1 NAME OF THE MEDICINAL PRODUCT

Balversa 3mg film coated tablets
Balversa 4mg film coated tablets
Balversa 5mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains either 3, 4 or 5mg of erdafitinib

3 PHARMACEUTICAL FORM

Film coated tablet.

3mg: Yellow, round biconvex, film-coated, debossed with "3" on one side and "EF" on the other side.

4mg: Orange, round biconvex, film-coated, debossed with "4" on one side and "EF" on the other side.

5mg: Brown, round biconvex, film-coated, debossed with "5" on one side and "EF" on the other side.

4 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.

5 DOSAGE AND ADMINISTRATION

5.1

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 *[see Clinical Studies (14.1)]*.

5.2 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 (PO_4) levels and tolerability at 14 to 21 days *[see Dosage and Administration (5.3)]*.

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)]*.

5.3 Dose Modifications for Adverse Reactions

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

Table 1: BALVERSA Dose Reduction Schedule

Dose	1st dose reduction	2nd dose reduction	3rd dose reduction	4th dose reduction	5th 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).

5.4 Pediatric Use

BALVERSA is not indicated for children and adolescents under 18 years old

Safety and effectiveness of BALVERSA in pediatric patients have not been established.

6 CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients listed in section 14.1.

7 WARNINGS AND PRECAUTIONS

7.1 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 (5.3)]*.

7.2 Hyperphosphatemia and Soft Tissue Mineralization

BALVERSA can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcinosis, non-uremic calciphylaxis and vascular calcification. 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. Cutaneous calcinosis, non-uremic calciphylaxis and vascular calcification have been observed in 0.3% of patients treated with BALVERSA.

Monitor for hyperphosphatemia throughout treatment. 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. Withhold, dose reduce, or permanently discontinue BALVERSA based on duration and severity of hyperphosphatemia according to Table 2 *[see Dosage and Administration (5.3)]*.

7.3 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 (10.1, 10.3) and Clinical Pharmacology (12.1)]*.

8 ADVERSE REACTIONS

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

- Ocular Disorders *[see Warning and Precautions (7.1)]*.
- Hyperphosphatemia *[see Warning and Precautions (7.2)]*.

8.1 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, nail disorder, 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, hyponatremia, palmar-plantar erythrodysesthesia syndrome, paronychia, nail disorder, keratitis, 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-dysesthesia 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-dysesthesia 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
Hyponatremia	11	10
General disorders and admin. site conditions	69	13
Fatigue[b]	54	10
Pyrexia	14	1
Skin and subcutaneous disorders	75	16
Nail disorder[c]	45	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
Blood creatinine increased	11	0

[a] Includes abdominal pain, abdominal discomfort, abdominal pain upper, and abdominal pain lower
[b] Includes asthenia, fatigue, lethargy, and malaise
[c] Includes onycholysis, onychoclasis, nail disorder, nail dystrophy, nail ridging, and onychomadesis
[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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form *http://sideeffects.health.gov.il*

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 decreased	10	0

[a] One of the 87 patients had no laboratory tests.

9 DRUG INTERACTIONS

9.1 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

Moderate CYP2C9 or Strong CYP3A4 Inhibitors	
Clinical Impact	• Co-administration of BALVERSA with moderate CYP2C9 or strong CYP3A4 inhibitors increased erdafitinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased erdafitinib plasma concentrations may lead to increased drug-related toxicity *[see Warnings and Precautions (7)]*.
Clinical Management	• Consider alternative therapies that are not moderate CYP2C9 or strong CYP3A4 inhibitors during treatment with BALVERSA. • If co-administration of a moderate CYP2C9 or strong CYP3A4 inhibitor is unavoidable, monitor closely for adverse reactions and consider dose modifications accordingly *[see Dosage and Administration (5.3)]*. If the moderate CYP2C9 or strong CYP3A4 inhibitor is discontinued, the BALVERSA dose may be increased in the absence of drug-related toxicity.
Dual CYP2C9 and Strong CYP3A4 Inducers	
Clinical Impact	• Co-administration of BALVERSA with a dual CYP2C9 and strong CYP3A4 inducer decreased erdafitinib plasma concentrations significantly [see Clinical Pharmacology (12.3)]. • Decreased erdafitinib plasma concentrations may lead to decreased activity.
Clinical Management	• Avoid co-administration of dual CYP2C9 and strong CYP3A4 inducers with BALVERSA.
Strong/Moderate CYP2C9 or CYP3A4 Inducers	
Clinical Impact	• Co-administration of BALVERSA with strong/moderate CYP2C9 or CYP3A4 inducers may decrease erdafitinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased erdafitinib plasma concentrations may lead to decreased activity.
Clinical Management	• If a strong/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 strong/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 strong/moderate CYP2C9 or CYP3A4 inducer is discontinued, continue BALVERSA at the same dose, in the absence of drug-related toxicity.
Serum Phosphate Level-Altering Agents	
Clinical Impact	• Co-administration of BALVERSA with other serum phosphate level-altering agents may increase or decrease serum phosphate levels *[see Pharmacodynamics (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 Dosage and Administration (5.3)]*.
Clinical Management	• 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 Dosage and Administration (5.3)]*.

9.2 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

P-glycoprotein (P-gp) Substrates	
Clinical Impact	• Co-administration of BALVERSA with P-gp substrates may increase the plasma concentrations of P-gp substrates *[see Clinical Pharmacology (12.3)]*. • Increased plasma concentrations of P-gp substrates may lead to increased toxicity of the P-gp substrates.
Clinical Management	• 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.

10 USE IN SPECIFIC POPULATIONS

10.1 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 ≥4 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.

10.2 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.

10.3 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 (10.1)]*.

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 (10.1)]*.

Infertility

Females

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

10.4 Pediatric Use

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.

10.5 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 (14.1)]*.

10.6 Renal Impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment [estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m²]. No data are available in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

10.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Limited data are available in patients with severe (Child-Pugh C) hepatic impairment. *[see Clinical Pharmacology (12.3)]*.

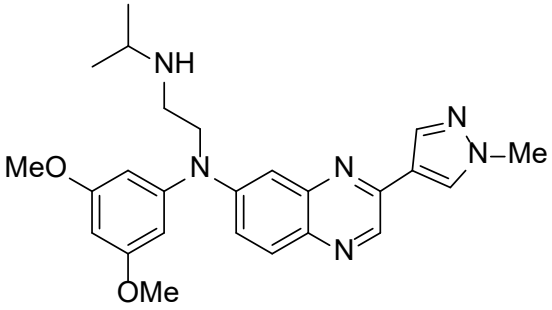
10.8 CYP2C9 Poor Metabolizers

*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 $C_{25}H_{30}N_6O_2$ and molecular weight is 446.56.

Chemical structure of erdafitinib is as follows:



BALVERSA® (erdafitinib) tablets are 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), Ferrosoferric 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 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 (5.3)]*.

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 (9.1)]*.

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 (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, or mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2). Limited data are available in patients with severe (Child-Pugh C) hepatic impairment. The pharmacokinetics of erdafitinib in patients with severe renal impairment and renal impairment requiring dialysis is unknown.

Drug Interaction Studies

Clinical Studies

Effect of Other Drugs on erdafitinib

Moderate 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 moderate CYP2C9 and 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.

CYP3A4/2C9 Inducers:

Mean ratios (90% CI) of C_{max} and AUC_{inf} for free erdafitinib were 78% (72.76, 83.12) and 45% (39.74, 51.59), respectively, when co-administered with carbamazepine (a strong CYP3A4 and weak CYP2C9 inducer) relative to erdafitinib alone *[see Interactions (7.1)]*.

Effect of Erdafitinib on Other Drugs

CYP3A4 Substrates:

Mean ratios (90% CI) of C_{max} and AUC_{inf} for midazolam (a sensitive CYP3A4 substrate) were 86.29% (73.52, 101.28) and 82.11% (70.83, 95.18), respectively, when co-administered with erdafitinib relative to midazolam alone. Erdafitinib does not have a clinically meaningful effect on midazolam PK.

OCT2 Substrates:

Mean ratios (90% CI) of C_{max} and AUC_{inf} for metformin (a sensitive OCT2 substrate) were 108.66% (90.31, 130.75) and 113.92% (93.22, 139.23), respectively, when co-administered with erdafitinib relative to metformin alone. Erdafitinib does not have a clinically meaningful effect on metformin PK.

In Vitro Studies

CYP Substrates:

Erdafitinib is a time dependent inhibitor and inducer of CYP3A4. 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, H_2-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

	BIRC[a] Assessment
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

15 PHARMACEUTICAL PARTICULARS

15.1 list of excipients

Microcrystalline cellulose

Mannitol

Croscarmellose sodium

Magnesium stearate

Maglumine

Opadry amb II 88A120003 Yellow (3mg):

Polyvinyl alcohol-partially hydrolyzed

Talc

Titanium dioxide

Iron oxide yellow

Glycerol monocaprylocaprate Type 1

Sodium lauryl sulfate

Opadry amb II 88A165000 Brown (5mg):

Polyvinyl alcohol-partially hydrolyzed

Talc

Titanium dioxide

Iron oxide red

Glycerol monocaprylocaprate Type 1

Sodium lauryl sulfate

Iron oxide yellow

Iron oxide black/ferrosoferric oxide

15.2 Shelf life

The expiry date of the product is indicated on the packaging materials.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

- 3 mg tablets: Bottle of 56-tablets with child resistant closure
- 4 mg tablets: Bottle of 28-tablets with child resistant closure Bottle of 56-tablets with child resistant closure
- 5 mg tablets: Bottle of 28-tablets with child resistant closure

Do not store above 25°C

17 MANUFACTURER

Janssen Cilag SpA Via C.Janssen, Borgo S.Michele, 04100 Latina, Italy

18 IMPORTER AND MARKETING AUTHORIZATION HOLDER

J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel

Balversa 3mg 165-77-36132-00
Balversa 4mg 165-78-36133-00
Balversa 5mg 165-79-36134-00

Revised on Apr2024

Based on USPI Jan2024