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Abstract: In 2019, the FDA approved several new drugs for use in primary care. This article highlights the following new drugs: risankizumab-rzaa (Skyrizi); halobetasol and tazarotene (Duobrii); dolutegravir and lamivudine (Dovato); romosozumab-aqqg (Evenity); brexanolone (Zulresso); solriamfetol (Sunosi); aclidinium and formoterol (Duaklir Pressair); and siponimod (Mayzent).

By Lauren Hartsell Crump, PharmD; Miranda Benfield, PharmD; Caleb Ramey; Ashley Arcara, BS; Sebin Yang, BA; Jenna Brown, BS; Geoffrey Mospan, PharmD, BCPS; and Cortney Mospan, PharmD, BCACP, BCGP

▼ Psoriasis

Risankizumab-rzaa (Skyrizi)

Psoriasis is a common immune-mediated inflammatory skin disease seen in up to 2% of adults.[1] Psoriasis also negatively affects patients' quality of life due to the appearance of their skin.[1] Plaque psoriasis is marked by erythematous oval plaques with scales caused by a hyperproliferative epidermis.[1] Interleukin-23 (IL-23) encourages proliferation of T helper cells (Th17), which produce IL-17, a proinflammatory cytokine.[2] IL-1, IL-6, and tumor necrosis factor-alpha are stimulated by IL-2 resulting in inflammation.[2] Risankizumab-rzaa, approved in April 2019, is a human IgG1 monoclonal antibody that targets IL-23 to stimulate skin clearing in patients with plaque psoriasis.[3,4] Risankizumab-rzaa is manufactured by AbbVie Inc.[4] Though risankizumab-rzaa was not FDA-approved when the Joint American Academy of Dermatology (AAD)-National Psoriasis Foundation (NPF) guidelines of care for the management and treatment of psoriasis with biologics were

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published, the AAD did support the use of risankizumab-rzaa as monotherapy.[5] A 90% improvement in the Psoriasis Area Severity Index at 16 weeks was seen in 75.3% of patients in the risankizumab-rzaa group, compared with 42% in the ustekinumab group.[6]

Indication

Risankizumab-rzaa is indicated to treat moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.[7]

Mechanism of action

Risankizumab-rzaa is a human IgG1 monoclonal antibody that binds to the p19 subunit of IL-23 and blocks the binding with IL-23 receptors.[3] By inhibiting IL-23, proinflammatory cytokines and chemokines are not released.[3]

Dosing and administration

Risankizumab-rzaa is packaged in two 75 mg prefilled syringes and should be refrigerated until time of use.[7] Syringes should be removed from the refrigerator 15 to 30 minutes prior to injection.[7] The recommended dose is 150 mg (two syringes) by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.[7] Patients may be trained on how to inject risankizumab-rzaa. The medication should not be injected into psoriatic skin.[7] There is no data to determine renal or hepatic dose adjustments at this time.

Contraindications

No reported contraindications exist, according to the package insert.[7]

Warnings and precautions

Risankizumab-rzaa may increase the risk of infections, such as upper respiratory tract and tinea infections.[7] Patients should be assessed for tuberculosis prior to initiating therapy.[7] Latent tuberculosis should be treated prior to starting therapy.[7] In phase 3 trials, some patients were treated concurrently with risankizumab-rzaa and tuberculosis prophylaxis with no reactivation.[7] It is recommended to complete all immunizations prior to initiating risankizumab-rzaa and avoid live vaccines while taking risankizumab-rzaa.[7]

Adverse reactions

Infections such as cellulitis, osteomyelitis, sepsis, and herpes zoster were observed in clinical trials.[7] Other adverse reactions, such as headache and fatigue, had similar rates when compared with the control arm.[6]

Pharmacokinetics

Steady-state concentrations were achieved by week 16.[7] No studies have been completed to determine the effects of renal impairment, hepatic impairment, or body weight on the effect of risankizumab.[7] No major drug interactions have been observed at this time.[7]

Clinical pearls

- If a dose is missed, administer as soon as possible and continue dosing at the next regularly scheduled time.[7]
- There is limited data in pregnancy and lactation. IgG1 is known to cross the placental barrier, suggesting risankizumab-rzaa may cross the placental barrier.[7]
- Antibodies may develop to risankizumab-rzaa and clinicians should monitor clinical response. Antibody titers may be obtained. Patients with elevated antibodies were associated with reduced clinical response in the study.[7]
- Risankizumab-rzaa has not been evaluated in the pediatric patient population.[7]
- The phase 3 clinical trial included 267 patients age 65 and older with no differences in safety or efficacy.[7]

REFERENCES

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009;361(5):496-509.
2. Tang C, Chen S, Qian H, Huang W. Interleukin-23: as a drug target for autoimmune inflammatory diseases. *Immunology*. 2012;135(2):112-124.
3. Papp KA, Blauvelt A, Bukhalo M, et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. *N Engl J Med*. 2017;376(16):1551-1560.
4. Paoli C. FDA approves Skyrizi for plaque psoriasis. National Psoriasis Foundation. 2019. www.psoriasis.org/advance/fda-approves-skyrizi-plaque-psoriasis?gclid=CjwKCAjw98rpBRAuEiwALmo-yvhFh3WYDGN2cn7leD-MgqpTkGRyvOhfquBUxxTmxazX1Bz5U9grRoBoCdEAQAvD_BwE.
5. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072.
6. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661.
7. Skyrizi (risankizumab-rzaa) [package insert]. North Chicago, IL: AbbVie Inc.; 2019.

▼ Psoriasis

Halobetasol propionate and tazarotene (Duobrii)

Halobetasol propionate and tazarotene, approved in April 2019, is a new topical lotion used to treat

plaque psoriasis in adults using a combination of a corticosteroid (halobetasol propionate) and a retinoid (tazarotene).[1,2] Halobetasol propionate and tazarotene is manufactured by Bausch Health.[1] The guidelines of care for the management of psoriasis and psoriatic arthritis from the AAD at this time do not include halobetasol propionate and tazarotene; however, current guidelines do discuss the potential synergistic effect when using tazarotene with corticosteroids.[3] Halobetasol propionate and tazarotene led to a 54% decrease in itching by week 2 and treatment success in 40% of patients by week 8.[4] Treatment success was characterized by a decrease in the area affected, quality-of-life improvements, and a significant decrease in signs and symptoms of psoriasis.[4]

Indication

Halobetasol propionate and tazarotene is indicated for topical treatment of plaque psoriasis in adults.[2]

Mechanism of action

The precise mechanism of halobetasol propionate and tazarotene in treating plaque psoriasis is unknown.[2] Halobetasol propionate minimizes inflammation, pruritus, proliferation and enhances vasoconstrictive effects.[2] Tazarotene is an anti-inflammatory agent, increases collagen, increases epidermal differentiation, and increases antiproliferation.[2] Tazarotene is utilized to decrease the risk of steroid-induced atrophy.[2]

Dosing and administration

A thin layer should be applied to the affected area once daily.[2] Dressings should not be used on top of the applications.[2] Halobetasol propionate and tazarotene should not be applied to the face, groin, or axillae.[2] There are no renal or hepatic dose adjustments at this time.[2]

Contraindications

Halobetasol propionate and tazarotene is contraindicated in pregnancy.[2]

Warnings and precautions

Women who are pregnant are at risk for systemic absorption of tazarotene, which is known to be teratogenic in animals.[2] Before initiation, a pregnancy test should be obtained 2 weeks before starting halobetasol propionate and tazarotene.[2] Female patients should be started on halobetasol propionate and tazarotene during a menstrual period and counseled on using effective contraception during treatment.[2]

Corticosteroids have the potential to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Risk of HPA axis suppression may increase with use of a topical corticosteroid over a large surface of the body, covering the lotion with a bandage or dressing, use on broken skin, liver failure, and young age.[2] Therefore, patients should not exceed 50 g of lotion per week.[2]

Patients utilizing corticosteroids topically are also at risk for systemic effects such as hyperglycemia and Cushing syndrome.[2]

Patients on halobetasol propionate and tazarotene are at an increased risk for sunburn.[2] Patients should use extra caution when taking other medications that increase photosensitivity.[2]

Postmarketing reports have reported topical corticosteroids may increase the risk of glaucoma and cataracts.[2]

Adverse reactions

Contact dermatitis, application site pain, striae, folliculitis, skin atrophy, and excoriation were all reported in a clinical trial.[2,4] These reactions occurred in at least 1% of subjects and occurred more frequently than in the placebo group.[2,4]

Pharmacokinetics

A pharmacokinetic study was conducted in patients with moderate-to-severe plaque psoriasis covering at least 20% of their body.[2] Steady-state concentrations of halobetasol propionate and tazarotene were achieved with once-daily application by day 28.[2]

Clinical pearls

- Women who are breastfeeding should not apply halobetasol propionate and tazarotene directly to their nipples to decrease the exposure of the infant to the medication.[2]
- Counsel patients on avoiding tanning beds, sunlamps, and occluding the area where the medication is applied.[2] Patients should also be instructed to wear appropriate SPF sunscreen, cover the skin, and avoid sun exposure when the UV index is highest.[2]
- Monitor for HPA axis suppression and vision changes.[2]
- Discontinue halobetasol propionate and tazarotene if local adverse reactions occur or if a skin infection

develops. Halobetasol propionate and tazarotene can be resumed when the skin integrity returns.[2]
- Halobetasol propionate and tazarotene should be discontinued when the skin clears.[2]
- Pediatric patients were not included in the clinical trials.[2]

REFERENCES

1. National Psoriasis Foundation. FDA approves Duobrii for plaque psoriasis. 2019. www.psoriasis.org/advance/fda-approves-duobrii-plaque-psoriasis.
2. Duobrii (halobetasol propionate and tazarotene) [package insert]. Laval, Quebec, Canada: Bausch Health; 2019.
3. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60(4):643-659.
4. Gold LS, Lebwohl MG, Sugarman JL, et al. Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: results of 2 phase 3 randomized controlled trials. *J Am Acad Dermatol*. 2018;79(2):287-293.

▼ HIV

Dolutegravir and lamivudine (Dovato)

Close to 11 million people in the US are living with HIV, and close to 15% are unaware of their status.[1] Men who have sex with men, gay, and bisexual patient populations represent those with the highest degree of disease burden and prevalence.[1] HIV infection targets a specific type of immune system T cell, known as a CD4 cell, that is necessary when fighting an infection.[2] In contrast to previous years, HIV therapy, which includes the combination of multiple antiretroviral therapy (ART) agents, can allow patients to experience a quality of life similar to someone who is uninfected.[2] In April 2019, the FDA approved the first complete two-drug regimen for the treatment of HIV-1 infection, dolutegravir (DTG) and lamivudine (3TC) branded under Dovato for ViiV Healthcare.[3] Based on clinical studies, 90% of patients in GEMINI-1 and 93% of patients in GEMINI-2 that were taking DTG/3TC were able to achieve HIV RNA levels of less than 50 copies/mL after 48 weeks of treatment.[4] Antiretroviral guidelines for adults and adolescents recommend DTG/3TC in ART-naive patients with HIV RNA levels less than 500,000 copies/mL only in situations when abacavir or tenofovir are contraindicated or not tolerated.[5]

Indication

DTG/3TC is indicated for patients who have not previously undergone ART.[6] DTG/3TC is indicated to treat HIV-1 infection as a standalone therapy in patients without a known resistance to either drug component.[6]

Mechanism of action

DTG is an integrase strand inhibitor that prevents HIV integrase from inserting viral DNA into host-cell DNA, preventing viral replication.[6] 3TC is a nucleoside analogue reverse transcriptase inhibitor that functions as a cytosine analogue, inhibiting reverse transcriptase and viral replication.[6]

Dosing and administration

DTG/3TC is a fixed-dose, oral, once-daily combination of 50 mg of DTG and 300 mg of 3TC that can be taken with or without food.[6] When used in the setting of carbamazepine or rifampin, an additional 50 mg DTG tablet should be taken at least 12 hours after DTG/3TC.[6] DTG/3TC is not recommended in patients with creatinine clearances less than 50 mL/min or in patients with severe hepatic impairment (Child-Pugh Score C).[6]

Contraindications

DTG/3TC is contraindicated in patients receiving dofetilide due to potentially increased dofetilide serum concentrations and in patients with a prior hypersensitivity reaction to DTG or 3TC.[6]

Warnings and precautions

DTG/3TC has a boxed warning for selection for 3TC-resistant hepatitis B virus (HBV) and for severe acute exacerbations of HBV.[6] Worsening hepatic function may occur in patients with underlying hepatitis B or C infections.[6] Patients should be tested for HBV prior to initiating DTG/3TC and should receive appropriate anti-HBV therapy if needed.[6]

Providers and patients should be aware of increased risk for neural tube defects when DTG/3TC is given during pregnancy, especially during the first trimester.[6] It is recommended to screen for pregnancy prior to starting DTG/3TC and switch regimens in patients who plan to become pregnant or are pregnant.[6]

Immune reconstitution syndrome, an immune system response to opportunistic infections in patients on combination ART, should be monitored for by providers.[6] Additionally, patients should be monitored for hypersensitivity reactions, hepatic steatosis, and lactic acidosis.[6]

Adverse reactions

After 48 weeks of treatment with DTG/3TC pooled from two clinical trials, patients experienced headache, nausea, diarrhea, insomnia, fatigue, and dizziness as the most common adverse reactions.[4,6]

Pharmacokinetics

The administration of DTG or 3TC after a high-fat meal did not produce any clinically significant changes in pharmacokinetics for either component.[6] TG is approximately 99% bound to plasma protein, has a 14-hour elimination half-life, is primarily metabolized through UGT1A1, and is mostly excreted in feces unchanged.[6] 3TC is 36% bound to plasma protein, has a 13-19 hour elimination half-life, is not extensively metabolized, and is mostly excreted in urine unchanged.[6]

Clinical pearls

- Patients of childbearing potential should use an effective form of contraception.[6]
- Mothers should not breastfeed while taking DTG/3TC due to potential transmission of HIV infection, potential viral resistance in infants positive for HIV, and potential adverse reactions related to therapy.[6]
- The efficacy and safety of DTG/3TC is unknown in pediatric populations.[6] Clinical trials with DTG/3TC did not include enough patients over the age of 65 to appropriately assess and extrapolate DTG/3TC use in this population.[4,6]
- Antacids and iron supplements should be taken 2 hours before or 6 hours after DTG/3TC administration.[6] Always assess medications when changes are made for potential drug-drug interactions.
- Monitoring parameters include viral load, CD4 counts, serum creatinine, liver function tests, and signs/symptoms of hypersensitivity reactions.[6]

REFERENCES

1. HIV.gov. Data & Trends: U.S. Statistics. 2019. www.hiv.gov/hiv-basics/overview/data-and-trends/statistics.
2. Centers for Disease Control and Prevention. About HIV/AIDS. 2019. www.cdc.gov/hiv/basics/whatishiv.html.
3. U.S. Food & Drug Administration. FDA approves first two-drug complete regimen for HIV-infected patients who have never received antiretroviral treatment. 2019. www.fda.gov/news-events/press-announcements/fda-approves-first-two-drug-complete-regimen-hiv-infected-patients-who-have-never-received.
4. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet*. 2019;393(10167):143-155.
5. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2018. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/11/what-to-start.
6. Dovato (dolutegravir and lamivudine) [Package Insert]. Research Triangle Park, NC: ViiV Healthcare; 2019.

▼ Osteoporosis

Romosozumab-aqqg (Evenity)

Osteoporosis is a disease state marked by loss of bone density and strength, which results in an increased risk of fracture. Nearly 200 million people worldwide have osteoporosis, with at least 10 million in the US alone.[1,2] Although osteoporosis can affect both genders, women are diagnosed more often than men with approximately 33% of women experiencing a fracture after the age of 50.[1] Evenity was FDA-approved on April 19, 2019, for the treatment of postmenopausal osteoporosis in patients with high risk of fracture and is manufactured by Amgen Inc.[2,3] Romosozumab-aqqg does not yet have a defined place in the clinical practice guidelines.[4] Romosozumab-aqqg has been shown in clinical trials to reduce vertebral fractures by as much as 48% and nonvertebral fractures by 19% when followed by alendronate therapy, as compared with alendronate-only treatment.[5,6]

Indication

Romosozumab-aqqg is indicated for treatment of osteoporosis in postmenopausal women with high fracture risk, including those with a history of fractures due to osteoporosis, multiple risk factors for fracture, and patients who are intolerant of other osteoporosis agents.[7]

Mechanism of action

Romosozumab-aqqg is a monoclonal antibody that targets and inhibits sclerostin, a protein that inhibits bone formation.[7] The result is a slowing of bone breakdown and stimulation of new bone growth through promotion of osteoblasts.[8]

Dosing and administration

Romosozumab-aqqg is available as a prefilled, single-use syringe (105 mg/1.17 mL) for injection subcutaneously into the thigh, upper arm, or the abdomen.[7] Patients should receive romosozumab-aqqg once monthly for 12 months.[7] Each dose of romosozumab-aqqg is 210 mg, requiring two syringes injected in succession

by a healthcare provider.[7] It is recommended to administer calcium and vitamin D supplementation daily throughout the duration of treatment.[7] No dose adjustment is required for renal impairment; however, these patients may be at greater risk for hypocalcemia.[7]

Contraindications

Romosozumab-aqqg is contraindicated for use in patients with hypocalcemia or known hypersensitivity to the medication.[7]

Warnings and precautions

Romosozumab-aqqg use has been correlated with an increase in cardiovascular events and should be avoided in patients with a history of myocardial infarction or stroke within the past year (boxed warning).[7] Patients who have other cardiovascular risk factors should be started on romosozumab-aqqg cautiously and monitored regularly.[7] Discontinue romosozumab-aqqg if a patient develops a myocardial infarction or stroke during therapy.[7]

Romosozumab-aqqg use can result in decreased serum calcium, and caution should be used in patients who have a documented history of hypocalcemia.[7] Hypocalcemia should be corrected prior to initiation of therapy, and calcium/vitamin D supplementation should be maintained throughout the duration of treatment.[7]

Hypersensitivity reactions have been documented for as many as 6.5% of patients receiving romosozumab-aqqg, and if such a reaction occurs, treatment should be discontinued.[7]

In rare instances, osteonecrosis of the jaw (ONJ) has occurred for those using romosozumab-aqqg. Patients should receive a baseline oral exam prior to beginning therapy, and prescribers should be wary of initiating additional drugs with risk of ONJ.[7]

Atypical fractures of the femur with little to no trauma have also been noted with romosozumab-aqqg.[7] These fractures can occur at any location along the femur, including subtrochanteric and diaphyseal fractures. These fractures are rare and may be preceded by prodromal pain several weeks before occurring. Patients should be counseled to monitor for new-onset pain in their thighs and inform the prescriber.[7]

Adverse reactions

The most common adverse events associated with romosozumab-aqqg in clinical trials were arthralgia (8.1% to 13.1%), followed by hypersensitivity reactions (6.5%), headache (5.2% to 6.6%), and injection site reactions (4.9%).[7] Adverse events with a less than 1% occurrence rate include myocardial infarction, hypocalcemia, ONJ, femur fracture, and cerebrovascular accident.[5,6,7]

Pharmacokinetics

Romosozumab-aqqg reaches maximum serum concentrations 5 days after administration, reaches steady-state concentrations after the third dose, and has a half-life of 12.8 days.[7] It is not yet known how romosozumab-aqqg is metabolized in the body, although it is believed to be degraded in a manner similar to endogenous antibodies.[7] Romosozumab-aqqg does not have any drug interactions listed in the package insert.[7]

Clinical pearls

- Romosozumab-aqqg is indicated only for use in postmenopausal women, and thus risk has not been evaluated in pregnant, lactating, or pediatric patients.[7]
- Romosozumab-aqqg is only indicated for a total of 12 months of therapy. If patients require additional osteoporosis treatment, a different agent must be selected.[7]
- Use caution when initiating patients on medications that may lower calcium or increase risk of ONJ.[7]
- Monitor for new-onset hip, groin, or thigh pain, symptoms of ONJ, and for signs or symptoms of hypocalcemia.[7]
- Patients should be counseled to maintain good oral hygiene and inform their dental provider that they are using romosozumab-aqqg.[7]

REFERENCES

1. Sözen T, Özı_ık L, Ba_aran NÇ. An overview and management of osteoporosis. *Eur J Rheumatol*. 2017;4(1):46-56.
2. U.S. Food & Drug Administration. FDA approves new treatment for osteoporosis in postmenopausal women at high risk of fracture. 2019. www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-osteoporosis-postmenopausal-women-high-risk-fracture.
3. Amgen Inc. Evenity (romosozumab-aqqg) injection 105 mg/1.17 mL. 2019. www.evenityhcp.com/?gclid=EAIaIQobChMIyMaV-97f5AIVQtbACh1dcgAqEAAYAiAAEgIdn_D_BwE&gclsrc=aw.ds.
4. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2019;104(5):1595-1622.
5. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med*. 2017;377(15):1417-1427.

6. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532-1543.
7. Evenity (romosozumab-aqqg) injection [package insert]. Amgen Inc.; 2019.
8. Lewiecki EM. Role of sclerostin in bone and cartilage and its potential as a therapeutic target in bone diseases. *Ther Adv Musculoskelet Dis*. 2014;6(2):48-57.

▼ Postpartum depression

Brexanolone (Zulresso)

Postpartum depression (PPD) is a common complication of childbearing with prevalence between 7% and 20%.[1] Due to potential negative effects on maternal-infant attachment, delays in infant growth and development, and increased risk of mental health conditions in the infant in later life, PPD has been identified as a major public health issue.[1,2] Psychotherapy or selective serotonin reuptake inhibitors can be used to treat PPD.[2] Manufactured by Sage Therapeutics, brexanolone was approved by the FDA in March 2019 through priority review and breakthrough therapy designation. It is the first neuroactive steroid gamma-aminobutyric acid (GABA) A receptor modulator.[3]

Indications

Brexanolone is indicated for the treatment of PPD in adults.[4] It is the first medication specifically indicated for PPD.[3]

Mechanism of action

The mechanism of action of brexanolone in PPD is not completely understood; however, it is thought to be related to activation of the GABA A receptor.[4]

Dosing and administration

Brexanolone is formulated as a 5 mg/mL single-dose 20 mL vial. It is administered as a continuous I.V. infusion over 60 hours under the supervision of a healthcare provider. The infusion rate will start at 30 mcg/kg/h, increase to 90 mg/kg/h, and then decrease back down to 30 mcg/kg/h. The infusion should be stopped if excessive sedation occurs and should not be restarted until the symptoms resolve. It can be resumed at the same dose or a decreased dose, as clinically appropriate. No reversal agent is currently available; however, in most cases, excessive sedation will resolve within 15 minutes of holding the infusion and no other intervention is necessary. Brexanolone should not be used in patients with end-stage renal disease (ESRD) due to potential accumulation of the stabilizing agent. Dosage adjustment in hepatic dysfunction is not necessary.[4]

This medication requires dilution prior to administration and will require preparation of at least five infusion bags as the diluted product is only stable for 12 hours at room temperature. Additional bags will be required for patients weighing at least 90 kg. Following dilution, brexanolone can be stored refrigerated for 96 hours. Use of a peristaltic infusion pump (a pump with a set of rollers that pushes fluid forward similar to peristalsis) in a dedicated line is recommended instead of a syringe pump, for example, to ensure accurate delivery and separation from other medications.[4]

Contraindications

No contraindications are currently listed within the manufacturer's prescribing information.[4]

Warnings and precautions

Brexanolone is only available through a Risk Mitigation Evaluation and Mitigation program that requires specific monitoring components and an authorized representative who oversees training, compliance, and patient enrollment.[4,5] It is also a schedule I.V. (C-IV) controlled substance. There is a boxed warning for excessive sedation and sudden loss of consciousness. Brexanolone has been associated with suicidal thoughts and behavior and should be discontinued in patients who experience worsening depression or suicidal thoughts.[4]

Adverse reactions

In phase III clinical trials, the most common adverse reactions were dry mouth, flushing, headache, loss of consciousness (dizziness), and sedation/somnolence.[4,6] Suicidal ideation and suicide attempts occurred during clinical trials, albeit, the risk of developing suicidal thoughts and behaviors with brexanolone is unknown due to low numbers of exposures.[4,6]

Pharmacokinetics

Brexanolone is highly protein-bound, which is independent of plasma concentrations. The half-life is approximately 9 hours. Brexanolone is metabolized through noncytochrome P450 pathways and is metabolized primarily through glucuronidation, keto-reduction, and sulfation. The three main circulating metabolites are inactive.[4] Excretion is fairly equal between the renal route at 42% and in feces at 47%.

Clinical pearls

- Brexanolone requires continuous monitoring for the duration of the infusion. Oxygen saturation using continuous pulse oximetry with an alarm and excessive sedation every 2 hours during planned nonsleep periods should be monitored because patients can develop sudden loss of consciousness during administration.[4]
- Therapy should be administered in the morning to recognize excessive sedation and to avoid confusion with normal nightly sleep patterns.[4]
- Brexanolone should not be used in pregnancy due to risk of fetal harm. It is excreted in human breast milk; however, the relative infant dose is 1% to 2% of the maternal weight-adjusted dose. There is no data on the effects on infants, and risks of therapy should be weighed before initiation.[4]
- Concomitant use of CNS depressants (benzodiazepines, alcohol) and antidepressants should be avoided due to increased risk of sedative effects.[4]
- Although phase III trials had a small patient population, brexanolone produced significant and clinically meaningful reductions in depression scores. Onset of benefit was rapid with a durable treatment response.[6] Of patients with a response to treatment, 94% (66 of 70 patients) did not experience relapse at day 30 of follow-up; however, relapse data beyond this point in unavailable.[6]

REFERENCES

1. Fitelson E, Kim S, Baker AS, Leight K. Treatment of postpartum depression: clinical, psychological and pharmacological options. *Int J Womens Health*. 2010;3:1-14.
2. Hirst KP, Moutier CY. Postpartum major depression. *Am Fam Physician*. 2010;82(8):926-933.
3. U.S. Food & Drug Administration. FDA approves first treatment for postpartum depression. 2019. www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-post-partum-depression.
4. Zulresso (brexanolone) [Package Insert]. Cambridge, MA: Sage Therapeutics, Inc; 2019.
5. U.S. Food & Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS): Zulresso (brexanolone). 2019. www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=387.
6. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018;392(10152):1058-1070.

▼ Sleep disorders

Solriamfetol (Sunosi)

An estimated 4% of the population suffers from obstructive sleep apnea (OSA), and narcolepsy affects 25 to 50 per 100,000 people.[1,2] Excessive sleepiness is present in 12% to 65% of individuals despite continuous positive airway pressure (CPAP) therapy.[3] Stimulant options can be utilized; however, there are limited, nonstimulant treatment options for excessive daytime sleepiness in those who suffer from narcolepsy or OSA.[4] Solriamfetol is a dopamine and norepinephrine reuptake inhibitor manufactured by Jazz Pharmaceuticals. It was approved in March 2019.[5]

Indications

Solriamfetol, an approved orphan drug, is indicated to improve wakefulness in patients with excessive sleepiness due to OSA or narcolepsy with a goal to improve wakefulness.[6] This medication will not treat the underlying airway obstruction in OSA, and this should be treated with CPAP use for at least 1 month prior to initiation of solriamfetol.[6] Airway obstruction treatment should be continued during treatment with solriamfetol.[6]

Mechanism of action

The mechanism of action of solriamfetol in improving wakefulness is unclear. It could be mediated through a novel mechanism, which is inhibition of the reuptake of dopamine and norepinephrine.[6]

Dosing and administration

Solriamfetol is available as a 75 mg (scored) and 150 mg tablet.[6] It should be taken in the morning upon awakening and should be avoided within 9 hours of planned bedtime due to potential interference with sleep. The starting dose for patients with narcolepsy is 75 mg once daily, while the starting dose in OSA is 37.5 mg once daily. The 75 mg tablet is functionally scored so tablets can be split in half at the score line. For both indications, the dose may be adjusted by doubling the dose every 3 days, with a max dose of 150 mg daily. Patients with renal impairment should be prescribed lower dosages based on their degree of impairment. Use in ESRD is not recommended. Solriamfetol is not recommended in patients with eGFR less than 15 mL/min/1.73 m^2. There are no recommended dose adjustments for hepatic impairment.[6]

Contraindications

Concomitant administration of solriamfetol with monoamine oxidase inhibitors (MAOI) or administration of an MAOI within the preceding 14 days prior to solriamfetol is contraindicated due to risk of a hypertensive reaction.[6]

Warnings and precautions

Solriamfetol is associated with BP and heart rate elevations that are dose-dependent. This is significant as this patient population is at an increased risk for cardiovascular events. BP and heart rate should be measured before treatment initiation and periodically throughout treatment. Avoid use in patients with unstable cardiovascular disease or serious dysrhythmias.[6] Solriamfetol should also be used cautiously in patients with a history of psychosis or bipolar symptoms. Anxiety, insomnia, and irritability were noted in clinical trials as potential psychiatric symptoms.[6-8]

Adverse reactions

The most commonly observed adverse reactions in phase III clinical trial were anxiety, decreased appetite, headache, insomnia, and nausea.[6-8]

Pharmacokinetics

The absorption of solriamfetol is delayed by 1 hour when taken with a high-fat meal; however, peak concentration is not affected. Solriamfetol has low protein binding at 13.3% to 19.4%. This medication is not significantly metabolized and 95% of a dose is excreted unchanged in the urine. There is minimal effect on or by metabolic enzymes; therefore, there are no significant drug interactions.[6]

Clinical pearls

- Although solriamfetol was not associated with withdrawal effects or rebound hypersomnia after discontinuation in clinical trials, it is a schedule I.V. controlled substance.[6-8]
- No evidence exists to support that abrupt discontinuation of solriamfetol will result in physical dependence or withdrawal; however, solriamfetol has shown elevated mood symptoms similar to or less than phentermine.[6]
- Data from case reports are not sufficient to determine the risks of major birth defects, adverse maternal and fetal outcomes, and miscarriage. Healthcare providers should register pregnant patients in solriamfetol's pregnancy exposure registry.[6]
- No data exist regarding the presence of solriamfetol in human milk; however, it is present in rat milk. When a drug is present in animal milk, it is likely present in human milk as well. The developmental benefits of breastfeeding should be considered with the mother's clinical need and potential adverse reactions. Monitor infants for agitation, insomnia, and reduced weight gain.[6]

REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328(17):1230-1235.
2. Longstreth WT Jr, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. *Sleep.* 2007;30(1):13-26.
3. Strollo PJ Jr, Hedner J, Collop N, et al. Solriamfetol for the treatment of excessive sleepiness in OSA: a placebo-controlled randomized withdrawal study. *Chest.* 2019;155(2):364-374.
4. Bhattarai J, Sumerall S. Current and future treatment options for narcolepsy: a review. *Sleep Sci.* 2017;10(1):19-27.
5. U.S. Food & Drug Administration. Drug Approval Package: Sunosi. 2019. www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211230Orig1Orig2s000TOC.cfm.
6. Sunosi (solriamfetol) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2019.
7. Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Ann Neurol.* 2019;85(3):359-370.
8. Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3). A randomized controlled trial. *Am J Respir Crit Care Med.* 2019;199(11):1421-1431.

▼ COPD

Aclidinium bromide and formoterol fumarate (Duaklir Pressair)

Chronic obstructive pulmonary disease (COPD) is the fourth-leading cause of death in the US.[1] COPD is characterized by a progressive airway obstruction and an abnormal inflammatory response that occurs in the lungs.[2] Aclidinium bromide and formoterol fumarate is a long-acting antimuscarinic (LAMA)/long-acting beta$_2$-agonist (LABA) combination inhaler.[3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend use of LAMA/LABA combination therapy in Stage D or Stage B or C with persistent symptoms or further exacerbations due to improvement in FEV$_1$ and reduction in symptoms compared with montherapy.[4] It was approved by the FDA for the maintenance treatment of COPD in March 2019 and is manufactured by Circassia Pharmaceuticals.[3]

Indications

Aclidinium bromide and formoterol fumarate is indicated for the maintenance treatment of COPD.[3]

Mechanism of action

As a LAMA, the mechanism of action of aclidinium bromide is the dilation of bronchioles by inhibition

of the M3 muscarinic receptor at the smooth muscle within the airways.[3] Formoterol fumarate, a selective LABA, locally dilates the bronchioles through activation of the B_2 receptor in the lungs when inhaled.[3] Combining bronchodilators with differing mechanisms of action may increase the degree of bronchodilation while decreasing the risk of adverse reactions compared with higher doses of a single bronchodilator.[4]

Dosing and administration

Aclidinium bromide and formoterol fumarate is a breath-actuated multidose dry powder inhaler that contains 400 mcg of aclidinium and 12 mcg of formoterol fumarate per actuation.[3] The recommended dose is one inhalation twice daily with one inhalation in the morning and one in the evening.[3] Although pharmacokinetic studies have not been performed, available data suggest renal and hepatic adjustments are not warranted.[3]

Contraindications

Contraindications to aclidinium bromide and formoterol fumarate include severe hypersensitivity (anaphylaxis, angioedema) to milk proteins, and hypersensitivity to aclidinium bromide, formoterol fumarate, or any other component of the product.[3] Aclidinium bromide and formoterol fumarate is not indicated for the treatment of asthma.[3]

Warnings and precautions

Aclidinium bromide and formoterol fumarate do not treat acute bronchospasm symptoms and should not be used in patients with acutely deteriorating COPD. Due to reported ECG changes, aclidinium bromide and formoterol fumarate should be used with caution in patients with severe cardiovascular disorders such as cardiac dysrhythmias and coronary insufficiency. This combination product should also be used with caution in patients with the following comorbidities: thyrotoxicosis, convulsive disorders, and those unusually responsive to sympathomimetic amines. Formoterol fumarate can produce hypokalemia and hypoglycemia, although these are generally transient and do not require treatment.[3]

Adverse reactions

The most common adverse reactions in phase III clinical trials include upper respiratory tract infection and headache. Additional risks of aclidinium bromide and formoterol fumarate use include paradoxical bronchospasm, immediate hypersensitivity reactions, cardiovascular effects, and worsening of narrow-angle glaucoma and urinary retention.[3] More serious adverse reactions could be associated with improper inhalation technique.

Pharmacokinetics

When patients are given the recommended dose, steady-state concentrations for aclidinium bromide and formoterol fumarate are achieved in 5 days. Aclidinium bromide is primarily metabolized by hydrolysis and is not expected to interfere with cytochrome P450 enzymes. Formoterol fumarate is metabolized into inactive metabolites by glucuronidation, O-demethylation, and conjugation.[3] CYP2D6 is primarily responsible for O-demethylation. The half-life for aclidinium bromide is about 12 hours.[3]

Clinical pearls

- Aclidinium bromide and formoterol fumarate is a dry powder inhaler dependent on patient inspiratory flow. Before initiation, it is critical to ensure patients have inspiratory effiency.[5] Inhaler technique should be assessed regularly.[4]
- Aclidinium bromide and formoterol fumarate lacks safety and effectiveness data in children; therefore, it is not indicated.[3]
- Drug interaction studies on aclidinium bromide and formoterol fumarate were not performed.[3] However, due to the lack of significant systemic absorption, significant drug interactions are not anticipated.
- Patients with COPD have not traditionally been treated with beta-blockers due to antagonistic mechanisms of action between beta-blockers and LABAs and risk for bronchospasm. However, a recent cohort study (TONADO) supported appropriate and cautious use of beta-blockers in patients with COPD and cardiovascular comorbidity.[3,6]

REFERENCES

1. National Heart, Lung, and Blood Institute. COPD Also known as Chronic Obstructive Pulmonary Disease, Emphysema. www.nhlbi.nih.gov/health-topics/copd.
2. MacNee W. Pathology, pathogenesis, and pathophysiology. *BMJ.* 2006;332(7551):1202-1204.
3. Duaklir Pressair (aclidinium bromide and formoterol fumarate) [Package Insert]. Morrisville, NC: Circassia Pharmaceuticals; 2019.
4. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmo-

nary disease 2019. 2019. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf.

5. Muralidharan P, Hayes D Jr, Mansour HM. Dry powder inhalers in COPD, lung inflammation and pulmonary infections. *Expert Opin Drug Deliv.* 2015;12(6):947-962.

6. Maltais F, Buhl R, Koch A, et al. _-Blockers in COPD: a cohort study from the TONADO research program. *Chest.* 2018;153(6):1315-1325.

▼ Multiple sclerosis

Siponimod (Mayzent)

Multiple sclerosis (MS) affects nearly 1 million people in the US.[1] It is characterized by destruction of the myelin sheath around neurons, resulting in various neurologic symptoms.[1] Eighty-five percent of MS patients have a relapsing-remitting course (RRMS), but more than 50% of RRMS patients ultimately develop secondary progressive MS (SPMS).[2,3] Manufactured by Novartis Pharmaceuticals Corporation, siponimod is a selective sphingosine 1-phosphate (S1P) receptor modulator that helps reduce the risk of MS disease progression.[3] Siponimod was approved by the FDA in March 2019.[4]

Indications

Siponimod is indicated for the treatment of relapsing forms of MS, including RRMS, clinically isolated syndrome, or active SPMS.[5]

Mechanism of action

Siponimod crosses the blood-brain barrier and selectively binds to S1P receptors. As an S1P modulator, it blocks the capacity of lymphocytes to exit lymph nodes. This reduces lymphocyte count in peripheral circulation and prevents migration of lymphocytes into the CNS.[3,5] The therapeutic effect of siponimod in MS is unknown but is thought to be associated with decreased inflammation by reducing lymphocytes circulating in the CNS.[5]

Dosing and administration

Siponimod is available as 0.25 mg and 2 mg film-coated tablets for oral administration.[5] Before initiation of siponimod, CYP2C9 genotype testing must be completed. When initiated, a 5-day titration is required to achieve the maintenance dosage of 2 mg. If a titration dose is missed for 24 hours or more, the titration regimen must be restarted. Missing four or more consecutive maintenance doses requires restarting the titration regimen. Patients with CYP2C9*1/*3 or *2/*3 genotype are recommended to use a reduced maintenance dose of 1 mg daily. No dose adjustment is needed for patients with renal or hepatic impairment.[5] Patients with cardiac issues are recommended to be monitored for 6 hours after administering the first dose where symptomatic bradycardia can be managed.[5]

Contraindications

Patients who have a CYP2C9*3/*3 genotype must not receive siponimod due to increased plasma levels of the drug placing the patient at risk for adverse reactions. Additional contraindications include a history of myocardial infarction, stroke, unstable angina, decompensated heart failure requiring hospitalization, or Class III/IV heart failure. Patients with Mobitz type II second/third degree AV block, or sick sinus syndrome are also contraindicated for use of siponimod unless heart rhythm is controlled by functioning pacemakers.[5]

Warnings and precautions

Siponimod may increase the risk of infection; therefore, immunosuppressive agents should be used with caution. Live, attenuated vaccines should be avoided during and until 4 weeks after stopping siponimod.[5] Patients experiencing visual changes, asthma, dyspnea, or signs and symptoms of liver damage during the therapy require reevaluation for appropriateness of therapy.[5]

Adverse reactions

The most commonly observed adverse reactions in phase III clinical trials were headache, hypertension, increased liver transaminase concentration, bradycardia varicella zoster reactivation, and lymphopenia.[3,5] Bradycardia symptoms require the dose titration necessary during treatment initiation. Adverse reactions lead to discontinuation in 8.5% of patients treated with siponimod.[3]

Pharmacokinetics

The oral bioavailability of siponimod is approximately 84%. This medication can be administered with or without food as food intake does not alter systemic exposure. Siponimod is highly bounded to plasma protein and metabolized via CYP2C9 and CYP3A4. Siponimod does not appear to have any renal clearance mechanisms.[5]

Clinical pearls

- Extensive baseline and continual monitoring parameters must be obtained, including but not limited to: complete blood cell count, liver function tests, ECG, ophthalmologic exam, pulmonary function tests.[5]

- Animal studies with siponimod demonstrated fetotoxicity and teratogenicity. Women of childbearing age should use effective contraception during therapy and for 10 days after stopping the therapy.[5]
- Pregnant women should avoid use of siponimod. Excretion of siponimod in milk has been observed in animal studies, but no human data are available.
- Clinical trials did not enroll sufficient numbers of patients 65 or older to determine if they respond differently to siponimod than younger patients. Clinical experience has not identified differences in response between these populations.[5]
- Before initiating siponimod, beta-blockers or other drugs with bradycardic properties may require adjustment. Consultation with a cardiologist is recommended for concomitant use of with antiarrhythmic/QT prolonging drugs.
- CYP2C9 and CYP3A4 inducers decrease siponimod exposure. Concomitant use with moderate CYP2C9 inducers and strong CYP3A4 inducers is not recommended. NP

REFERENCES

1. National Multiple Sclerosis Society. What is MS? 2019. www.nationalmssociety.org/What-is-MS.
2. Noonan CW, Williamson DM, Henry JP, et al. The prevalence of multiple sclerosis in 3 US communities. *Prev Chronic Dis*. 2010;7(1):A12.
3. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet*. 2018;391(10127):1263-1273.
4. U.S. Food and Drug Administration. FDA approves new oral drug to treat multiple sclerosis. 2019. www.fda.gov/news-events/press-announcements/fda-approves-new-oral-drug-treat-multiple-sclerosis.
5. Mayzent (siponimod) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019.

Lauren Hartsell Crump is a PGY-1 pharmacy resident at Novant Health Presbyterian Medical Center, Charlotte, N.C.

Miranda Benfield is a PGY-1 pharmacy resident at Carolinas Medical Center, Charlotte, N.C.

Caleb Ramey is a PharmD candidate at Wingate University School of Pharmacy, Wingate, N.C.

Ashley Arcara is a PharmD candidate at Wingate University School of Pharmacy, Wingate, N.C.

Sebin Yang is a PharmD candidate at Wingate University School of Pharmacy, Wingate, N.C.

Jenna Brown is a PharmD candidate at Wingate University School of Pharmacy, Wingate, N.C.

Geoffrey Mospan is an assistant professor of pharmacy at Wingate University School of Pharmacy, Wingate, N.C.

Cortney Mospan is an assistant professor of pharmacy at Wingate University School of Pharmacy, Wingate, N.C.

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