PDL DRUG REVIEW

Proprietary Name: Balversa®
Common Name: erdafitinib
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Erdafitinib, the active ingredient of Balversa®, is a kinase inhibitor that binds to and inhibits enzymatic activity of fibroblast growth factor receptor 1 (FGFR1), FGFR2, FGFR3, and FGFR4 based on in vitro data. Erdafitinib inhibited FGFR phosphorylation and signaling and decreased cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplifications, and fusion.

Indication: For the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has:

- Susceptible FGFR3 or FGFR2 genetic alterations, and
- Progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy

Select patients for therapy based on an FDA-approved companion diagnostic for Balversa®. This indication is approved under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

There is no pregnancy category for this medication; however, the risk summary indicates that based on the mechanism of action and findings in animal reproduction studies, Balversa® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to inform a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Pregnancy testing is recommended for females of reproductive potential prior to starting treatment with Balversa®. Advise females of reproductive potential and male patients with female partners of reproductive potential to use effective contraception during treatment and for one month after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-Coated Tablets: 3mg, 4mg, 5mg

Recommended Dosage: Select patients for the treatment of locally advanced or metastatic urothelial carcinoma with Balversa® based on the presence of susceptible FGFR genetic alterations in tumor specimens as detected by an FDA-approved companion diagnostic. Information on FDA-approved tests for the detection of FGFR genetic alterations in urothelial cancer is available at http://www.fda.gov/CompanionDiagnostics.

The recommended starting dose is 8mg PO QD, with a dose increase to 9mg QD based on serum phosphate levels and tolerability at 14 to 21 days. If vomiting occurs any time after taking Balversa®, the next dose should be taken the next day. Continue treatment until disease progression or unacceptable toxicity occurs.

Assess serum phosphate levels 14 to 21 days after starting treatment and increase the Balversa® dose to 9mg QD if serum phosphate level is <5.5mg/dl and there are no ocular disorders or Grade 2 or greater adverse reactions. Monitor phosphate levels monthly for hyperphosphatemia.

Dose modifications, such as dose interruption, reduction, or discontinuation, may be required for adverse reactions, including hyperphosphatemia, central serous retinopathy/retinal pigment epithelial detachment, or other reactions. Refer to the prescribing information for further information.

Clinically meaningful trends in the pharmacokinetics of erdafitinib were not seen in mild or moderate renal impairment or mild hepatic impairment. The pharmacokinetics of erdafitinib in patients with severe renal impairment, renal impairment requiring dialysis, or moderate and severe hepatic impairment are not known.

Drug Interactions: Is it recommended to consider alternative therapies that are not strong inhibitors of CYP2C9 or CYP3A4 during treatment with Balversa®. If coadministration of a strong CYP2C9 or CYP3A4 inhibitor is unavoidable, monitor closely for adverse reactions and consider dose modifications accordingly. Avoid coadministration of strong inducers of CYP2C9 or CYP3A4 with Balversa®. If a moderate CYP2C9 or CYP3A4 inducer must be co-administered at the start of Balversa® treatment, administer Balversa® dose as recommended (8mg QD with potential to increase to 9mg QD based on serum phosphate on days 14 to 21). If a moderate CYP2C9 or CYP3A4 inducer must be coadministered after the initial dose increase period based on serum phosphate levels and tolerability, increase Balversa® to 9mg. Coadministration of Balversa® with other serum phosphate level-altering agents may increase or decrease serum phosphate levels. Avoid the concomitant use of serum phosphate level-altering agents with Balversa® before initial dose increase period based on serum phosphate levels. Avoid coadministration of Balversa® with sensitive substrates of CYP3A4 with narrow therapeutic indices. As co-administration of Balversa® with OCT2 substrates may increase the plasma concentrations of OCT2 substrates, consider alternative therapies that are not OCT2 substrates or consider reducing the dose of OCT2 substrates (e.g. metformin) based on tolerability. Last, if coadministration of Balversa® with P-gp substrates is unavoidable, separate Balversa® by at least 6 hours before or after administration of P-gp substrates with narrow therapeutic index.

Erdafitinib plasma levels were predicted to be higher in patients with the CYP2C9*3/*3 genotype. It is recommended to monitor for increased adverse reactions in patients who are known or suspected to have CYP2C9*3/*3 genotype.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Balversa®) for all grades. There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included stomatitis (56%), diarrhea (47%), dry mouth (45%), constipation (28%), abdominal pain (23%), nausea (21%), vomiting (13%), decreased appetite (38%), fatigue (54%), pyrexia (14%), onycholysis (41%), dry skin (34%), palmar-plantar erythrodysesthesia (26%), alopecia (26%), nail discoloration (11%), dry eye (28%), vision blurred (17%), lacrimation increased (10%), dysgeusia (37%), paronychia (17%), urinary tract infection (17%), conjunctivitis (11%), oropharyngeal pain (11%), dyspnea (10%), hematuria (11%), musculoskeletal pain (20%), arthralgia (11%), and weight decreased (16%). Laboratory abnormalities included hemoglobin decreased (35%), platelets decreased (19%), leukocytes decreased (17%), neutrophils decreased (10%), phosphate increased (76%), creatinine increased (52%), sodium decreased (40%), alanine aminotransferase increased (41%), alkaline phosphatase increased (41%), albumin decreased (37%), aspartate aminotransferase increased (30%), magnesium decreased (30%), phosphate decreased (24%), calcium increased (22%), potassium increased (16%), and fasting glucose increased (10%).

Balversa® can cause ocular disorders, including central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) resulting in visual field defect. CSR/RPED was reported in 25% of patients treated with Balversa®, with

a median time to first onset of 50 days. Grade 3 CSR/RPED, involving central field of vision, was reported in 3% of patients. CSR/RPED resolved in 13% of patients and was ongoing in 13% of patients at the study cutoff. Dry eye symptoms were reported in 28% during treatment. It is recommended that all patients should receive dry eye prophylaxis with ocular demulcents as needed. Monthly ophthalmological exams during the first 4 months of treatment and every 3 months thereafter are recommended, and urgently at any time for visual symptoms.

Increases in phosphate levels are an effect of Balversa®, with hyperphosphatemia reported in 76% of patients treated with Balversa®. The median onset time for any grade event of hyperphosphatemia was 20 days after starting Balversa®. Monitor for hyperphosphatemia and follow the recommended dose modification guidelines.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Janssen Products

Analysis: The safety and efficacy of Balversa® were assessed in a multicenter, open-label, single-arm study that included patients with locally advanced or metastatic urothelial carcinoma (mUC). Fibroblast growth factor receptor (FGFR) mutation status for screening and enrollment of patients was determined by a clinical trial assay. Adults enrolled (N=87) had progressed on or after at least 1 prior chemotherapy and had at least 1 of the following genetic alterations: FGFR3 gene mutations or FGFR gene fusions. The median age was 67 years, while 79% were male and 74% were Caucasian. Most patients (92%) had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients were randomized to treatment and continued until disease progression or unacceptable toxicity. The main efficacy outcome measures were objective response rate (ORR) and duration of response (DOR), as determined by blinded independent review committee (BIRC) according to RECIST v1.1. Results can be seen in the table below, which was adapted from the prescribing information. Note that responders included patients who had previously not responded to anti PD-L1/PD-1 therapy.

	BIRC assessment (N=87)
ORR	32.2%
Complete Response (CR)	2.3%
Partial Response (PR)	29.9%
Median DOR, months	5.4

The following table includes the efficacy results by FGFR genetic alteration.

	BIRC assessment
FGFR3 Point Mutation	N=64
ORR	40.6%
FGFR3 Fusion	N=18
ORR	11.1%
FGFR2 Fusion	N=6

	BIRC assessment
ORR	0

Place in Therapy: Balversa® is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations and progressed during or following at least 1 line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. In a single-arm phase 3 study, the overall response rate for Balversa® was 32.2% and a duration of response of 5.4 months.

It is recommended that Balversa® be placed on the Recommended Drug List as non-recommended and require prior authorization to confirm appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

Reference

[1] Balversa [package insert]. Horsham, PA: Janssen Products, LP; 2019.