ganaxolone

Ztalmy

Pharmaceutical company: Marinus Pharmaceuticals

Pharmacologic classification: Neuroactive steroid GABA type A receptor positive modulator

Therapeutic classification: Anticonvulsant

Controlled substance schedule: Pending

AVAILABLE FORMS

Oral suspension: 50 mg

INDICATIONS AND DOSAGES

Seizures associated with cyclin-dependent kinase-like 5 deficiency disorder

Patients age 2 and older weighing over 28 kg: Initially, 150 mg t.i.d. (450 mg daily). Titrate to 300 mg t.i.d., then 450 mg t.i.d. to the maximum dosage of 600 mg t.i.d. (1,800 mg daily) based on tolerability. Titrate no more frequently than every 7 days.

Patients age 2 and older weighing 28 kg or less: Initially, 6 mg/kg t.i.d. (18 mg/kg/day). Titrate to 11 mg/kg t.i.d., then 16 mg/kg t.i.d. to the maximum dosage of 21 mg/kg t.i.d. (63 mg/kg/daily) based on tolerability.

Adjust-a-dose: When discontinuing ganaxolone, decrease the dose gradually, when possible, to minimize the risk of increased seizure frequency and status epilepticus. For those with hepatic impairment, monitor for adverse reactions; reduce dose as needed.

CONTRAINDICATIONS AND CAUTIONS

- Use cautiously in those with hepatic impairment, or with depression.
- Alert: Anticonvulsant drugs may increase the risk of suicidality as soon as the first week of treatment.
- This drug has the potential for abuse. Physical dependence risk hasn’t been determined, but abrupt discontinuation of anticonvulsant drugs isn’t recommended because of the risk of seizures.
- Safety and effectiveness in children under age 2 haven’t been established.
- Dialyzable drug: Unknown.

PREGNANCY-LACTATION-REPRODUCTION

- Enroll patients in pregnancy exposure registry at 1-888-233-2334 or https://www.aedpregnancyregistry.org/. There are no adequate and well-controlled studies during pregnancy.
- This drug is excreted in human milk. The effects on milk production and the breastfed infant are unknown. Use cautiously during breastfeeding.

INTERACTIONS

Drug-drug. CNS depressants (opioids, antidepressants): may cause somnolence and sedation. Use cautiously together when driving or operating machinery.

Strong or moderate CYP450 inducers (anticonvulsant drugs [carbamazepine, phenytoin, phenobarbital, primidone], rifampin): May decrease ganaxolone levels. Avoid use together. If use together is unavoidable,
consider increased ganaxolone dosage; don’t exceed maximum daily dose. In patients on a stable ganaxolone dosage who are initiating or increasing the dosages of enzyme-inducing anticonvulsant drugs, ganaxolone dosage may need to be increased; don’t exceed maximum daily dose.

**Drug-lifestyle.** *Alcohol use:* May increase somnolence and sedation. Use caution when driving or operating machinery.

**ADVERSE REACTIONS**

**CNS:** *seizures,* somnolence, pyrexia, sedation.

**EENT:** nasal congestion.

**GI:** salivary hypersecretion.

**Musculoskeletal:** gait disturbance.

**Respiratory:** upper respiratory infection, bronchitis.

**Other:** seasonal allergy, flulike syndrome.

Reactions in bold italics are *life-threatening.*

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**mitapivat**

Pyrukynd

*Pharmaceutical company:* Agios Pharmaceuticals

*Pharmacologic classification:* Pyruvate kinase activator

*Therapeutic classification:* Hemolysis inhibitor

**AVAILABLE FORMS**

*Tablets:* 5 mg, 20 mg, 50 mg

**INDICATIONS AND DOSAGES**

**Hemolytic anemia in those with pyruvate kinase (PK) deficiency**

*Adults:* Initially, 5 mg PO b.i.d. for 4 weeks. If hemoglobin remains below normal range or the patient required a transfusion within the last 8 weeks, increase to 20 mg b.i.d. for 4 weeks. If hemoglobin remains below normal range or patient required a transfusion within the last 8 weeks, increase to 50 mg b.i.d. If hemoglobin decreases during maintenance therapy of 5 mg or 20 mg b.i.d., consider titrating up to maximum of 50 mg b.i.d. Discontinue if there is no benefit by 24 weeks.

*Adjust-a-dose:* If used with moderate CYP3A inhibitors, maximum mitapivat dose is 20 mg b.i.d. If use with moderate CYP3A inducers is unavoidable, titrate mitapivat beyond 50 mg b.i.d., but don’t exceed a maximum of
100 mg b.i.d.

For those with adverse reaction, intolerability, or for hemoglobin above normal, reduce dose to the next lower dose level, 20 mg b.i.d. or 5 mg b.i.d. Taper the dose gradually to discontinue the drug. If the risk to the patient is greater than the risk of acute hemolysis because of sudden withdrawal of the drug, stop the drug without tapering.

CONTRAINDICATIONS AND CAUTIONS

- Avoid use in those with moderate or severe hepatic impairment.
- Safety and effectiveness in children haven’t been determined.
- **Dialyzable drug:** Unlikely.

PREGNANCY-LACTATION-REPRODUCTION

- There are no adequate and well-controlled studies during pregnancy. Use cautiously during pregnancy.
- Untreated PK deficiency during pregnancy may precipitate acute hemolysis, preterm labor, miscarriage, and severe anemia requiring frequent transfusion. Additionally, preeclampsia and severe hypertension have been reported.
- Patients using hormonal contraception should use an alternative nonhormonal method or add a barrier method during treatment.
- There are no data on the safety of breastfeeding. Consider the benefits of breastfeeding, clinical need of the drug to the mother, and potential adverse effects on the infant.

INTERACTIONS

**Drug-drug.** *CYP3A substrates (midazolam, hormonal contraceptives like ethinyl estradiol), CYP2B6 substrates, CYP2C substrates, UGT1A1 substrates):* May decrease substrate level. Monitor for loss of therapeutic effect of substrates with narrow therapeutic index. Use of alternative nonhormonal contraceptive or adding a barrier method of contraception is recommended.

*Moderate CYP3A inducers (efavirenz):* May decrease mitapivat levels. Consider alternative therapy. If use together is unavoidable, monitor hemoglobin and titrate beyond 50 mg b.i.d., if necessary, but don’t exceed a maximum recommended dose of 100 mg b.i.d.

*Moderate CYP3A inhibitors (fluconazole):* May increase mitapivat levels, and risk of adverse reactions. Monitor hemoglobin. Don’t titrate mitapivat beyond 20 mg b.i.d.

*P-glycoprotein (P-gp) substrates: (P-gp) substrates: May increase levels of drugs that are P-gp substrates. Monitor for adverse reactions of P-gp substrates with narrow therapeutic index.

*Strong CYP3A inducers (rifampin):* May decrease mitapivat levels. Avoid use together.

*Strong CYP3A inhibitors (itraconazole):* May increase mitapivat levels and risk of adverse reactions. Avoid use together.

ADVERSE REACTIONS

**CNS:** paresthesia.

**CV:** hot flush, flushing, hypertension, *arrhythmia.*

**EENT:** oropharyngeal pain, dry mouth.

**GI:** gastroenteritis, constipation.
Hematologic: acute hemolysis.

Metabolic: hypertriglyceridemia, increased urate level, estrone and estradiol decreases in males, testosterone increases in males.

Musculoskeletal: back pain, arthralgia, musculoskeletal pain.

Other: breast discomfort.

Reactions in bold italics are life-threatening.

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**otesconazole**

Vivjoa

*Pharmaceutical company:* Mycovia Pharmaceuticals

*Pharmacologic classification:* Azole antifungal

*Therapeutic classification:* Antifungal

**AVAILABLE FORMS**

*Capsules:* 150 mg

**INDICATIONS AND DOSAGES**

Reduce incidence of recurrent vulvovaginal candidiasis (RVVC) in patients with a history of RVVC who are not of reproductive potential

*Adult:* 600 mg PO as a single dose on day 1, then 450 mg as a single dose on day 2, then beginning day 14, give 150 mg every 7 days for 11 weeks (weeks 2 through 12). Or, if given in combination with fluconazole; on day 1, day 4, and day 7, give fluconazole 150 mg PO; then on days 14 through 20, give otesconazole 150 mg once daily; then beginning day 28, give otesconazole 150 mg PO every 7 days for 11 weeks (weeks 4 through 14).

**CONTRAINDICATIONS AND CAUTIONS**

- Contraindicated in patients hypersensitive to the drug or its components.
- Safety and efficacy have not been established in females who are premenarchal.
- This drug is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) or in patients with severe renal impairment or end-stage renal disease with or without dialysis.
- Use cautiously in older adults.
- *Dialyzable drug:* Unlikely.

**PREGNANCY-LACTATION-REPRODUCTION**
- This drug may cause fetal harm based on animal studies. The drug’s exposure window is about 690 days (5 half-lives).
- This drug is contraindicated in patients of reproductive potential (biological females who are not postmenopausal or who don’t have another reason for permanent infertility [tubal ligation, hysterectomy, salpingo-oophorectomy]) and during pregnancy.
- This drug is contraindicated during breastfeeding.

INTERACTIONS

**Drug-drug.** Breast cancer resistance protein substrates (rosuvastatin): May increase level and adverse effects of substrate. Use the lowest possible starting dose of the substrate or consider reducing the dose of the substrate drug. Monitor for adverse effects.

ADVERSE REACTIONS

**CNS:** headache.

**GI:** nausea, dyspepsia.

**GU:** dysuria, menorrhagia, metrorrhagia, vulvovaginal burning, discomfort, or pain.

**Other:** hot flush.

Reactions in bold italics are life-threatening.

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