Dickson. (12/18/2023) Abrysvo product information. https://www.mdwebportal.net/mdwp/ProductInfo.aspx?id=%20J5eMCrNe8yLXTHzzCMKFwwXYXrRzJneHeUdXauNfCsw=&item=296566
3. Arexvy (RSVpreF3) [package insert]. Durham, NC: GlaxoSmithKline Biologicals; 2023
4. Abrysvo (RSVPreF) [package insert]. New York, NY: Pfizer Inc; 2023

Date: 12/18/2023
Prepared by: Tyler Stromberg PharmD
Reviewed by: Kasey Leggette Peña, PharmD, BCPP

Appendix E

Viloxazine Extended Release (Qelbree®)

Classification

Norepinephrine Reuptake Inhibitor, Selective

Pharmacology

The therapeutic effects of this novel non stimulant medication (viloxazine ER, Qelbree) are thought to be owing to its action as a norepinephrine reuptake inhibitor; however, contemporary preclinical studies indicate that it may also act on serotonergic signaling the brain.

Indication

Viloxazine ER is a selective norepinephrine reuptake inhibitor indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Steady State reached after two days of once-daily administration. Bioavailability ~ 88%. Median Time to peak plasma concentration (Tmax) was approximately 5 hrs (range 3-9hr) Effect of Food: Administration with a high-fat meal (800 to 1000 calories) decrease the Cmax and AUC by 9% and 8% respectively. Tmax increased by about 2 hours after administration. Opening and sprinkling the contents on applesauce decrease Cmax and AUC by 10% and 5% respectively.
Distribution	72-82% plasma protein bound
Elimination	The mean half-life (t1/2): 7.02hr
Metabolism	Metabolized by CYP2D6, UGT1A9, and UGT2B15. The major metabolite is 5-hydroxy-viloxazine glucuronide
Excretion	90% renal excretion, <1% feces

Dosage/Administration

Dosing Considerations

- Pediatric patients 6 to 11 years of age: Recommended starting dosage is 100 mg once daily. May titrate in increments of 100 mg weekly to the maximum recommended dosage of 400 mg once daily.
- Pediatric patients 12 to 17 years of age: Recommended starting dosage is 200 mg once daily. May titrate after 1 week, by an increment of 200mg, to the maximum recommended dosage of 400 mg once daily.

- Adult patients: Recommended starting dosage is 200 mg once daily. May titrate in increments of 200 mg weekly, to maximum recommended dosage of 600 mg once daily.
- Renal Impairment: Adult
    - Mild to moderate impairment (eGFR 30 to 89 mL/minute/1.73 m ^{2}): No dosage adjustment necessary.
    - Severe impairment (eGFR <30 mL/minute/1.73 m^2): Oral: Initial dose: 100 mg once daily; may titrate by 50 to 100 mg increments at weekly intervals based on response and tolerability; maximum daily dose: 200 mg/day.
- Renal Impairment: Pediatric
    - Mild to moderate impairment (eGFR 30 to 89 mL/minute/1.73 m^2): No dosage adjustment necessary.
    - Severe impairment (eGFR <30 ml/minute/1.73 m^2): Oral: Initial dose: 100 mg once daily; may titrate in 50 to 100 mg increments at weekly intervals based on response and tolerability; maximum daily dose: 200 mg/day.

Stability and Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Capsules may be opened and the entire contents sprinkled into applesauce or pudding. Capsules may be administered orally with or without food.

Use in Special Population

Hepatic Impairment: No dose adjustments required.

Renal impairment: See above dosing.

Geriatric Patient: Clinical Trials of Qelbree in the treatment of ADHD did not include sufficient numbers of patient aged 65 and older to determine whether or not they respond differently from younger patients.

Pregnancy: Based on findings from animal reproduction studies, viloxazine may cause maternal harm when used during pregnancy. Consider discontinuing of viloxazine if pregnancy occurs during treatment.

Lactation: It is not known if viloxazine is present in breast milk.

Contraindication

- Concomitant administration of monoamine oxidase inhibitors (MAOI), or dosing within 14 days after discontinuing an MAOI.
- Concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.

Precautions

Suicidal thoughts and Behaviors: Higher rates of suicidal thoughts and behaviors were reported in pediatric and adult patients with ADHD treated with Qelbree than in patients treated with placebo. Among 1019 pediatric patients exposed to Qelbree 100 mg to 400 mg in short-term trials, a total of nine patients (0.9%) reported suicidal ideation (N=6), behavior (N=1) or both (N=2). An additional patient treated with Qelbree reported suicidal behavior during the clinical trials but did not report it on the C-SSRS. Among 463 patients treated with placebo in these studies, two patients (0.4%) reported suicidal ideation on the C-SSRS. No patients treated with placebo reported suicidal behavior. No completed suicides occurred in these trials. Among 189 adults treated with Qelbree, a total of three patients (1.6%) reported suicidal ideation on the C-SSRS, versus 0 of 183 adults treated with placebo. No adults treated with either Qelbree or placebo reported suicidal behavior on the C-SSRS in the study. No attempted or completed suicides occurred in the trial. Patients treated with Qelbree had higher rates of insomnia and irritability. Although a causal link between the emergence of insomnia and irritability and the emergence of suicidal impulses has not been established, there is a concern that these and other symptoms such as depressed mood, anxiety, agitation, akathisia, mania, hypomania, panic attacks, impulsive behavior, and aggression may represent precursors to emerging suicidal ideation or behavior. Thus, patients being treated with Qelbree should be observed for the emergence of precursor symptoms. Closely monitor all Qelbree-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Consider changing the therapeutic regimen, including possibly discontinuing Qelbree, in patients who are experiencing emergent suicidal thoughts and behaviors or symptoms that might be precursors to emerging suicidal ideation or behavior, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.

Blood Pressure and Heart Rate Increases: Qelbree can cause an increase in heart rate and diastolic blood pressure.

Pediatric Patients: In a clinical study in pediatric patients 6 to 11 years of age, 34/154 (22%) of patients treated with Qelbree 100 mg daily had a ≥20 beat per minute (bpm) increase in heart rate at any time point in the clinical trial, compared to 15/159 (9%) of patients who received placebo. This finding was observed in 84/268 (31%) who received the 200 mg daily dosage, compared to 39/262 (15%) of patients in the placebo group, and in 28/100 (28%) of patients who received the 400 mg daily dosage, compared to 24/103 (23%) of patients who received placebo.

In a clinical study in pediatric patients 12 to 17 years of age, 22/99 (22%) of patients treated with Qelbree 200 mg daily had a ≥20 bpm increase in heart rate at any time point in the clinical trial, compared to 15/104 (14%) of patients who received placebo. This finding was observed in 69/205 (34%) who received the 400 mg daily

dosage, compared to 35/201 (17%) of patients in the placebo group. In pediatric patients 12 to 17 years of age, 52/205 (25%) of patients treated with Qelbree 400 mg daily had a ≥ 15 mmHg increase in diastolic blood pressure at any time in the clinical trial, compared to 26/201 (13%) of patients in the placebo group.

Adult Patients: In a clinical study in adult patients (18 to 60 years of age), 52/178 (29%) of patients treated daily with Qelbree (200 mg to 600 mg) had a ≥20 bpm increase in heart rate at any time point in the clinical trial, compared to 23/181 (13%) of patients who received placebo. Of patients treated daily with Qelbree (200 to 600 mg), 23/178 (13%) had a ≥ 15 mmHg increase in diastolic blood pressure at any time in the clinical trial, compared to 16/181 (9%) of patients in the placebo group. Assess heart rate and blood pressure prior to initiating treatment with Qelbree, following increases in dosage, and periodically while on therapy.

Activation of Mania or Hypomania: Noradrenergic drugs may induce a manic or mixed episode in patients with bipolar disorder. Prior to staring treatment, screen patients to determine if they are at risk for bipolar disorder.

Somnolence and Fatigue: Qelbree can cause somnolence and fatigue. In the short-term clinical trials of pediatric patients, somnolence was 16% in the Qelbree group and 4% in the placebo group. Fatigue was reported 6% to 2%, respectively. In adults, Somnolence was reported 6% vs 2% and fatigue 12% vs 3%.

Black Box Warning

Suicidal Thoughts and Behaviors: In clinical trials, higher rates of suicidal thoughts and behavior were reported in patients treated with Qelbree than in patients treated with placebo. Closely monitor for worsening and emergence of suicidal thoughts and behaviors.

Adverse Effects

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified.

- >10%:
  - Cardiovascular: Increased diastolic blood pressure (13% to 25%), increased heart rate (22% to 34%; tachycardia: 4% [adults])
  - Gastrointestinal: Nausea (4% to 12%)
  - Nervous system: Drowsiness (including lethargy and sedated state; 6% to 19%), fatigue (4% to 12%), headache (including migraine; 10% to 17%), insomnia (children and adolescents: 2% to 5%; adults: 23%)
- 1% to 10%:
  - Gastrointestinal: Abdominal pain (children and adolescents: 6% to 7%), constipation (adults: 6%), decreased appetite (5% to 10%), gastroesophageal reflux disease (adults: 2%), vomiting (3% to 6%), xerostomia (adults: 10%)
  - Nervous system: Dizziness (adults: 4%), irritability (2% to 5%), suicidal ideation (≤2%)
  - Respiratory: Upper respiratory tract infection (including nasopharyngitis, pharyngitis, sinusitis; children and adolescents: 7% to 8%)
  - Miscellaneous: Fever (children and adolescents: 1% to 3%)
- <1%:
  - Nervous system: Suicidal tendencies
  - Frequency not defined: Endocrine & metabolic: Weight loss (adolescents)

Monitoring

Prior to initiation of viloxazine, conduct a physical exam to assess for cardiac disease and assessment of medical history and family history of sudden death or ventricular arrhythmias; patients should receive furth evaluation if findings suggest cardiac disease (ECG or echocardiogram); promptly conduct cardiac evaluation in patients who develop exertional chest pain, unexplained syncope, or any other symptoms of cardiac disease during treatment.

Screen patients for personal or family history of suicide, bipolar disorder, and depression before starting viloxazine. During the initial few months of therapy or at times of dose changes monitor for the emergence of suicidal ideation, depression, irritability, agitation, unusual changes in behavior, anxiety, panic attacks, insomnia, impulsivity, aggressiveness, hostility, akathisia, psychosis, hypomania, and mania.

Monitor blood pressure and pulse at baseline, following dose increases, and periodically during treatment.

Monitor liver enzyme, serum creatine/GFR.

Interactions

- Agomelatine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Agomelatine. *Risk X: Avoid combination*
- Alosetron: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk X: Avoid combination*
- ALPRAZolam: CYP3A4 Inhibitors (Weak) may increase the serum concentration of ALPRAZolam. *Risk C: Monitor therapy*
- Anagrelide: CYP1A2 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Anagrelide. CYP1A2 Inhibitors (Strong) may increase the serum concentration of Anagrelide. *Risk C: Monitor therapy*
- Asenapine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Asenapine. *Risk C: Monitor therapy*
- Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. Management: Consider alternatives to strong CYP1A2 inhibitors during therapy with bendamustine due to the potential for increased bendamustine plasma concentrations and increased bendamustine toxicity. *Risk D: Consider therapy modification*
- Bromazepam: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bromazepam. *Risk C: Monitor therapy*
- Caffeine and Caffeine Containing Products: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Caffeine and Caffeine Containing Products. *Risk C: Monitor therapy*
- CarBAMazepine: CYP3A4 Inhibitors (Weak) may increase the serum concentration of CarBAMazepine. *Risk C: Monitor therapy*
- ClomiPRAMINE: CYP1A2 Inhibitors (Strong) may increase the serum concentration of ClomiPRAMINE. *Risk C: Monitor therapy*
- CloZAPine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of CloZAPine. Management: Reduce the dose of clozapine to one-third of the original dose when adding a strong CYP1A2 inhibitor and monitor patient response closely. Return to the original clozapine dose when the strong CYP1A2 inhibitor is discontinued. *Risk D: Consider therapy modification*
- CycloSPORINE (Systemic): CYP3A4 Inhibitors (Weak) may increase the serum concentration of CycloSPORINE (Systemic). *Risk C: Monitor therapy*
- Dofetilide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Dofetilide. *Risk C: Monitor therapy*
- DULoxetine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of DULoxetine. *Risk X: Avoid combination*
- Fenfluramine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Fenfluramine. Management: Limit fenfluramine dose to 20 mg/day without concurrent stiripentol or to 17 mg/day with concomitant stiripentol and clobazam when used with a strong CYP1A2 inhibitor. *Risk D: Consider therapy modification*

- Fezolinetant: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Fezolinetant. *Risk X: Avoid combination*
- Finerenone: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Finerenone. *Risk C: Monitor therapy*
- Flibanserin: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Flibanserin. *Risk C: Monitor therapy*
- Fosphenytoin-Phenytoin: Viloxazine may increase the serum concentration of Fosphenytoin-Phenytoin. *Risk C: Monitor therapy*
- Iobenguane Radiopharmaceutical Products: Selective Norepinephrine Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane Radiopharmaceutical Products. Management: Discontinue all drugs that may inhibit or interfere with catecholamine transport or uptake for at least 5 biological half-lives before iobenguane administration. Do not administer these drugs until at least 7 days after each iobenguane dose. *Risk X: Avoid combination*
- Ixabepilone: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Ixabepilone. *Risk C: Monitor therapy*
- Lemborexant: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Lemborexant. Management: The maximum recommended dosage of lemborexant is 5 mg, no more than once per night, when coadministered with weak CYP3A4 inhibitors. *Risk D: Consider therapy modification*
- Levobupivacaine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Levobupivacaine. *Risk C: Monitor therapy*
- Lidocaine (Systemic): CYP1A2 Inhibitors (Strong) may increase the serum concentration of Lidocaine (Systemic). *Risk C: Monitor therapy*
- Lomitapide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Lomitapide. Management: Patients on lomitapide 5 mg/day may continue that dose. Patients taking lomitapide 10 mg/day or more should decrease the lomitapide dose by half. The lomitapide dose may then be titrated up to a max adult dose of 30 mg/day. *Risk D: Consider therapy modification*
- Lonafarnib: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Lonafarnib. Management: Avoid concurrent use of lonafarnib with weak CYP3A4 inhibitors. If concurrent use is unavoidable, reduce the lonafarnib dose to or continue at a dose of 115 mg/square meter. Monitor for evidence of arrhythmia, syncope, palpitations, or similar effects. *Risk D: Consider therapy modification*
- Melatonin: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Melatonin. *Risk X: Avoid combination*
- Mexiletine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Mexiletine. *Risk C: Monitor therapy*
- Midazolam: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Midazolam. *Risk C: Monitor therapy*

- Monoamine Oxidase Inhibitors: Viloxazine may enhance the hypertensive effect of Monoamine Oxidase Inhibitors. *Risk X: Avoid combination*
- NiMODipine: CYP3A4 Inhibitors (Weak) may increase the serum concentration of NiMODipine. *Risk C: Monitor therapy*
- OLANZapine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of OLANZapine. *Risk C: Monitor therapy*
- Ozanimod: May enhance the hypertensive effect of Selective Norepinephrine Reuptake Inhibitors. *Risk C: Monitor therapy*
- Pentoxifylline: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Pentoxifylline. *Risk C: Monitor therapy*
- Pimozide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Pimozide. *Risk X: Avoid combination*
- Pirfenidone: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Pirfenidone. Management: Avoid concomitant use of pirfenidone and strong CYP1A2 inhibitors whenever possible. If combined, decrease the pirfenidone dose to 801 mg per day (267 mg three times daily) and monitor for increased pirfenidone toxicities. *Risk D: Consider therapy modification*
- Pomalidomide: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Pomalidomide. Management: Avoid when possible. If coadministration is necessary, reduce the pomalidomide dose to 2 mg and monitor for increased pomalidomide effects/toxicities. *Risk D: Consider therapy modification*
- Propranolol: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Propranolol. Management: Use a lower initial propranolol dose and be more cautious during propranolol dose titration when combined with strong CYP1A2 inhibitors. *Risk D: Consider therapy modification*
- Ramelteon: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Ramelteon. *Risk X: Avoid combination*
- Ramosetron: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Ramosetron. *Risk C: Monitor therapy*
- Riluzole: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Riluzole. *Risk C: Monitor therapy*
- Roflumilast-Containing Products: Viloxazine may increase serum concentrations of the active metabolite(s) of Roflumilast-Containing Products. Viloxazine may increase the serum concentration of Roflumilast-Containing Products. *Risk C: Monitor therapy*
- ROPINIRole: CYP1A2 Inhibitors (Strong) may increase the serum concentration of ROPINIRole. *Risk C: Monitor therapy*
- ROPivacaine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of ROPivacaine. *Risk C: Monitor therapy*
- Simvastatin: CYP3A4 Inhibitors (Weak) may increase serum concentrations of the active metabolite(s) of Simvastatin. CYP3A4 Inhibitors (Weak) may increase the serum concentration of Simvastatin. *Risk C: Monitor therapy*

- Sirolimus (Conventional): CYP3A4 Inhibitors (Weak) may increase the serum concentration of Sirolimus (Conventional). *Risk C: Monitor therapy*
- Sirolimus (Protein Bound): CYP3A4 Inhibitors (Weak) may increase the serum concentration of Sirolimus (Protein Bound). Management: Reduce the dose of protein bound sirolimus to 56 mg/m^2 when used concomitantly with a weak CYP3A4 inhibitor. *Risk D: Consider therapy modification*
- Tacrolimus (Systemic): CYP3A4 Inhibitors (Weak) may increase the serum concentration of Tacrolimus (Systemic). *Risk C: Monitor therapy*
- Tasimelteon: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Tasimelteon. *Risk X: Avoid combination*
- Theophylline Derivatives: Viloxazine may increase the serum concentration of Theophylline Derivatives. *Risk X: Avoid combination*
- Thioridazine: CYP2D6 Inhibitors (Weak) may increase the serum concentration of Thioridazine. Management: Consider avoiding concomitant use of thioridazine and weak CYP2D6 inhibitors. If combined, monitor closely for QTc interval prolongation and arrhythmias. Some weak CYP2D6 inhibitors list use with thioridazine as a contraindication. *Risk D: Consider therapy modification*
- TiZANidine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of TiZANidine. *Risk X: Avoid combination*
- Triazolam: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Triazolam. *Risk C: Monitor therapy*
- Ubrogepant: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Ubrogepant. Management: In patients taking weak CYP3A4 inhibitors, the initial and second dose (given at least 2 hours later if needed) of ubrogepant should be limited to 50 mg. *Risk D: Consider therapy modification*

Efficacy

ADHD Studies in Pediatric Patients

The efficacy of Qelbree in the treatment of ADHD in pediatric patients 6 to 17 years of age was evaluated in three short-term, randomized, placebo-controlled monotherapy trials (Studies 1, 2, and 3).

Study 1 was a multicenter, randomized, double-blind, three-arm placebo controlled, parallel group monotherapy trial in patients 6 to 11 years of age with ADHD. Total duration of treatment was 6 weeks, including a 1-week titration period (starting at 100 mg once daily) and 5-week maintenance phase. Patients were randomized to receive 100 mg, 200 mg, or placebo, given once daily as a single dose. The primary endpoint was the change from baseline to the end of study on the total score on the ADHD Rating Scale (ADHD-RS-5), an 18-question scale that assesses hyperactivity, impulsivity, and inattentive symptoms. Higher ADHD-RS-5 scores reflect more severe symptoms. The Clinical Global Impression-Improvement (CGI-I) score at the end of the study was a secondary endpoint. A total of 477 patients were randomized in Study 1; 399 completed the study, and 78 discontinued. The change from baseline (reduction) in ADHD-RS-5 total score was statistically significantly greater in patients

treated with Qelbree 100 mg or with Qelbree 200 mg than in patients on placebo (see Table 4). Compared with patients on placebo, a statistically significantly greater reduction (improvement) in CGI-I score at the end of the study was observed both in patients treated with Qelbree 100 mg and in patients treated with Qelbree 200 mg.

Study 2 was a multicenter, randomized, double-blind, three-arm, placebo controlled, parallel-group monotherapy trial in patients 6 to 11 years of age with ADHD. Total duration of treatment was 8 weeks, including a 3-week titration period (starting at 100 mg once daily), and a 5-week maintenance phase. Patients were randomized to receive Qelbree 200 mg, Qelbree 400 mg, or placebo, given once daily as a single dose. The primary endpoint was the change from baseline to the end of study on the total score on the ADHD Rating Scale (ADHD-RS-5). The Clinical Global Impression-Improvement (CGI-I) score at the end of the study was a secondary endpoint. A total of 313 patients were randomized in Study 2; 251 completed the study, and 62 discontinued. The change from baseline (reduction) in ADHD-RS-5 total score was statistically significantly greater in patients treated with Qelbree 200 mg or with Qelbree 400 mg than in patients on placebo (see Table 4). Compared with patients on placebo, a statistically significantly greater reduction (improvement) in CGI-I score at the end of the study was observed both in patients treated with Qelbree 200 mg and in patients treated with Qelbree 400 mg.

Study 3 was a multicenter, randomized, double-blind, three-arm, placebo controlled, parallel-group monotherapy trial in patients 12 to 17 years of age with ADHD. Total duration of treatment was 6 weeks, including 1-week titration period (starting at 200mg once daily) and a 5-week maintenance phase. Patients were randomized to receive Qelbree 200 mg, Qelbree 400 mg, or placebo, given once daily as a single dose. The primary endpoint was the change from baseline to the end of study on the total score on the ADHD Rating Scale (ADHD-RS-5). The Clinical Global Impression-Improvement (CGI-I) score at the end of the study was a secondary endpoint. A total of 310 patients were randomized in Study 3; 266 completed and 44 discontinued. The change from baseline (reduction) in ADHD-RS-5 total score was statistically significantly greater in patients treated with Qelbree 200 mg or with Qelbree 400 mg than in patients on placebo (see Table 4). Compared with patients on placebo, a statistically significantly greater reduction (improvement) in CGI-I score at the end of the study was observed both in patients treated with Qelbree 200 mg and in patients treated with Qelbree 400 mg.

Table 4. Primary Efficacy Results for Change from Baseline in ADHD-RS-5 Total Score in Pediatric Patients (6 to 17 years) with ADHD (Studies 1, 2, 3)

Study Number (Age range)	Treatment Group	Primary Efficacy Measure: ADHD-RS-5 Total Score			
		n	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 1 (6 to 11 years)	100 mg/day†	147	45.0 (6.53)	-16.6 (1.16)	-5.8 (-8.9, -2.6)
	200 mg/day†	158	44.0 (6.80)	-17.7 (1.12)	-6.9 (-10.0, -3.8)
	Placebo	155	43.6 (7.05)	-10.9 (1.14)	--
Study 2 (6 to 11 years)	200 mg/day†	107	43.8 (6.54)	-17.6 (1.43)	-6.0 (-10.0, -1.9)
	400 mg/day†	97	45.0 (6.55)	-17.5 (1.52)	-5.8 (-9.9, -1.7)
	Placebo	97	43.5 (6.79)	-11.7 (1.48)	--
Study 3 (12 to 17 years)	200 mg/day†	94	39.9 (7.22)	-16.0 (1.45)	-4.5 (-8.4, -0.6)
	400 mg/day†	103	39.4 (7.59)	-16.5 (1.38)	-5.1 (-8.9, -1.3)
	Placebo	104	40.5 (6.79)	-11.4 (1.37)	--

Table from Qelbree package insert, Supernus Pharmaceuticals, Revised 4/2022

ADHD Study in Adults

The efficacy of Qelbree in the treatment of ADHD in adults 18 to 65 years of age was evaluated in a short-term, randomized, placebo-controlled, flexible-dose monotherapy trial (Study 4). Study 4 (NCT04016779) was a multicenter, randomized, double-blind, placebo-controlled, flexible-dose, parallel-group monotherapy trial in adults 18 to 65 years of age with ADHD. Total duration of treatment was 6 weeks, starting at 200 mg once daily Week 1 and titrating up 400 mg once daily Week 2. Dose was adjusted by 200 mg per day once a week to a minimum of 200 mg once daily and maximum of 600 mg once daily thereafter. Patients were randomized to receive Qelbree (200 mg to 600 mg), or placebo, given once daily as a single dose. The primary endpoint was the change from baseline to the end of study on the total score on the ADHD Investigator Symptom Rating Scale (AISRS), an 18-item scale corresponding to 18 symptoms of ADHD. Higher AISRS scores reflect more severe symptoms. The change from baseline in the Clinical Global Impression-Severity of Illness (CGI-S) score at the end of the study was the key secondary endpoint. A total of 374 adult patients were randomized in Study 4; 267 completed and 107 discontinued. The average dose at end of study was 504 mg per day. The change from baseline (reduction) in the AISRS Total score was statistically significantly greater in adults treated with Qelbree than in adults on placebo (see Table 5). In addition, the change from baseline (reduction) in the CGI-S score was statistically significantly greater in adults treated with Qelbree than in adults on placebo.

Table 5. Primary Efficacy Results for Change from Baseline AISRS Total Score in Adults (18 to 60 years of age) with ADHD (Study 4)

Study Number (Population)	Treatment Group	n	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 4 (Adults)	Qelbree† (200 mg to 600 mg)	175	38.5 (6.56)	-15.5 (0.91)	-3.7 (-6.2, -1.2)
	Placebo	179	37.6 (6.62)	-11.7 (0.90)	--

Table from Qelbree package insert, Supernus Pharmaceuticals, Revised 4/2022

Dosage Forms/Cost (AWP)

- Qelbree ER 100mg Capsules 30ct $403.15
- Qelbree ER 150mg Capsules 30ct $403.15
- Qelbree ER 200mg Capsules 30ct $403.15
- Qelbree ER 200mg Capsules 60ct $806.29

Recommendation

Recommend adding Qelbree in all strengths to the HHSC Psychiatric Drug Formulary, Qelbree is an effective medication that is not a stimulant for the treatment of ADHD, its niche in therapy appears to be the treatment of the impulsivity aspect of the ADHD disease state. Providing another medication to the arsenal to treat this aspect without escalation to a stimulant would be a boon to our formulary.

References

1. Qelbree package insert, Supernus Pharmaceuticals, Revised 4/2022
2. Qelbree: Drug information. Lexi-Drugs. Lexicomp. Wolters Kluwer Health Inc. Riverwoods, IL. Available at: https://www.uptodate.com/contents/viloxazine-drug-information?search=qelbree&source=panel_search_result&selectedTitle=1~5&usage_type=panel&kp_tab=drug_general&display_rank=1 Accessed September 20, 2023
3. Nasser A, Liranso T, Adewole T, et al. A Phase III, Randomized, Placebo-controlled Trial to Assess the Efficacy and Safety of Once-daily SPN-812 (Viloxazine Extended-release) in the Treatment of Attention-deficit/Hyperactivity Disorder in School-age Children. *Clin Ther*. 2020;42(8):1452-1466. doi:10.1016/j.clinthera.2020.05.021
4. Nasser, A., Liranso, T., Adewole, T., Fry, N., Hull, J. T., Chowdhry, F., Busse, G. D., Melyan, Z., Cutler, A. J., Findling, R. L., & Schwabe, S. (2021). A Phase 3 Placebo-Controlled Trial of Once-Daily 400-mg and 600-mg SPN-812 (Viloxazine Extended-Release) in Adolescents with ADHD. *Psychopharmacology bulletin*, *51*(2), 43–64.
5. Nasser A, Hull JT, Chaturvedi SA, et al. A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of Viloxazine

Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder. *CNS Drugs*. 2022;36(8):897-915. doi:10.1007/s40263-022-00938-w

Date: 10/27/2023
Prepared by: John Fullerton, Pharm D.
Reviewed by: Lufkin SSLC P&T Committee 10/31/23

Appendix F

Cefadroxil (Duricef®) capsule and powder for suspension

Classification

First Generation Cephalosporin Antibiotic

Pharmacology

Cefadroxil is a semisynthetic cephalosporin antibiotic for oral administration. Cephalosporin antibiotics inhibit bacterial cell wall synthesis by binding to one or more of the penicillin-binging proteins which inhibits transpeptidation of peptidoglycan synthesis.

Indication

- Treatment of skin and soft tissue infections caused by *staphylococci* and/or *streptococci.*
- Treatment of pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci).
- Treatment of urinary tract infections caused by *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* species.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Rapidly absorbed after oral administration. Time to peak 70-90 minutes.
Distribution	V_d: 0.31 L/kg, 20% protein bound. The urine antibiotic concentration following a 1 g dose was maintained above the MIC for susceptible urinary pathogens for 20 to 22 hours.
Metabolism	Half-life elimination 1 to 2 hours in adults; 1.3-1.8 hours in children, 20-24 hours in adults with renal failure.
Excretion	>90% as unchanged drug in the urine within 24 hours.

Dosage/Administration

Administration with food may reduce gastrointestinal side effects.

Adult Dosing

Urinary Tract Infections:
1 or 2 g per day as single or divided dose for uncomplicated infections. For all other urinary tract infections, the dose is 2 g per day divided twice daily.

Skin and Skin Structure Infections:
1 g per day in single or divided dose.

Pharyngitis and Tonsillitis:
1 g per day in single or divided dose.

Children Dosing

Urinary Tract Infections:
30 mg/kg/day in divided doses every 12 hours; max 2 g per day.

Pharyngitis, Tonsillitis, and Impetigo:
30 mg/kg/day in single or divided dose every 12 hours; max dose 1 g per day.

Other Skin and Skin Structure Infections:
30 mg/kg/day in divided doses every 12 hours; max 1 g per day.

Renal Impairment Dosing

Adjust dose for adults with CrCl 50 mL/min or less as follows- 1 g initial dose followed by a maintenance dose of 500 mg at the following dosage interval based on CrCl:

0 to 10 mL/min= 36 hours

10 to 25 mL/min= 24 hours

25 to 50 mL/min= 12 hours

Note: Other resources indicate dosage adjustment is not needed for those with CrCl 40 mL/min or above and the dosage interval may be every 24 hours for those with CrCl less than 20 mL/min.

Reconstitution Directions for Oral Suspension

Initially tap bottle lightly to loosen powder. Shake well after each portion addition of water as noted below.

100 mL Bottle Size: Suspend in 60 mL water, add water in 2 portions

75 mL Bottle Size: Suspend in 45 mL water, add water in 2 portions

50 mL Bottle Size: Suspend in 30 mL water, add water in 2 portions

After reconstitution store in refrigerator. Shake well before using. Keep container tightly closed. Discard unused portion after 14 days.

Use in Special Populations

Because elderly patients mare more likely to have decreased renal function, care should be taken in dose selection and monitoring renal function should be considered.

No adequate or well controlled studies in pregnant women, although cephalosporin antibiotics are generally considered compatible during pregnancy. Cefadroxil has not been studied for use during labor and delivery.

Caution should be exercised when cefadroxil is administered to a nursing mother although the relative infant dose is low at 2.6% for a standard 1 g per day dose.

Contraindication

Known allergy to the cephalosporin group of antibiotics.

Precautions

- Hypersensitivity reactions to cefadroxil, cephalosporins, penicillins or other drugs. Cross-sensitivity among beta-lactam antibiotics may occur in up to 10% of patients with a history of penicillin allergy. The suspension may contain sulfur dioxide (sulfite) and hypersensitivity reactions may occur.
- *Clostridium difficile associated diarrhea* (CDAD) has been reported with use of antibacterial agents, including cefadroxil, caused by alteration in the normal flora of the colon leading to overgrowth of *C. difficile.*
- Use with caution in the presence of markedly impaired renal function CrCl 50 mL/min or less.
- Use with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Adverse Effects

- Gastrointestinal symptoms such as dyspepsia, nausea, vomiting, abdominal pain and diarrhea. Rarely pseudomembranous colitis symptoms or *Clostridolides diffficile*-associated diarrhea may occur during and after antibiotic treatment.
- Hypersensitivity reactions such as rash, urticaria, angioedema and pruritus have been reported and usually subside after discontinuation of the medication. Rarely anaphylaxis, erythema multiforme, Stevens-Johnson syndrome or eosinophilia may occur. Toxic epidermal necrolysis and serum sickness have also been reported.
- Hepatic dysfunction including cholestasis, elevations in transaminase, alkaline phosphatase, elevated bilirubin, elevated LDH, and rarely idiosyncratic hepatic failure.
- Genitourinary complications including genital pruritus, genital moniliasis, vaginitis.
- Hematologic events including agranulocytosis, neutropenia, thrombocytopenia, aplastic anemia, pancytopenia, hemorrhage, prolonged PT time, positive Coombs' test.
- Renal side effects including elevated BUN, increased creatinine, renal dysfunction, toxic nephropathy.
- Cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, where the dose was not renally adjusted.

Monitoring

Culture and susceptibility tests should be initiated prior to and during therapy. Culture and susceptibility information should be considered in selecting or modifying antibacterial therapy when available.

Monitor renal function.

Monitor for possible C. difficile overgrowth including watery and bloody stools (with or without stomach cramps and fever) during and after completion of antibiotic course.

Interactions

- Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics.
- Cefadroxil is an OAT1/3 Substrate.
- Aminoglycosides- may enhance the nephrotoxic effect of aminoglycosides.
- Furosemide- may enhance nephrotoxic effect of cephalosporins.
- Immune Checkpoint Inhibitors (Anti-PD-1, -PD-L1, -CTLA4)- antibiotics may diminish therapeutic effect of immune checkpoint inhibitors.
- Lactobacillus and Estriol- antibiotics may diminish therapeutic effect.
- Probenecid- may increase serum concentration of cephalosporins.
- Vitamin K antagonist (eg, warfarin): Cephalosporins may enhance the anticoagulant effect.

Efficacy

Cefadroxil is active against many gram-positive aerobic cocci, but is much less active against gram-negative bacteria with an antibacterial profile similar to cephalexin. The main advantage of cefadroxil over cephalexin is the longer half-life allowing twice daily dosing versus four times daily dosing. Following equivalent oral doses, serum levels of cefadroxil are higher and more sustained than cephalexin 1.5 hours post ingestion. Cefadroxil has been shown to be active against the following organisms both in vitro and in clinical infections: *Beta-hemolytic streptococci, Staphylococci, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella species, Moraxella catarrhalis*. Cefadroxil has been shown to be effective in clinical trials against these strains for the treatment of urinary tract infections, skin and skin structure infections, as well as pharyngitis/tonsillitis.

Skin and skin structure and musculoskeletal infections

Cefadroxil 30 mg/kg per day was compared to cephalexin 15 mg/kg dosed twice daily (maximum dose 1 g each) for the treatment of gram-positive skin infections in children. Treatment was evaluated in 289 children with the most common skin infection being impetigo. Cefadroxil was found to be significantly better than cephalexin at eradicating the organism, 96% vs. 89% respectively. Clinically, there

was no difference treatment response between the two antibiotics with side effects being mild and infrequent with either antibiotic.

Another study compared cefadroxil, cephalexin and other antibiotics and their ability to inhibit growth of MSSA in the laboratory setting. Bacterial samples were obtained from children with bone, joint and/or other musculoskeletal infections caused by MSSA. A total of 48 isolates were obtained from blood (81%), bone (15%) and synovial fluid (4%) with cultures included in the analysis. Cefadroxil and cephalexin inhibited the growth of MSSA at similar concentrations with statistically equivalent MICs (p=0.28), suggesting similar antibacterial potency.

According to the Infectious Diseases Society of America (IDSA) treatment guidelines, for impetigo and ecthyma non-purulent skin infections, oral penicillinase-resistant penicillin or first-generation cephalosporins are usually effective.

Uncomplicated urinary tract infection

The safety and efficacy of cefadroxil 1 g twice daily and cephalexin 500 mg four times daily in the treatment of uncomplicated urinary tract infection was evaluated in 660 patients. The trial was a randomized, double-blind design evaluating cure rate based on urine cultures 5 to 9 days post-treatment. Cure rates were similar with the two antibiotics, 93% of cefadroxil patients and 91% of cephalexin patients. Side effects reported were similar between the two groups, 13% cefadroxil and 15% cephalexin. Nausea was more common with cefadroxil and vaginitis was more common with cephalexin. Another study in uncomplicated UTI comparing the two antibiotics with same dosing also found comparable treatment effects; however, this study only included 28 female patients.

IDSA guidelines generally to not recommend use of first-generation cephalosporins in the treatment of uncomplicated urinary tract infections as a first-line treatment. However, if the recommended antimicrobials for UTI are not feasible, cephalosporins can be considered. When cephalosporins are used for the treatment of uncomplicated UTI, a second-generation or third-generation of cephalosporin is generally selected as first-generation cephalosporins such as cefadroxil and cephalexin are less well studied.

Dosage Forms/Cost (AWP)

- Capsule 500 mg: $3.60 per capsule
- Oral suspension 250 mg per 5 mL (100 mL bottle): $60.80
- Oral suspension 500 mg per 5 mL (75 mL bottle): $63.12
- Oral suspension 500 mg per 5 mL (100 mL bottle): $84.17

Safety Considerations

- Look Alike-Sound Alike: Brand name Duricef (no longer available) may be confused with Ultracet
- High Risk-High Alert: No

- Hazardous Drug Status: No

Summary/Conclusion

Cefadroxil is a first-generation cephalosporin available in oral dosage forms similar to the formulary antibiotic cephalexin. Although the two antibiotics have a similar spectrum of antimicrobial activity, cefadroxil requires less frequent administration. Both antibiotics are available generic and are relatively inexpensive.

Recommendation

Cefadroxil capsules and oral suspension are recommended for formulary addition.

References

1. Cefadroxil capsules [prescribing information]. Baltimore, MD. Lupin Pharmaceuticals Inc; December, 2020.
2. Cefadroxil powder, for suspension [prescribing information]. Saddle Brook, NJ. Rising Health LLC; October, 2022.
3. Cefadroxil: Drug Information. In: UpToDate, Post TW (Ed), Wolters Kluwer. https://www.uptodate.com (Accessed on November 22, 2023.)
4. Linder CW, Nelson K, Paryani S, et al. Comparative evaluation of cefadroxil and cephalexin in children and adolescents with pyodermas. Clin Ther 1993; 15:46-56.
5. Haynes AS, Prinzi A, Silveira LJ, et al. Cefadroxil comparable to cephalexin: Minimum inhibitory concentrations among Methicillin-Susceptible *Staphylococcus aureus* isolates from pediatric musculoskeletal infections. Microbiology Spectrum 222; 10(4): 1-5.
6. Stevens DL, Bisno AL, Chambers HF, et. al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infections Diseases Society of America. Clinical Infectious Diseases 2014; 59(2):e10-52.
7. Henness DM, Richards D. Clinical comparison of cefadroxil and cephalexin in uncomplicated urinary tract infection. Infection 1980; 8:S629-S632.
8. Bolding OT. Comparison of the efficacy and safety of cefadroxil and cephalexin in treating acute urinary tract infections in women. J Int Med Res 1980;8(suppl 1):34-39.
9. Gupta, K., Hooton, T. M., Naber, K. G., Wullt, B., Colgan, R., Miller, L. G. et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical Infectious Diseases 2011; 52:e103-e120.

Date: 11/22/23

Prepared by: Lisa M. Mican, Pharm.D., BCPP
Director of Pharmacy, Clinical Coordinator
Austin State Hospital