Pharmacy Benefits Management Updates

VA Pharmacy Benefit Management Service (PBM) continually issues or revises its guidances for hematology and oncology care providers on a number of cancer care medications. Below are excerpts from recently released **Criteria for Use** documents. The complete documents, including the inclusion criteria, dosage and administration guidance, monitoring information, and discontinuation criteria should be consulted and can be found at www.pbm.va.gov or vaww.cmopnational.va.gov/cmop/PBM/default.aspx.

ENZALUTAMIDE (XTANDI) Criteria for Use, January 2017

Exclusion Criteria: If the answer to ANY item below is met, then the patient should NOT receive enzalutamide.

- ☐ Brain metastases or active epidural disease
- ☐ Severe renal impairment (creatinine clearance < 30 mL/min)
- ☐ History of seizure (including febrile seizure, loss of consciousness, or transient ischemic attack within the previous 12 months, any condition predisposing to seizure: prior stroke, brain AV malformation, head trauma with loss of consciousness requiring hospitalization)
- ☐ ECOG Performance Status > 2
- ☐ Inability to swallow capsules

Issues for Consideration

- Enzalutamide is not indicated for use in women. Based on the mechanism of action, can cause fetal harm if used during pregnancy. Pregnancy Category X—use contraindicated during pregnancy. Exclude pregnancy before prescribing enzalutamide, discuss risks if pregnancy occurs, and provide contraceptive counseling.
- Use in patients taking concomitant medications that may lower the seizure threshold was not studied; caution patients about the risk of activities where the sudden loss of consciousness could cause serious harm if concomitant use cannot be avoided.
- Use in patients at risk for or with a strong history of falls: in the phase 3 clinical trial, falls or injuries from falls occurred in 4.6% of enzalutamide patients vs 1.3% of placebo patients.
- Avoid strong inhibitors of CYP2C8 (eg, gemfibrozil); if concomitant use of a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of enzalutamide to 80 mg once daily according to the package insert.
- Co-administration with strong or moderate inducers of CYP3A4 (eg, carbamazepine, phenobarbital, phenytoin, rifampin, bosentan, efavirenz, modafinil, nafcillin, St. John's Wort) or CYP2C8 (eg, rifampin) should be avoided if possible. If patient must be co-administered a strong CYP3A4 inducer, increase enzalutamide dose from 160 mg to 240 mg once daily.
- Drugs that are substrates of CYP3A4 (eg, alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), or CYP2C19 (eg, S-mephenytoin) with a narrow therapeutic index should be avoided. If enzalutamide is co-administered with warfarin, additional INR testing should be conducted.
- Use in patients with hepatic impairment: Pharmacokinetics of enzalutamide and its metabolite were examined in volunteers with normal, Child-Pugh Class A, Child-Pugh Class B, and Child-Pugh Class C hepatic impairment. The composite AUC for enzalutamide and its metabolite after a single 160-mg dose was similar across all levels of hepatic impairment compared with normal volunteers.
- There have been postmarketing reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide. PRES is a neurologic disorder presenting with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual/neurological disturbances with or without associated hypertension. Diagnosis of PRES requires brain imaging, preferably by MRI. Enzalutamide should be discontinued in patients developing PRES.
- Sequencing of enzalutamide and abiraterone has been evaluated in several small retrospective analyses; the majority of the analyses are in the post chemotherapy setting. From this limited observational data, it is unclear if there is a preferred sequencing of abiraterone and enzalutamide. There is some evidence for cross-resistance. There are ongoing investigations into mechanisms of resistance to enzalutamide and abiraterone.

DARATUMUMAB (DARZALEX) Criteria for Use, January 2017

Exclusion Criteria: If the answer to ANY item below is met, then the patient should NOT receive daratumumab.

- ☐ Patient is noncompliant with medication, follow-up, or laboratory appointments
- ☐ Patient unable or unwilling to be observed an extended period of time that may be necessary for first infusion (refer to **Issues for Consideration**)
- ☐ Hemoglobin < 8 g/dL; Must transfuse to hemoglobin above 8 gm/dL prior to therapy initiation
- ☐ Absolute neutrophil count (ANC) < 1,000/mm^3
- ☐ Platelet count < 50,000/mm^3 (< 30,000/mm^3 if myeloma involvement in bone marrow > 50%)
- ☐ ECOG Performance Status > 2
- ☐ Total bilirubin > 3x the upper limit of the normal range (except for Gilbert syndrome: direct bilirubin 2x ULN) or ALT and AST > 3x ULN
- ☐ NYHA Class III or IV heart failure (refer to **Issues for Consideration**)
- ☐ Ongoing or active systemic infection, including active hepatitis B or C, or known HIV (refer to **Issues for Consideration**)
- ☐ Positive pregnancy test

Issues for Consideration

- Drug infusion time will be dependent upon patient tolerance and exposure to daratumumab. Median duration of the first infusion was ~ 7 hours in the SIRIUS trial, followed by infusion times of 4.2 and 3.4 hours, subsequently.
- Type and screen patients shortly prior to starting treatment. When the sample is provided to the blood bank, inform them that the patient will be receiving daratumumab.
- Those with NYHA Class III or IV heart failure, recent MI, conduction abnormalities, angina or arrhythmias uncontrolled by medications, were not eligible for clinical trials and may be at greater risk of cardiac complications.
- Patients with active hepatitis B, C, or HIV were excluded from clinical trials with daratumumab, therefore safety and efficacy data are unknown in these patient populations. The risk of infections was slightly higher in the daratumumab-treated arms of the comparative studies. Use of daratumumab should only be considered in those with well-controlled hepatitis B, hepatitis C, or HIV.

ELOTUZUMAB (EMPLICITI) Criteria for Use, January 2017

Exclusion Criteria: If the answer to ANY item below is met, then the patient should NOT receive elotuzumab.

- ☐ Patient is noncompliant with medication, follow-up, or laboratory appointments
- ☐ Patient is not a candidate for lenalidomide therapy (ie, is lenalidomide-refractory or possesses contraindications to therapy)
- ☐ Patient is not a candidate for high-dose dexamethasone therapy
- ☐ Hemoglobin < 8 g/dL; Must transfuse to hemoglobin above 8 gm/dL prior to therapy initiation
- ☐ Absolute neutrophil count (ANC) < 1,000/mm^3
- ☐ Platelet count < 50,000/mm^3 (< 30,000/mm^3 if myeloma involvement in bone marrow > 50%)
- ☐ ECOG Performance Status > 2
- ☐ Total bilirubin > 2x the upper limit of the normal range (except for Gilbert syndrome: direct bilirubin > 2 mg/dL) or ALT and AST > 3x ULN
- ☐ NYHA Class III or IV heart failure (refer to **Issues for Consideration**)
- ☐ Ongoing or active systemic infection, including active hepatitis B or hepatitis C, or known HIV (refer to **Issues for Consideration**)
- ☐ Positive pregnancy test
- ☐ Patient intends to breastfeed during therapy

Issues for Consideration

- Those with NYHA Class III or IV heart failure, recent MI, conduction abnormalities, angina or arrhythmias uncontrolled by medications, were not eligible for clinical trials and may be at greater risk of cardiac complications.
- Patients with active hepatitis B, hepatitis C, or HIV were excluded from clinical trials with elotuzumab, therefore safety and efficacy data are unknown in these patient populations. The risk of infections (OI, fungal, viral) was greater in the elotuzumab arm vs control arm of the comparative clinical trial. Use of elotuzumab should only be considered in those with well-controlled hepatitis B, hepatitis C, or HIV.
- Disappointing response rates as monotherapy in the relapsed/refractory setting suggest that elotuzumab should be given in combination with lenalidomide and dexamethasone.
- Impact of elotuzumab/lenalidomide/dexamethasone on overall survival is not known as these data were not mature at the time ELOQUENT-2 was published.

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CARFILZOMIB (KYPROLIS) Criteria for Use, December 2016

Exclusion Criteria: If the answer to ANY item below is met, then the patient should NOT receive carfilzomib.

- ☐ Care for the oncologic disease being treated not provided by a VA or VA purchased care (eg, Choice Program, Fee Basis) oncology provider
- ☐ Patient is noncompliant with medication, follow-up, or laboratory appointments
- ☐ Hemoglobin < 8 g/dL; Must transfuse to hemoglobin above 8 g/dL prior to therapy initiation
- ☐ Absolute neutrophil count (ANC) < 1,000/mm^3
- ☐ Platelet count < 50,000/mm^3 (< 30,000/mm^3 if myeloma involvement in bone marrow > 50%)
- ☐ ECOG Performance Status > 2
- ☐ Total bilirubin > 1.5 x the upper limit of the normal range or ALT and AST > 3 x ULN
- ☐ NYHA Class III and IV heart failure (refer to **Issues for Consideration**; those at risk for cardiac failure and ischemia were also excluded from clinical trials)
- ☐ LVEF < 40%
- ☐ Uncontrolled hypertension
- ☐ Grade 3 or 4 peripheral neuropathy
- ☐ Ongoing or active systemic infection, including active hepatitis B or C, or known HIV

Issues for Consideration

- A significant percentage of patients on carfilzomib develop dyspnea. This drug should be used with caution in patients with underlying lung disease. Close monitoring for worsening of dyspnea is advised.
- Risk of cardiac failure increases in those aged > 75 years; those with NYHA Class III and IV heart failure, recent MI, conduction abnormalities, angina or arrhythmias uncontrolled by medications, were not eligible for clinical trials and may be at greater risk of cardiac complications. Refer to Prescribing Information for management recommendations.
- Those aged > 75 years experienced greater toxicity than their younger counterparts.
- Patients on dialysis: administer carfilzomib after the dialysis procedure.
- Phase III evidence in heavily pretreated relapsed/refractory patients (median 5 prior regimens) of carfilzomib vs low-dose steroids ± cyclophosphamide indicates that the median overall survival is not significantly different between these treatment arms.

IXAZOMIB (NILARO) Criteria for Use, December 2016

Exclusion Criteria: If the answer to ANY item below is met, then the patient should NOT receive ixazomib

- ☐ Care for the oncologic disease being treated not provided by a VA or VA purchased care (eg, Choice Program, Fee Basis) oncology provider
- ☐ Patient is not a candidate for lenalidomide or dexamethasone therapy
- ☐ Patient is refractory to lenalidomide or proteasome-inhibitor therapy (defined as disease progression while on treatment or within 60 days of last dose)
- ☐ Absolute neutrophil count (ANC) < 1,000/mm^3
- ☐ Platelet count < 75,000/mm^3
- ☐ ECOG Performance Status > 2
- ☐ Patient with CNS involvement
- ☐ Patient receiving concurrent therapy with a strong CYP3A inducer (ie, rifampin, phenytoin, carbamazepine) that cannot be discontinued
- ☐ Uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina or myocardial infarction within 6 months prior to start
- ☐ Ongoing or active systemic infection, including active hepatitis B, hepatitis C, or known HIV

Issues for Consideration

- Indirect comparisons of phase 3 data (KRd vs Rd and IRd vs Rd) show that in similar populations of pretreated relapsed, refractory myeloma patients, those receiving KRd experienced longer PFS (26.3 vs 21 months), greater CR (32% vs 12%), greater ORR (87% vs 78%) and longer duration of response (28.6 vs 20.5 months). Therefore, providers may want to consider using carfilzomib in those meeting its criteria for use.
- Ixazomib is cytotoxic. Capsules should not be opened or crushed. Waste should be considered hazardous.
- Avoid concomitant use of strong CYP3A inducers (rifampin, phenytoin, carbamazepine, and St. John's Wort).