Vemurafenib (Zelboraf)

Drug type
- A B-Raf enzyme inhibitor (also known as INN, PLX4032, RG7204, or RO5185426)

Indications
- Indicated for treatment of unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test

Mechanism of action
- Inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E
- Inhibits other kinases in vitro (eg, CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, FGR) at similar concentrations
- Shown to cause apoptosis in melanoma cell lines
  - Some mutations in *BRAF* gene result in constitutively activated BRAF proteins
  - Can cause cell proliferation in absence of growth factors normally required for proliferation

Dosage and administration
- Film-coated 240-mg tablet
- Take in morning and evening, approximately 12 hours apart; swallow tablet whole with a glass of water; do not chew or crush tablet; may take with or without food
- Missed doses
  - If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen; do not take both doses at the same time
- Duration of treatment is until disease progression occurs or unacceptable toxicity occurs

Pregnancy and lactation
- Pregnancy category D
- Lactation
  - Unknown whether distributed in breast milk
  - Breastfeeding not recommended during therapy

Cautions
- Cutaneous squamous cell carcinomas occurred in 24% of patients
- Serious hypersensitivity reactions reported during and on reinitiation, including anaphylaxis
- Severe hypersensitivity reactions
- QT prolongation
- Severe dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Liver enzymes may become elevated
- Mild-to-moderate photosensitivity
- Serious ophthalmologic reactions, including uveitis, iritis, blurry vision, photophobia, and retinal vein occlusion
- New primary malignant melanomas
- BRAF mutation test required to confirm eligibility for treatment; has not been studied with wild-type BRAF melanoma

Adverse effects
- May include, but are not limited to, the following:
  - Alopecia
  - Arthralgia
  - Fatigue
  - Nausea
  - Photosensitivity reaction
  - Pruritus
  - Rash
  - Skin papilloma

Continued on page 34

Drug interactions

- Inhibits CYP1A2 (moderate), 2A6, 2C9, 2C19, 2D6 (weak), and 3A4/5; the drug is a CYP3A4 inducer as well as a substrate.
- Warfarin (CYP2C9 substrate): 18% increase in warfarin AUC when coadministered; monitor INR closely
- Drugs with a narrow therapeutic window that are metabolized by CYP3A4, CYP1A2, or CYP2D6
  - Avoid concomitant use
  - If used together, consider a dose reduction of the CYP1A2 or CYP3A4, or CYP2D6 substrate drug.
- Caffeine (CYP2D6):
  - Increases caffeine AUC 2.6-fold
  - Decrease caffeine intake until effect has been determined
- Dextromethorphan (CYP2D6 substrate)
  - Decreases dextromethorphan AUC by 39%;
  - Consider lower dose of dextromethorphan if needed
- Vemurafenib is a substrate of CYP3A4
  - Strong CYP3A4 inhibitors
  - Strong CYP3A4 inducers

What to tell your patient

- Your doctor has prescribed this medication to treat your melanoma.
- This medication has been shown to work only in patients with a particular *BRAF* gene mutation.
- Currently this medication is only available through specialty pharmacies that send it directly to your home
- Take one tablet twice a day with water, with or without food, 12 hours apart
  - If you forget a dose, you can take the missed dose when you remember up until 4 hours before the next dose. Do not take the missed dose less than 4 hours before your next dose.
- You may have an allergic reaction to this medication.
  - Stop taking it and tell your nurse or doctor right away if you have any of the following symptoms:
    - A fast heartbeat; feeling faint; rash or redness all over your body; swelling of the face, lips, or tongue; throat tightness or hoarseness; or trouble breathing or swallowing
  - Stop taking the drug and tell your nurse or doctor right away if you get a severe skin reaction, such as:
    - Blisters on your skin; blisters or sores in your mouth; fever; peeling of your skin; or redness or swelling of your face, hands, or soles of your feet.
- This medication may cause cutaneous squamous cell carcinoma, a skin cancer that usually does not spread.
  - You should check your skin regularly, and let your nurse or doctor know if you see any skin changes such as a new wart, a sore or reddish bump that bleeds or does not heal, or a change in size or color of a mole.
  - Your nurse or doctor will check your skin before you start the medication, and every 2 months while you are taking this medication, and for 6 months after you stop treatment. New melanomas may form, but this is rare; your nurse or doctor will check for these also.
- The drug may cause you to get sunburned.
  - It causes photosensitivity, an increase in your sensitivity to the sun, so you should avoid being in the sun.
  - Wear protective clothing, a hat, and sunglasses and use broad-spectrum UVA/UVB sunscreen (SPF 30 and higher) and lip balm when you go outside.
- The most common side effects are joint pain (arthralgia), rash, hair loss (alopecia), fatigue, photosensitivity reactions, itching (pruritus), and skin papilloma.
- Tell your nurse or doctor if you have any heart problems, including a condition called QT syndrome; kidney or liver problems; plan to have surgery, dental, or other medical procedure; or if you are pregnant or plan to become pregnant
- Tell your nurse or doctor all the medicines you currently take, including herbal supplements
  - Most importantly, tell your nurse or doctor if you are taking warfarin (Coumadin), drugs to treat a fungal infection, HIV medicines, seizure drugs, an antidepressant, or medicines for an irregular heartbeat.
- While on this medication you should use an effective birth-control method, since this drug may harm the fetus.
  - You should not breastfeed an infant while taking this medication ■

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