

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BALVERSA™ safely and effectively. See full prescribing information for BALVERSA.

BALVERSA (erdafitinib) tablets, for oral use
Initial U.S. Approval: 2019

-----**INDICATIONS AND USAGE**-----

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 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. (1, 2.1)

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. (1, 14)

-----**DOSAGE AND ADMINISTRATION**-----

- Confirm the presence of FGFR genetic alterations in tumor specimens prior to initiation of treatment with BALVERSA. (2.1)
- Recommended initial dosage: 8 mg orally once daily with a dose increase to 9 mg daily if criteria are met. (2.2)
- Swallow whole with or without food. (2.2)

-----**DOSAGE FORMS AND STRENGTHS**-----

Tablets: 3 mg, 4 mg, and 5 mg. (3)

-----**CONTRAINDICATIONS**-----

None. (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Ocular disorders: BALVERSA can cause central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED). Perform monthly ophthalmological examinations during the first four months of treatment, every 3 months afterwards, and at any time for visual symptoms. Withhold BALVERSA when CSR/RPED occurs and permanently discontinue if it does not resolve within 4 weeks or if Grade 4 in severity. (2.3, 5.1)
- Hyperphosphatemia: Increases in phosphate levels are a pharmacodynamic effect of BALVERSA. Monitor for hyperphosphatemia and manage with dose modifications when required. (2.3, 5.2)
- Embryo-fetal toxicity: Can cause fetal harm. Advise patients of the potential risk to the fetus and to use effective contraception (5.3, 8.1, 8.3).

BALVERSA™ (erdafitinib) tablets

-----**ADVERSE REACTIONS**-----

The most common adverse reactions including laboratory abnormalities (≥20%) were phosphate increased, stomatitis, fatigue, creatinine increased, diarrhea, dry mouth, onycholysis, alanine aminotransferase increased, alkaline phosphatase increased, sodium decreased, decreased appetite, albumin decreased, dysgeusia, hemoglobin decreased, dry skin, aspartate aminotransferase increased, magnesium decreased, dry eye, alopecia, palmar-plantar erythrodysesthesia syndrome, constipation, phosphate decreased, abdominal pain, calcium increased, nausea, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP, at 1-800-526-7736 (1-800-JANSSEN and www.BALVERSA.com) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- Strong CYP2C9 or CYP3A4 inhibitors: Consider alternative agents or monitor closely for adverse reactions. (7.1)
- Strong CYP2C9 or CYP3A4 inducers: Avoid concomitant use with BALVERSA. (7.1)
- Moderate CYP2C9 or CYP3A4 inducers: Increase BALVERSA dose up to 9 mg. (7.1)
- Serum phosphate level-altering agents: Avoid concomitant use with agents that can alter serum phosphate levels before the initial dose modification period. (2.3, 7.1)
- CYP3A4 substrates: Avoid concomitant use with sensitive CYP3A4 substrates with narrow therapeutic indices. (7.2)
- OCT2 substrates: Consider alternative agents or consider reducing the dose of OCT2 substrates based on tolerability. (7.2)
- P-gp substrates: Separate BALVERSA administration by at least 6 hours before or after administration of P-gp substrates with narrow therapeutic indices. (7.2)

-----**USE IN SPECIFIC POPULATIONS**-----

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

BALVERSA™ is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC), 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 [see *Dosage and Administration (2.1) and Clinical Studies (14)*].

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 [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION**2.1 Patient Selection**

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 [see *Clinical Studies (14.1)*].

Information on FDA-approved tests for the detection of FGFR genetic alterations in urothelial cancer is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage and Schedule

The recommended starting dose of BALVERSA is 8 mg (two 4 mg tablets) orally once daily, with a dose increase to 9 mg (three 3 mg tablets) once daily based on serum phosphate (PO₄) levels and tolerability at 14 to 21 days [see *Dosage and Administration (2.3)*].

Swallow tablets whole with or without food. If vomiting occurs any time after taking BALVERSA, the next dose should be taken the next day. Treatment should continue until disease progression or unacceptable toxicity occurs.

If a dose of BALVERSA is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for BALVERSA the next day. Extra tablets should not be taken to make up for the missed dose.

Dose Increase based on Serum Phosphate Levels

Assess serum phosphate levels 14 to 21 days after initiating treatment. Increase the dose of BALVERSA to 9 mg once daily if serum phosphate level is < 5.5 mg/dL and there are no ocular disorders or Grade 2 or greater adverse reactions. Monitor phosphate levels monthly for hyperphosphatemia [see *Pharmacodynamics (12.2)*].

2.3 Dose Modifications for Adverse Reactions

The recommended dose modifications for adverse reactions are listed in Table 1.

Table 1: BALVERSA Dose Reduction Schedule

Dose	1 st dose reduction	2 nd dose reduction	3 rd dose reduction	4 th dose reduction	5 th dose reduction
9 mg → (three 3 mg tablets)	8 mg (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop
8 mg → (two 4 mg tablets)	6 mg (two 3 mg tablets)	5 mg (one 5 mg tablet)	4 mg (one 4 mg tablet)	Stop	

Table 2 summarizes recommendations for dose interruption, reduction, or discontinuation of BALVERSA in the management of specific adverse reactions.

Table 2: Dose Modifications for Adverse Reactions

Adverse Reaction	BALVERSA Dose Modification
Hyperphosphatemia	
In all patients, restrict phosphate intake to 600-800 mg daily. If serum phosphate is above 7.0 mg/dL, consider adding an oral phosphate binder until serum phosphate level returns to < 5.5 mg/dL.	
5.6-6.9 mg/dL (1.8-2.3 mmol/L)	Continue BALVERSA at current dose.
7.0-9.0 mg/dL (2.3-2.9 mmol/L)	Withhold BALVERSA with weekly reassessments until level returns to < 5.5 mg/dL (or baseline). Then restart BALVERSA at the same dose level. A dose reduction may be implemented for hyperphosphatemia lasting > 1 week.
> 9.0 mg/dL (> 2.9 mmol/L)	Withhold BALVERSA with weekly reassessments until level returns to < 5.5 mg/dL (or baseline). Then may restart BALVERSA at 1 dose level lower.
> 10.0 mg/dL (> 3.2 mmol/L) or significant alteration in baseline renal function or Grade 3 hypercalcemia	Withhold BALVERSA with weekly reassessments until level returns to < 5.5 mg/dL (or baseline). Then may restart BALVERSA at 2 dose levels lower.
Central Serous Retinopathy/Retinal Pigment Epithelial Detachment (CSR/RPED)	
Grade 1: Asymptomatic; clinical or diagnostic observations only	Withhold until resolution. If resolves within 4 weeks, resume at the next lower dose level. Then, if no recurrence for a month, consider re-escalation. If stable for 2 consecutive eye exams but not resolved, resume at the next lower dose level.
Grade 2: Visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline	Withhold until resolution. If resolves within 4 weeks, may resume at the next lower dose level.
Grade 3: Visual acuity worse than 20/40 or > 3 lines of decreased vision from baseline	Withhold until resolution. If resolves within 4 weeks, may resume two dose levels lower. If recurs, consider permanent discontinuation.
Grade 4: Visual acuity 20/200 or worse in affected eye	Permanently discontinue.
Other Adverse Reactions^a	
Grade 3	Withhold BALVERSA until resolves to Grade 1 or baseline, then may resume dose level lower.
Grade 4	Permanently discontinue.

^a Dose adjustment graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAEv4.03).

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 3 mg: Yellow, round biconvex, film-coated, debossed with “3” on one side; and “EF” on the other side.
- 4 mg: Orange, round biconvex, film-coated, debossed with “4” on one side; and “EF” on the other side.
- 5 mg: Brown, round biconvex, film-coated, debossed with “5” on one side; and “EF” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS**5.1 Ocular Disorders**

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. CSR/RPED led to dose interruptions and reductions in 9% and 14% of patients, respectively and 3% of patients discontinued BALVERSA.

Dry eye symptoms occurred in 28% of patients during treatment with BALVERSA and were Grade 3 in 6% of patients. All patients should receive dry eye prophylaxis with ocular demulcents as needed.

Perform monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms. Ophthalmological examination should include assessment of visual acuity, slit lamp examination, fundoscopy, and optical coherence tomography.

Withhold BALVERSA when CSR occurs and permanently discontinue if it does not resolve within 4 weeks or if Grade 4 in severity. For ocular adverse reactions, follow the dose modification guidelines [see *Dosage and Administration* (2.3)].

5.2 Hyperphosphatemia

Increases in phosphate levels are a pharmacodynamic effect of BALVERSA [see *Pharmacodynamics* (12.2)]. Hyperphosphatemia was reported as adverse reaction in 76% of patients treated with BALVERSA. The median onset time for any grade event of hyperphosphatemia was 20 days (range: 8 –116) after initiating BALVERSA. Thirty-two percent of patients received phosphate binders during treatment with BALVERSA.

Monitor for hyperphosphatemia and follow the dose modification guidelines when required [see *Dosage and Administration* 2.2, 2.3].

5.3 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animal reproduction studies, BALVERSA can cause fetal harm when administered to a pregnant woman. In an embryo-fetal toxicity study, oral administration of erdafitinib to pregnant rats during the period of organogenesis caused malformations and embryo-fetal death at maternal exposures that were less than the human exposures at the maximum human recommended dose based on area under the curve (AUC). Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with BALVERSA and for one month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with BALVERSA and for one month after the last dose [see *Use in Specific Populations* (8.1, 8.3) and *Clinical Pharmacology* (12.1)].

6 ADVERSE REACTIONS

The following serious adverse reactions are also described elsewhere in the labeling:

- Ocular Disorders [see *Warning and Precautions* (5.1)].
- Hyperphosphatemia [see *Warning and Precautions* (5.2)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BALVERSA was evaluated in the BLC2001 study that included 87 patients with locally advanced or metastatic urothelial carcinoma which had susceptible FGFR3 or FGFR2 genetic alterations, and which progressed during or following at least one line of prior chemotherapy including within 12 months of neoadjuvant or adjuvant chemotherapy [see *Clinical Studies* (14.1)]. Patients were treated with BALVERSA at 8 mg orally once daily; with a dose increase to 9 mg in patients with phosphate levels <5.5 mg/dL on Day 14 of Cycle 1. Median duration of treatment was 5.3 months (range: 0 to 17 months).

The most common adverse reactions (ARs) including laboratory abnormalities (≥20%) were phosphate increased, stomatitis, fatigue, creatinine increased, diarrhea, dry mouth, onycholysis, alanine aminotransferase increased, alkaline phosphatase increased, sodium decreased, decreased appetite, albumin decreased, dysgeusia, hemoglobin decreased, dry skin, aspartate aminotransferase increased, magnesium decreased, dry eye, alopecia, palmar-plantar erythrodysesthesia syndrome, constipation, phosphate decreased, abdominal pain, calcium increased, nausea, and musculoskeletal pain. The most common Grade 3 or greater ARs (>1%) were stomatitis, nail dystrophy, palmar-plantar erythrodysesthesia syndrome, paronychia, nail disorder, keratitis, onycholysis, and hyperphosphatemia.

An adverse reaction with a fatal outcome in 1% of patients was acute myocardial infarction.

Serious adverse reactions occurred in 41% of patients including eye disorders (10%). Permanent discontinuation due to an adverse reaction occurred in 13% of patients. The most frequent reasons for permanent discontinuation included eye disorders (6%).

Dosage interruptions occurred in 68% of patients. The most frequent adverse reactions requiring dosage interruption included hyperphosphatemia (24%), stomatitis (17%), eye disorders (17%), and palmar-plantar erythro-dysaesthesia syndrome (8%).

Dose reductions occurred in 53% of patients. The most frequent adverse reactions for dose reductions included eye disorders (23%), stomatitis (15%), hyperphosphatemia (7%), palmar-plantar erythro-dysaesthesia syndrome (7%), paronychia (7%), and nail dystrophy (6%).

Table 3 presents ARs reported in ≥10% of patients treated with BALVERSA at 8 mg once daily.

Table 3: Adverse Reactions Reported in ≥ 10% (Any Grade) or ≥5% (Grade 3-4) of Patients

Adverse Reaction	BALVERSA 8 mg daily (N=87)	
	All Grades (%)	Grade 3-4 (%)
Any	100	67
Gastrointestinal disorders	92	24
Stomatitis	56	9
Diarrhea	47	2
Dry mouth	45	0
Constipation	28	1
Abdominal pain ^a	23	2
Nausea	21	1
Vomiting	13	2
Metabolism and nutrition disorders	90	16
Decreased appetite	38	0
General disorders and admin. site conditions	69	13
Fatigue ^b	54	10
Pyrexia	14	1
Skin and subcutaneous disorders	75	16
Onycholysis ^c	41	10
Dry skin ^d	34	0
Palmar-plantar erythrodysesthesia	26	6
Alopecia	26	0
Nail discoloration	11	0
Eye disorders	62	11
Dry eye ^e	28	6
Vision blurred	17	0
Lacrimation increased	10	0
Nervous system disorders	57	5
Dysgeusia	37	1
Infections and infestations	56	20
Paronychia	17	3
Urinary tract infection	17	6
Conjunctivitis	11	0
Respiratory, thoracic and mediastinal disorders	40	7
Oropharyngeal pain	11	1
Dyspnea ^f	10	2
Renal and urinary tract disorders	38	10
Hematuria	11	2
Musculoskeletal and connective tissue disorders	31	0
Musculoskeletal pain ^g	20	0
Arthralgia	11	0
Investigations	44	5
Weight decreased ^h	16	0

^a Includes abdominal pain, abdominal discomfort, abdominal pain upper, and abdominal pain lower

^b Includes asthenia, fatigue, lethargy, and malaise

^c Includes onycholysis, onychoclasia, nail disorder, nail dystrophy, and nail ridging

^d Includes dry skin and xerostomia

^e Includes dry eye, xerophthalmia, keratitis, foreign body sensation, and corneal erosion

^f Includes dyspnea and dyspnea exertional

^g Includes back pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal chest pain, neck pain, pain in extremity

^h Includes weight decreased and cachexia

Table 4: Laboratory Abnormalities Reported in ≥ 10% (All Grade) or ≥ 5% (Grade 3-4) of Patients

Laboratory Abnormality	BALVERSA 8 mg daily (N=86 ^a)	
	All Grades (%)	Grade 3-4 (%)
Hematology		
Hemoglobin decreased	35	3
Platelets decreased	19	1
Leukocytes decreased	17	0
Neutrophils decreased	10	2
Chemistry		
Phosphate increased	76	1
Creatinine increased	52	5
Sodium decreased	40	16
Alanine aminotransferase increased	41	1
Alkaline phosphatase increased	41	1
Albumin decreased	37	0
Aspartate aminotransferase increased	30	0
Magnesium decreased	30	1
Phosphate decreased	24	9
Calcium increased	22	3
Potassium increased	16	0
Fasting glucose increased	10	0

^a One of the 87 patients had no laboratory tests.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BALVERSA

Table 5 summarizes drug interactions that affect the exposure of BALVERSA or serum phosphate level and their clinical management.

Table 5: Drug Interactions that Affect BALVERSA

Strong CYP2C9 or CYP3A4 Inhibitors	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of BALVERSA with strong inhibitors of CYP2C9 or CYP3A4 increased erdafitinib plasma concentrations [see <i>Clinical Pharmacology</i> (12.3)]. Increased erdafitinib plasma concentrations may lead to increased drug-related toxicity [see <i>Warnings and Precautions</i> (5)].
Clinical Management	<ul style="list-style-type: none"> Consider alternative therapies that are not strong inhibitors of CYP2C9 or CYP3A4 during treatment with BALVERSA. If co-administration of a strong inhibitor of CYP2C9 or CYP3A4 is unavoidable, monitor closely for adverse reactions and consider dose modifications accordingly [see <i>Dosage and Administration</i> (2.3)]. If the strong inhibitor is discontinued, the BALVERSA dose may be increased in the absence of drug-related toxicity.
Strong CYP2C9 or CYP3A4 Inducers	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of BALVERSA with strong inducers of CYP2C9 or CYP3A4 may decrease erdafitinib plasma concentrations significantly [see <i>Clinical Pharmacology</i> (12.3)]. Decreased erdafitinib plasma concentrations may lead to decreased activity.
Clinical Management	<ul style="list-style-type: none"> Avoid co-administration of strong inducers of CYP2C9 or CYP3A4 with BALVERSA.
Moderate CYP2C9 or CYP3A4 Inducers	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of BALVERSA with moderate inducers of CYP2C9 or CYP3A4 may decrease erdafitinib plasma concentrations [see <i>Clinical Pharmacology</i> (12.3)]. Decreased erdafitinib plasma concentrations may lead to decreased activity.
Clinical Management	<ul style="list-style-type: none"> If a moderate CYP2C9 or CYP3A4 inducer must be co-administered at the start of BALVERSA treatment, administer BALVERSA dose as recommended (8 mg once daily with potential to increase to 9 mg once daily based on serum phosphate levels on Days 14 to 21 and tolerability). If a moderate CYP2C9 or CYP3A4 inducer must be co-administered after the initial dose increase period based on serum phosphate levels and tolerability, increase BALVERSA dose up to 9 mg. When a moderate inducer of CYP2C9 or CYP3A4 is discontinued, continue BALVERSA at the same dose, in the absence of drug-related toxicity.

Table 5: Drug Interactions that Affect BALVERSA (continued)

Serum Phosphate Level-Altering Agents	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of BALVERSA with other serum phosphate level-altering agents may increase or decrease serum phosphate levels [see <i>Pharmacodynamics</i> (12.2)]. Changes in serum phosphate levels due to serum phosphate level-altering agents (other than erdafitinib) may interfere with serum phosphate levels needed for the determination of initial dose increased based on serum phosphate levels [see <i>Dosage and Administration</i> (2.3)].
Clinical Management	<ul style="list-style-type: none"> Avoid co-administration of serum phosphate level-altering agents with BALVERSA before initial dose increase period based on serum phosphate levels (Days 14 to 21) [see <i>Dosage and Administration</i> (2.3)].

7.2 Effect of BALVERSA on Other Drugs

Table 6 summarizes the effect of BALVERSA on other drugs and their clinical management.

Table 6: BALVERSA Drug Interactions that Affect Other Drugs

CYP3A4 Substrates	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of BALVERSA with CYP3A4 substrates may alter the plasma concentrations of CYP3A4 substrates [see <i>Clinical Pharmacology</i> (12.3)]. Altered plasma concentrations of CYP3A4 substrates may lead to loss of activity or increased toxicity of the CYP3A4 substrates.
Clinical Management	<ul style="list-style-type: none"> Avoid co-administration of BALVERSA with sensitive substrates of CYP3A4 with narrow therapeutic indices.
OCT2 Substrates	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of BALVERSA with OCT2 substrates may increase the plasma concentrations of OCT2 substrates [see <i>Clinical Pharmacology</i> (12.3)]. Increased plasma concentrations of OCT2 substrates may lead to increased toxicity of the OCT2 substrates.
Clinical Management	<ul style="list-style-type: none"> Consider alternative therapies that are not OCT2 substrates or consider reducing the dose of OCT2 substrates (e.g., metformin) based on tolerability.
P-glycoprotein (P-gp) Substrates	
Clinical Impact	<ul style="list-style-type: none"> Co-administration of BALVERSA with P-gp substrates may increase the plasma concentrations of P-gp substrates [see <i>Clinical Pharmacology</i> (12.3)]. Increased plasma concentrations of P-gp substrates may lead to increased toxicity of the P-gp substrates.
Clinical Management	<ul style="list-style-type: none"> If co-administration of BALVERSA with P-gp substrates is unavoidable, separate BALVERSA administration by at least 6 hours before or after administration of P-gp substrates with narrow therapeutic index.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal reproduction studies, BALVERSA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. There are no available data on BALVERSA use in pregnant women to inform a drug-associated risk. Oral administration of erdafitinib to pregnant rats during organogenesis caused malformations and embryo-fetal death at maternal exposures that were less than the human exposures at the maximum recommended human dose based on AUC (see *Data*). Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data**Animal Data**

In an embryo-fetal toxicity study, erdafitinib was orally administered to pregnant rats during the period of organogenesis. Doses $\geq 4\text{mg/kg/day}$ (at total maternal exposures $<0.1\%$ of total human exposures at the maximum recommended human dose based on AUC) produced embryo-fetal death, major blood vessel malformations and other vascular anomalies, limb malformations (ectrodactyly, absent or misshapen long bones), an increased incidence of skeletal anomalies in multiple bones (vertebrae, sternebrae, ribs), and decreased fetal weight.

8.2 Lactation**Risk Summary**

There are no data on the presence of erdafitinib in human milk, or the effects of erdafitinib on the breastfed child, or on milk production. Because of the potential for serious adverse reactions from erdafitinib in a breastfed child, advise lactating women not to breastfeed during treatment with BALVERSA and for one month following the last dose.

8.3 Females and Males of Reproductive Potential**Pregnancy Testing**

Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with BALVERSA.

Contraception**Females**

BALVERSA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with BALVERSA and for one month after the last dose [see *Use in Specific Population* (8.1)].

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with BALVERSA and for one month after the last dose [see *Use in Specific Populations* (8.1)].

Infertility**Females**

Based on findings from animal studies, BALVERSA may impair fertility in females of reproductive potential [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

Safety and effectiveness of BALVERSA in pediatric patients have not been established. In 4 and 13-week repeat-dose toxicology studies in rats and dogs, toxicities in bone and teeth were observed at an exposure less than the human exposure (AUC) at the maximum recommended human dose. Chondroid dysplasia/metaplasia were reported in multiple bones in both species, and tooth abnormalities included abnormal/irregular denting in rats and dogs and discoloration and degeneration of odontoblasts in rats.

8.5 Geriatric Use

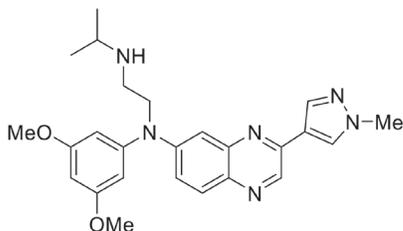
Of the 416 patients treated with BALVERSA in clinical studies, 45% were 65 years of age or older, and 12% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients [see *Clinical Studies* (14)].

8.6 CYP2C9 Poor Metabolizers

CYP2C9*3/*3 Genotype: Erdafitinib plasma concentrations were predicted to be higher in patients with the CYP2C9*3/*3 genotype. Monitor for increased adverse reactions in patients who are known or suspected to have CYP2C9*3/*3 genotype [see *Pharmacogenomics* (12.5)].

11 DESCRIPTION

Erdafitinib, the active ingredient in BALVERSA, is a kinase inhibitor. The chemical name is N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine. Erdafitinib is a yellow powder. It is practically insoluble, or insoluble to freely soluble in organic solvents, and slightly soluble to practically insoluble, or insoluble in aqueous media over a wide range of pH values. The molecular formula is $\text{C}_{25}\text{H}_{30}\text{N}_6\text{O}_2$ and molecular weight is 446.56. Chemical structure of erdafitinib is as follows:



BALVERSA (erdafitinib) is supplied as 3 mg, 4 mg or 5 mg film-coated tablets for oral administration and contains the following inactive ingredients:

Tablet Core: Croscarmellose sodium, Magnesium stearate (from vegetable source), Mannitol, Meglumine, and Microcrystalline Cellulose.

Film Coating (Opadry amb II): Glycerol monocaprylocaprate Type I, Polyvinyl alcohol-partially hydrolyzed, Sodium lauryl sulfate, Talc, Titanium dioxide, Iron oxide yellow, Iron oxide red (for the orange and brown tablets only), Ferrous ferric oxide/iron oxide black (for the brown tablets only).

12 CLINICAL PHARMACOLOGY**12.1 Mechanism of Action**

Erdafitinib is a kinase inhibitor that binds to and inhibits enzymatic activity of FGFR1, FGFR2, FGFR3 and FGFR4 based on *in vitro* data. Erdafitinib also binds to RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2. Erdafitinib inhibited FGFR phosphorylation and signaling and decreased cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplifications, and fusions. Erdafitinib demonstrated antitumor activity in FGFR-expressing cell lines and xenograft models derived from tumor types, including bladder cancer.

12.2 Pharmacodynamics**Cardiac Electrophysiology**

Based on evaluation of QTc interval in an open-label, dose escalation and dose expansion study in 187 patients with cancer, erdafitinib had no large effect (i.e., $> 20\text{ ms}$) on the QTc interval.

Serum Phosphate

Erdafitinib increased serum phosphate level as a consequence of FGFR inhibition. BALVERSA should be increased to the maximum recommended dose to achieve target serum phosphate levels of 5.5–7.0 mg/dL in early cycles with continuous daily dosing [see *Dosage and Administration* (2.3)].

In erdafitinib clinical trials, the use of drugs which can increase serum phosphate levels, such as potassium phosphate supplements, vitamin D supplements, antacids, phosphate-containing enemas or laxatives, and medications known to have phosphate as an excipient were prohibited unless no alternatives exist. To manage phosphate elevation, phosphate binders were permitted. Avoid concomitant use with agents that can alter serum phosphate levels before the initial dose increase period based on serum phosphate levels [see *Drug Interactions* (7.1)].

12.3 Pharmacokinetics

Following administration of 8 mg once daily, the mean (coefficient of variation [CV%]) erdafitinib steady-state maximum observed plasma concentration (C_{max}), area under the curve (AUC_{tau}), and minimum observed plasma concentration (C_{min}) were 1,399 ng/mL (51%), 29,268 ng•h/mL (60%), and 936 ng/mL (65%), respectively.

Following single and repeat once daily dosing, erdafitinib exposure (maximum observed plasma concentration [C_{max}] and area under the plasma concentration time curve [AUC]) increased proportionally across the dose range of 0.5 to 12 mg (0.06 to 1.3 times the maximum approved recommended dose). Steady state was achieved after 2 weeks with once daily dosing and the mean accumulation ratio was 4-fold.

Absorption

Median time to achieve peak plasma concentration (t_{max}) was 2.5 hours (range: 2 to 6 hours).

Effect of Food

No clinically meaningful differences with erdafitinib pharmacokinetics were observed following administration of a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50% of total caloric content of the meal from fat) in healthy subjects.

Distribution

The mean apparent volume of distribution of erdafitinib was 29 L in patients.

Erdafitinib protein binding was 99.8% in patients, primarily to alpha-1-acid glycoprotein.

Elimination

The mean total apparent clearance (CL/F) of erdafitinib was 0.362 L/h in patients.

The mean effective half-life of erdafitinib was 59 hours in patients.

Metabolism

Erdafitinib is primarily metabolized by CYP2C9 and CYP3A4. The contribution of CYP2C9 and CYP3A4 in the total clearance of erdafitinib is estimated to be 39% and 20% respectively. Unchanged erdafitinib was the major drug-related moiety in plasma, there were no circulating metabolites.

Excretion

Following a single oral dose of radiolabeled erdafitinib, approximately 69% of the dose was recovered in feces (19% as unchanged) and 19% in urine (13% as unchanged).

Specific Populations

No clinically meaningful trends in the pharmacokinetics of erdafitinib were observed based on age (21-88 years), sex, race, body weight (36-132 kg), mild (eGFR [estimated glomerular filtration rate, using modification of diet in renal disease equation] 60 to 89 mL/min/1.73 m²) or moderate (eGFR 30-59 mL/min/1.73 m²) renal impairment or mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1.0–1.5 x ULN and any AST).

The pharmacokinetics of erdafitinib in patients with severe renal impairment, renal impairment requiring dialysis, moderate or severe hepatic impairment is unknown.

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

Strong CYP2C9 Inhibitors:

Erdafitinib mean ratios (90% CI) for C_{max} and AUC_{inf} were 121% (99.9, 147) and 148% (120, 182), respectively, when co-administered with fluconazole, a strong CYP2C9 inhibitor and moderate CYP3A4 inhibitor, relative to erdafitinib alone.

Strong CYP3A4 Inhibitors:

Erdafitinib mean ratios (90% CI) for C_{max} and AUC_{inf} were 105% (86.7, 127) and 134% (109, 164), respectively, when co-administered with itraconazole (a strong CYP3A4 inhibitor and P-gp inhibitor) relative to erdafitinib alone.

Strong CYP3A4/2C9 Inducers:

Simulations suggested that rifampicin (a strong CYP3A4/2C9 inducer) may significantly decrease erdafitinib C_{max} and AUC.

In Vitro Studies

CYP Substrates:

Erdafitinib is a time dependent inhibitor and inducer of CYP3A4. The effect of erdafitinib on a sensitive CYP3A4 substrate is unknown. Erdafitinib is not an inhibitor of other major CYP isozymes at clinically relevant concentrations.

Transporters:

Erdafitinib is a substrate and inhibitor of P-gp. P-gp inhibitors are not expected to affect erdafitinib exposure to a clinically relevant extent. Erdafitinib is an inhibitor of OCT2.

Erdafitinib does not inhibit BCRP, OATP1B, OATP1B3, OAT1, OAT3, OCT1, MATE-1, or MATE-2K at clinically relevant concentrations.

Acid-Lowering Agents:

Erdafitinib has adequate solubility across the pH range of 1 to 7.4. Acid-lowering agents (e.g., antacids, H₂-antagonists, proton pump inhibitors) are not expected to affect the bioavailability of erdafitinib.

12.5 Pharmacogenomics

CYP2C9 activity is reduced in individuals with genetic variants, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Erdafitinib exposure was similar in subjects with CYP2C9*1/*2 and *1/*3 genotypes relative to subjects with CYP2C9*1/*1 genotype (wild type). No data are available in subjects characterized by other genotypes (e.g., *2/*2, *2/*3, *3/*3). Simulation suggested no clinically meaningful differences in erdafitinib exposure in subjects with CYP2C9*2/*2 and *2/*3 genotypes. The exposure of erdafitinib is predicted to be 50% higher in subjects with the CYP2C9*3/*3 genotype, estimated to be present in 0.4% to 3% of the population among various ethnic groups.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity studies have not been conducted with erdafitinib.

Erdafitinib was not mutagenic in a bacterial reverse mutation (Ames) assay and was not clastogenic in an *in vitro* micronucleus or an *in vivo* rat bone marrow micronucleus assay.

Fertility studies in animals have not been conducted with erdafitinib. In the 3-month repeat-dose toxicity study, erdafitinib showed effects on female reproductive organs (necrosis of the ovarian corpora lutea) in rats at an exposure less than the human exposure (AUC) at maximum recommended human dose.

14 CLINICAL STUDIES

14.1 Urothelial Carcinoma with Susceptible FGFR Genetic Alterations

Study BLC2001 (NCT02365597) was a multicenter, open-label, single-arm study to evaluate the efficacy and safety of BALVERSA in 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 (CTA). The efficacy population consists of a cohort of eighty-seven patients who were enrolled in this study with disease that had progressed on or after at least one prior chemotherapy and that had at least 1 of the following genetic alterations: FGFR3 gene mutations (R248C, S249C, G370C, Y373C) or FGFR gene fusions (FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7), as determined by the CTA performed at a central laboratory. Tumor samples from 69 patients were tested retrospectively by the QIAGEN *therascreen*® FGFR RGQ RT-PCR Kit, which is the FDA-approved test for selection of patients with mUC for BALVERSA.

Patients received a starting dose of BALVERSA at 8 mg once daily with a dose increase to 9 mg once daily in patients whose serum phosphate levels were below the target of 5.5 mg/dL between days 14 and 17; a dose increase occurred in 41% of patients. BALVERSA was administered until disease progression or unacceptable toxicity. The major 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.

The median age was 67 years (range: 36 to 87 years), 79% were male, and 74% were Caucasian. Most patients (92%) had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Sixty-six percent of patients had visceral metastases. Eighty-four (97%) patients received at least one of cisplatin or carboplatin previously. Fifty-six percent of patients only received prior cisplatin-based regimens, 29% received only prior carboplatin-based regimens, and 10% received both cisplatin and carboplatin-based regimens. Three (3%) patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy only. Twenty-four percent of patients had been treated with prior anti PD-L1/PD-1 therapy.

Efficacy results are summarized in Table 7 and Table 8. Overall response rate was 32.2%. Responders included patients who had previously not responded to anti PD-L1/PD-1 therapy.

Table 7: Efficacy Results

Endpoint	BIRC ^a assessment
	N=87
ORR (95% CI)	32.2% (22.4, 42.0)
Complete response (CR)	2.3%
Partial response (PR)	29.9%
Median DoR in months (95% CI)	5.4 (4.2, 6.9)

^a BIRC: Blinded Independent Review Committee

ORR = CR + PR

CI = Confidence Interval

Table 8: Efficacy Results by FGFR Genetic Alteration

FGFR Genetic Alteration	BIRC ^a assessment
	N=64
FGFR3 Point Mutation	N=64
ORR (95% CI)	40.6% (28.6, 52.7)
FGFR3 Fusion ^{b, c}	N=18
ORR (95% CI)	11.1% (0, 25.6)
FGFR2 Fusion ^c	N=6
ORR	0

^a BIRC: Blinded Independent Review Committee

^b Both responders had FGFR3-TACC3_V1 fusion

^c One patient with a FGFR2-CASP7/FGFR3-TACC3_V3 fusion is reported in both FGFR2 fusion and FGFR3 fusion above

ORR = CR + PR

CI = Confidence Interval

16 HOW SUPPLIED/STORAGE AND HANDLING

BALVERSA™ (erdafitinib) tablets are available in the strengths and packages listed below:

- 3 mg tablets: Yellow, round biconvex, film-coated, debossed with “3” on one side and “EF” on the other side.
 - Bottle of 56-tablets with child resistant closure (NDC 59676-030-56).
 - Bottle of 84-tablets with child resistant closure (NDC 59676-030-84).
- 4 mg tablets: Orange, round biconvex, film-coated, debossed with “4” on one side and “EF” on the other side.
 - Bottle of 28-tablets with child resistant closure (NDC 59676-040-28).
 - Bottle of 56-tablets with child resistant closure (NDC 59676-040-56).
- 5 mg tablets: Brown, round biconvex, film-coated, debossed with “5” on one side and “EF” on the other side.
 - Bottle of 28-tablets with child resistant closure (NDC 59676-050-28).

Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

FGFR genetic alterations: Advise patients that evidence of a susceptible FGFR3 or FGFR2 mutation or gene fusion within the tumor specimen is necessary to identify patients for whom treatment is indicated [see *Dosage and Administration (2.1)*].

Ocular disorders: Advise patients to contact their healthcare provider if they experience any visual changes [see *Warnings and Precautions (5.1)*]. In order to prevent or treat dry eyes, advise patients to use artificial tear substitutes, hydrating or lubricating eye gels or ointments frequently, at least every 2 hours during waking hours [see *Dosage and Administration (2.3)*].

Skin, mucous or nail disorders: Advise patients to contact their healthcare provider if they experience progressive or intolerable skin, mucous or nail disorders [see *Adverse Reactions (6.1)*].

Hyperphosphatemia: Advise patients that their healthcare provider will assess their serum phosphate level between 14 and 21 days of initiating treatment and will adjust the dose if needed [see *Warnings and Precautions (5.2)*]. During this initial phosphate-assessment period, advise patients to avoid concomitant use with agents that can alter serum phosphate levels. Advise patients that, after the initial phosphate assessment period, monthly phosphate level monitoring for hyperphosphatemia should be performed during treatment with BALVERSA [see *Drug Interactions (7.1)*].

Drug Interactions: Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, and herbal products [see *Drug Interactions (7.1, 7.2)*].

Dosing Instructions: Instruct patients to swallow the tablets whole once daily with or without food. If vomiting occurs any time after taking BALVERSA, advise patients to take the next dose the next day. [see *Dosage and Administration (2.1)*].

Missed dose: If a dose is missed, advise patients to take the missed as soon as possible. Resume the regular daily dose schedule for BALVERSA the next day. Extra tablets should not be taken to make up for the missed dose [see *Dosage and Administration (2.3)*].

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare providers of a known or suspected pregnancy [see *Warning and Precautions (5.3) and Use in Specific Population (8.1)*].

Advise female patients of reproductive potential to use effective contraception during treatment and for one month after the last dose of BALVERSA. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for one month after the last dose of BALVERSA [see *Use in Specific Populations (8.3)*].

Lactation: Advise females not to breastfeed during treatment with BALVERSA and for one month after the last dose [see *Use in Specific Populations (8.2)*].

Product of Switzerland

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

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PATIENT INFORMATION
BALVERSA™ (bal-VER-sah)
(erdafitinib) tablets

What is BALVERSA?

BALVERSA is a prescription medicine used to treat adults with bladder cancer (urothelial cancer) that has spread or cannot be removed by surgery:

- which has a certain type of abnormal “FGFR” gene, **and**
- who have tried at least one other chemotherapy medicine that contains platinum, and it did not work or is no longer working.

Your healthcare provider will test your cancer for certain types of abnormal FGFR genes and make sure that BALVERSA is right for you.

It is not known if BALVERSA is safe and effective in children.

Before taking BALVERSA tell your healthcare provider about all of your medical conditions, including if you:

- have vision or eye problems.
- are pregnant or plan to become pregnant. BALVERSA can harm your unborn baby. You should not become pregnant during treatment with BALVERSA.

Females who can become pregnant:

- Your healthcare provider may do a pregnancy test before you start treatment with BALVERSA.
- You should use effective birth control during treatment and for 1 month after the last dose of BALVERSA. Talk to your healthcare provider about birth control methods that may be right for you.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant.

Males with female partners who can become pregnant:

- You should use effective birth control when sexually active during treatment with BALVERSA and for 1 month after the last dose.
- are breastfeeding or plan to breastfeed. Do not breastfeed during treatment and for 1 month after the last dose of BALVERSA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take BALVERSA?

- Take BALVERSA exactly as your healthcare provider tells you.
- Take BALVERSA 1 time each day.
- Swallow BALVERSA tablets whole with or without food.
- Your healthcare provider may change your dose of BALVERSA, temporarily stop or completely stop treatment if you get certain side effects.
- If you miss a dose of BALVERSA, take the missed dose as soon as possible on the same day. Take your regular dose of BALVERSA the next day. Do not take more BALVERSA than prescribed to make up for the missed dose.
- If you vomit after taking BALVERSA, do not take another BALVERSA tablet. Take your regular dose of BALVERSA the next day.

What are the possible side effects of BALVERSA?**BALVERSA may cause serious side effects, including:**

- **Eye problems.** Eye problems are common with BALVERSA but can also be serious. Eye problems include dry or inflamed eyes, inflamed cornea (front part of the eye) and disorders of the retina, an internal part of the eye. Tell your healthcare provider right away if you develop blurred vision, loss of vision or other visual changes. You should use artificial tear substitutes, hydrating or lubricating eye gels or ointments at least every 2 hours during waking hours to help prevent dry eyes. During treatment with BALVERSA, your healthcare provider will send you to see an eye specialist.
- **High phosphate levels in the blood (hyperphosphatemia).** Hyperphosphatemia is common with BALVERSA but can also be serious. Your healthcare provider will check your blood phosphate level between 14 and 21 days after starting treatment with BALVERSA, and then monthly, and may change your dose if needed.

The most common side effects of BALVERSA include:

- mouth sores
- feeling tired
- change in kidney function
- diarrhea
- dry mouth
- nails separate from the bed or poor formation of the nail
- change in liver function
- low salt (sodium) levels
- decreased appetite
- change in sense of taste
- low red blood cells (anemia)
- dry skin
- dry eyes
- hair loss
- redness, swelling, peeling or tenderness, mainly on the hands or feet ('hand-foot syndrome')
- constipation
- stomach (abdominal) pain
- nausea
- muscle pain

Tell your healthcare provider right away if you develop any nail or skin problems including nails separating from the nail bed, nail pain, nail bleeding, breaking of the nails, color or texture changes in your nails, infected skin around the nail, an itchy skin rash, dry skin, or cracks in the skin.

BALVERSA may affect fertility in females who are able to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all possible side effects of BALVERSA. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BALVERSA?

- Store BALVERSA tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep BALVERSA and all medicines out of the reach of children.**General information about the safe and effective use of BALVERSA.**

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use BALVERSA for a condition for which it was not prescribed. Do not give BALVERSA to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about BALVERSA that is written for healthcare professionals.

What are the ingredients in BALVERSA?

Active ingredient: erdafitinib

Inactive ingredients:

Tablet Core: Croscarmellose sodium, Magnesium stearate (from vegetable source), Mannitol, Meglumine, and Microcrystalline Cellulose.
Film Coating (Opadry amb II): Glycerol monocaprylocaprate Type I, Polyvinyl alcohol-partially hydrolyzed, Sodium lauryl sulfate, Talc, Titanium dioxide, Iron oxide yellow, Iron oxide red (for the orange and brown tablets only), Ferrousferic oxide/iron oxide black (for the brown tablets only).

Manufactured by: Janssen-Cilag SpA, Latina, Italy

Manufactured for: Janssen Products, LP, Horsham, PA 19044

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For more information call Janssen Products, LP at 1-800-526-7736 (1-800-JANSSEN) or go to www.BALVERSA.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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