producing smooth muscle relaxation and inflow of blood to the corpus cavernosum. Avanafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE-5), which is responsible for degradation of cGMP in the corpus cavernosum; when sexual stimulation causes local release of NO, inhibition of PDE-5 by avanafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum; at recommended doses, it has no effect in the absence of sexual stimulation.

Pharmacodynamics/Kinetics
Absorption: Rapid
Protein binding: ~99%
Metabolism: Hepatic via CYP3A4 (major), CYP2C (minor); forms metabolites (active and inactive)
Half-life elimination: Terminal: ~5 hours
Time to peak, plasma: 30 to 45 minutes (fasting); 1.12 to 1.25 hours (high-fat meal)
Excretion: Feces (~62%); urine (~21%)

Dosing
Adult Erectile dysfunction: Oral: Initial: 100 mg taken ~15 minutes prior to sexual activity; taken as one single dose and not more than once daily; dose may be increased to 200 mg ~15 minutes prior to sexual activity or decreased to 50 mg ~30 minutes prior to sexual activity using the lowest dose that provides benefit; maximum 200 mg daily
Dosing adjustment with concomitant medications:
Alpha-blocker (dose should be stable at time of avanafil initiation): Initial avanafil dose: 50 mg taken as one single dose and not more than once daily.
Moderate CYP34A inhibitors (including amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil): Maximum avanafil dose: 50 mg taken as one single dose and not more than once daily.
Strong CYP3A4 inhibitors (including atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, saquinavir, ritonavir, telithromycin): Avoid concomitant use of avanafil.
Geriatric Elderly ≥65 years: Refer to adult dosing.
Renal Impairment: Adult
CrCl ≥30 mL/minute: No dosage adjustment necessary.
CrCl <30 mL/minute: Has not been studied; use is not recommended by the manufacturer.
ESRD requiring hemodialysis: Has not been studied; use is not recommended by the manufacturer.
Hepatic Impairment: Adult
Mild-to-moderate hepatic impairment (Child-Pugh class A or B): No dosage adjustment necessary.
Severe hepatic impairment (Child-Pugh class C): Has not been studied; use is not recommended by the manufacturer.

Administration: Adult May be administered with or without food, ~15 to 30 minutes prior to sexual activity.
Monitoring Parameters Monitor for response, adverse reactions, blood pressure, and heart rate.
Dosage Forms: US Excipient information presented when available (limited, particularly for generics); consult specific product labeling.
Tablet, Oral:
Stendra: 50 mg, 100 mg, 200 mg

◆ **Avandia** *see* Rosiglitazone *on page 1980*

Avapritinib (A va PRI ti nib)

Brand Names: US Ayvakit
Index Terms Ayvakit; BLU-285; PDGFR alpha/KIT mutant-specific inhibitor BLU-285
Pharmacologic Category Antineoplastic Agent, PDGFR-alpha Blocker; Antineoplastic Agent, Tyrosine Kinase Inhibitor
Use Gastrointestinal stromal tumor, unresectable or metastatic: Treatment of unresectable or metastatic gastrointestinal stromal tumor harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations in adults.
Pregnancy Considerations Based on the mechanism of action and data from animal reproduction studies, in utero exposure to avapritinib may cause fetal harm. Evaluate pregnancy status prior to use in females of reproductive potential. Females of reproductive potential and males with female partners of reproductive potential should use effective contraception during therapy and for 6 weeks after the last dose of avapritinib.
Breastfeeding Considerations It is not known if avapritinib is present in breast milk.
Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during treatment and for 2 weeks after the last avapritinib dose.
Prescribing and Access Restrictions Avapritinib is available through a select network of specialty pharmacies. For more information, refer to https://ayvakit.com/hcp/.
Contraindications There are no contraindications listed in the manufacturer's labeling.
Warnings/Precautions Intracranial hemorrhage, including subdural hematoma and cerebral hemorrhage has been reported. Onset of intracranial hemorrhage ranged from ~2 to 19 months after avapritinib initiation. Withhold avapritinib if intracranial hemorrhage develops and resume at a reduced dose after resolution, or permanently discontinue based on toxicity severity. CNS effects commonly occurred, including cognitive impairment, dizziness, sleep disorders, mood disorders, speech disorders, and hallucinations. Some events were severe (grade 3 or 4). The median time to onset of the first CNS effects was ~6 weeks (range: 1 day to ~2 years). CNS effects may require therapy interruption, dose reduction, and/or permanent discontinuation (based on severity of the toxicity). Nausea, vomiting, and diarrhea were commonly reported but were usually grade 1 or 2. Select patients for the treatment of unresectable or metastatic gastrointestinal stromal tumor based on the presence of a PDGFRA exon 18 mutation. In a clinical study, PDGFRA exon 18 mutations were identified by local or central assessment using a polymerase chain reaction– or next-generation sequencing–based assay. Potentially significant drug-drug interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy.
Adverse Reactions Adverse reactions include unapproved dosing regimens.
Cardiovascular: Edema, facial edema, hypertension, peripheral edema, subdural hematoma
Central nervous system: Agitation, amnesia, anxiety, central nervous system toxicity, cerebral hemorrhage, cognitive dysfunction, dementia, disturbance in attention, dizziness, drowsiness, dysphoria, encephalopathy, fatigue, hallucination, headache, intracranial hemorrhage, irritability, mood disorder, personality changes, retrograde amnesia, sleep disorder, speech disturbance, suicidal ideation
Dermatologic: Alopecia, hair discoloration, palmar-plantar erythrodysesthesia, skin rash
Endocrine & metabolic: Ageusia, decreased serum albumin, decreased serum magnesium, decreased serum phosphate, decreased serum potassium, decreased serum sodium, dysgeusia, hyperthyroidism, hypothyroidism, thyroid disease, weight loss
Gastrointestinal: Abdominal pain, constipation, decreased appetite, diarrhea, dyspepsia, gastrointestinal hemorrhage, nausea, severe abdominal pain, severe vomiting, vomiting
Genitourinary: Testicular swelling
Hematologic & oncologic: Anemia, decreased neutrophils, increased INR, leukopenia, prolonged partial thromboplastin time, thrombocytopenia, tumor hemorrhage
Hepatic: Hyperbilirubinemia, increased serum alanine aminotransferase, increased serum alkaline phosphatase, increased serum aspartate aminotransferase, increased serum bilirubin
Infection: Sepsis
Neuromuscular & skeletal: Asthenia
Ophthalmic: Increased lacrimation, ocular edema, periorbital edema
Renal: Acute renal failure, increased serum creatinine
Respiratory: Dyspnea, pharyngeal edema, pleural effusion, pneumonia
Miscellaneous: Fever

Drug Interactions
Metabolism/Transport Effects Substrate of CYP2C9 (minor), CYP3A4 (major); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential
Avoid Concomitant Use
Avoid concomitant use of Avapritinib with any of the following: Azelastine (Nasal); Bromperidol; Conivaptan; CYP3A4 Inducers (Moderate); CYP3A4 Inducers (Strong); CYP3A4 Inhibitors (Strong); Fusidic Acid (Systemic); Idelalisib; Orphenadrine; Oxomemazine; Paraldehyde; Thalidomide
Increased Effect/Toxicity
Avapritinib may increase the levels/effects of: Alcohol (Ethyl); Azelastine (Nasal); Blonanserin; Brexanolone; Buprenorphine; CNS Depressants; Flunitrazepam; HYDROcodone; Methotrimeprazine; MetyroSINE; Opioid Agonists; Orphenadrine; OxyCODONE; Paraldehyde; Piribedil; Pramipexole; ROPINIRole; Rotigotine; Selective Serotonin Reuptake Inhibitors; Suvorexant; Thalidomide; Zolpidem

The levels/effects of Avapritinib may be increased by: Alizapride; Brimonidine (Topical); Bromopride; Bromperidol; Cannabidiol; Cannabis; Chlormethiazole; Chlorphenesin Carbamate; Clofazimine; Conivaptan; CYP3A4 Inhibitors (Moderate); CYP3A4 Inhibitors (Strong); Dimethindene (Topical); Doxylamine; Dronabinol; Droperidol; Erdafitinib; Esketamine; Fosaprepitant; Fusidic Acid (Systemic); HydrOXYzine; Idelalisib; Kava Kava; Larotrectinib; Lemborexant; Lofexidine; Magnesium Sulfate; Methotrimeprazine; Minocycline (Systemic); Nabilone; Oxomemazine; Palbociclib; Perampanel; Rufinamide; Simeprevir; Sodium Oxybate; Stiripentol; Tapentadol; Tetrahydrocannabinol; Tetrahydrocannabinol and Cannabidiol; Trimeprazine

Decreased Effect

The levels/effects of Avapritinib may be decreased by: CYP3A4 Inducers (Moderate); CYP3A4 Inducers (Strong); Deferasirox; Erdafitinib; Ivosidenib; Sarilumab; Siltuximab; Tocilizumab

Food Interactions The C_{max} and $AUC_{0-\infty}$ were increased by 59% and 29%, respectively, when administered with a high-calorie, high-fat meal (compared to fasting). Management: Administer avapritinib at least 1 hour before or 2 hours after a meal.

Hazardous Drugs Handling Considerations

This medication is not on the NIOSH (2016) list; however, it may meet the criteria for a hazardous drug. Avapritinib may cause reproductive toxicity, teratogenicity, and has a structural or toxicity profile similar to existing hazardous agents.

Use appropriate precautions for receiving, handling, storage, preparation, dispensing, administration, and disposal. Follow NIOSH and USP 800 recommendations **and** institution-specific policies/procedures for appropriate containment strategy (NIOSH 2016; USP-NF 2020).

Storage/Stability Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F).

Mechanism of Action Avapritinib is a potent tyrosine kinase inhibitor that blocks PDGFRA; it targets PDGFRA and PDGFR D842 mutants, as well as KIT exon 11, 11/17, and 17 mutants. Certain PDGFRA and KIT mutations may result in autophosphorylation and constitutive activation of these receptors, which may contribute to tumor cell proliferation. Avapritinib inhibits autophosphorylation of KIT D816V and PDGFRA D842V, which are mutants associated with resistance to approved kinase inhibitors.

Pharmacodynamics/Kinetics

Distribution: V_d: 1,200 L.
Protein binding: 98.8%.
Metabolism: Primarily hepatic via CYP3A4 (major) and CYP2C9 (minor).
Half-life elimination: 32 to 57 hours.
Time to peak: 2 to 4.1 hours.
Excretion: Feces: 70% (11% as unchanged drug); urine: 18% (<1% as unchanged drug). Clearance: 19.5 L/hour.

Dosing

Adult & Geriatric

Gastrointestinal stromal tumor, unresectable or metastatic (with a PDGFRA exon 18 mutation): Oral: 300 mg once daily until disease progression or unacceptable toxicity.

Missed/vomited doses: Do not make up for a missed dose within 8 hours of the next scheduled dose. If vomiting occurs, do not take an additional dose; resume dosing with the next scheduled daily dose.

Dosage adjustment for concomitant therapy:

CYP3A inhibitors: Avoid concomitant use with moderate or strong CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce dose to 100 mg once daily.

CYP3A inducers: Avoid concomitant use with moderate or strong CYP3A4 inducers.

Renal Impairment: Adult

Note: Renal function estimated by Cockcroft-Gault equation.

CrCl 30 to 89 mL/minute: No dosage adjustment necessary.

CrCl ≤29 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling.

End-stage renal disease: There are no dosage adjustments provided in the manufacturer's labeling.

Hepatic Impairment: Adult

Mild (total bilirubin ≤ ULN and AST > ULN **or** total bilirubin 1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) impairment: No dosage adjustment necessary.

Severe impairment (total bilirubin >3 times ULN and any AST): There are no dosage adjustments provided in the manufacturer's labeling.

Adjustment for Toxicity: Adult

Recommended Avapritinib Dosage Reduction Levels

Initial dose	300 mg once daily
First dose reduction	200 mg once daily
Second dose reduction	100 mg once daily
If further dose reductions are necessary	Permanently discontinue avapritinib in patients unable to tolerate 100 mg once daily.

CNS effects:

Grade 1: Continue avapritinib at the same dose or withhold dose until improvement to baseline or resolution; resume at the same or reduced dose.

Grade 2 or 3: Withhold avapritinib until improvement to baseline, grade 1, or resolution; resume at the same or reduced dose.

Grade 4: Permanently discontinue avapritinib.

Intracranial hemorrhage:

Grade 1 or 2: Withhold avapritinib until resolution for the first occurrence of intracranial hemorrhage; resume at a reduced dose. If subsequent intracranial hemorrhage occurs, permanently discontinue avapritinib.

Grade 3 or 4: Permanently discontinue avapritinib.

Other toxicity:

Grade 3 or 4: Withhold avapritinib until improvement to ≤ grade 2; resume at the same or reduced dose per clinical assessment.

Administration: Adult Oral: Administer on an empty stomach, at least 1 hour before or 2 hours after a meal.

Monitoring Parameters Assess PDGFRA exon 18 mutation status. Evaluate pregnancy status prior to use in females of reproductive potential. Monitor for CNS effects (eg, cognitive impairment, dizziness, sleep/mood/speech disorders, hallucinations) and for signs/symptoms of intracranial hemorrhage. Monitor adherence.

Dosage Forms: US Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Ayvakit: 100 mg, 200 mg, 300 mg

- **Avapro** *see* Irbesartan *on page 1205*
- **Avapro HCT** *see* Irbesartan and Hydrochlorothiazide *on page 1206*
- **AVAR** *see* Sulfur and Sulfacetamide *on page 2093*
- **AVAR-e** *see* Sulfur and Sulfacetamide *on page 2093*
- **AVAR-e Green** *see* Sulfur and Sulfacetamide *on page 2093*
- **AVAR-e LS** *see* Sulfur and Sulfacetamide *on page 2093*
- **AVAR LS** *see* Sulfur and Sulfacetamide *on page 2093*
- **Avastin** *see* Bevacizumab *on page 272*

Avatrombopag (a va TROM boe PAG)

Brand Names: US Doptelet

Index Terms AKR501; Avatrombopag Maleate; Doptelet; E5501; YM477

Pharmacologic Category Colony Stimulating Factor; Hematopoietic Agent; Thrombopoietic Agent; Thrombopoietin Receptor Agonist

Use

Chronic immune thrombocytopenia: Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment.

Chronic liver disease-associated thrombocytopenia: Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

Pregnancy Considerations Based on findings from animal reproduction studies, in utero exposure to avatrombopag may cause fetal harm.

Breastfeeding Considerations It is not known if avatrombopag is present in breast milk. Due to the potential for serious adverse events in the breastfed infant, the manufacturer does not recommend breastfeeding during chronic therapy or for ≥2 weeks after the last avatrombopag dose. If receiving avatrombopag for brief periods (eg, prior to an invasive procedure), lactating females should pump and discard breast milk during treatment and for ≥2 weeks after the last avatrombopag dose.

Contraindications There are no contraindications listed in the manufacturer's labeling.