เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

BALVERSA™

1 Name of the Medicinal Product

1.1 Product Name

BALVERSA (Erdafitinib)

1.2 Strength

3 mg and 4 mg

1.3 Pharmaceutical Dosage Form

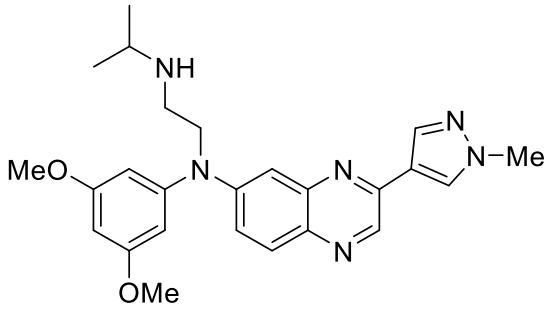
Film-coated Tablets

2 Quality and Quantitative Composition

2.1 Qualitative Declaration

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:



2.2 Quantitative Declaration

BALVERSA (erdafitinib) tablets are supplied as 3 mg and 4 mg film-coated tablets for oral administration

3 Pharmaceutical Form

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.

4 Clinical Particulars

4.1 Therapeutic indication

BALVERSA is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC) with susceptible FGFR3 genetic alterations whose disease has progressed on or after at least one line of prior systemic therapy.

Select patients for therapy based on a validated test for BALVERSA *[see Posology and method of administration (4.2.1) and Clinical Studies]*.

Limitations of Use
BALVERSA is not recommended for the treatment of patients who are eligible for and have not received prior PD-1 or PD-L1 inhibitor therapy *[see Clinical Studies].*

4.2 Posology and method of administration

4.2.1 Patient Selection

Select patients for the treatment of locally advanced or metastatic urothelial carcinoma with BALVERSA based on the presence of susceptible *FGFR3* genetic alterations in tumor specimens as detected by a validated test *[see Clinical Studies]*.

4.2.2 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 tolerability, including hyperphosphatemia, at 14 to 21 days *[see Posology and method of administration (4.2.3)].*

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 < 9.0 mg/dL and there are no ocular

disorders or Grade 2 or greater adverse reactions. If the phosphate level is 9.0 mg/dL or higher follow the relevant dose modifications in Table 2. Monitor phosphate levels monthly for hyperphosphatemia *[see Pharmacodynamics (5.1)]*.

4.2.3 Dose Modifications for Adverse Reactions

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

Table 1: BALVERSA Dose Reduction Schedule

Dose	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.	
<6.99 mg/dL	Continue BALVERSA at current dose.
7-8.99 mg/dL	• Continue BALVERSA at current dose. • Start phosphate binder with food until phosphate level is <7 mg/dL. • Reduce the dose if serum phosphate remains ≥7 mg/dL for a period of 2 months or if clinically necessary.
9-10 mg/dL	• Withhold BALVERSA with weekly reassessments until level returns to <7 mg/dL. Then restart BALVERSA at the same dose level. • Start phosphate binder with food until serum phosphate level returns to <7 mg/dL. • Reduce the dose if serum phosphate remains ≥9 mg/dL for a period of 1 month or if clinically necessary.
>10 mg/dL	• Withhold BALVERSA with weekly reassessments until level returns to <7 mg/dL. Then may restart BALVERSA at the first reduced dose level. • If hyperphosphatemia (≥10 mg/dL) for >2 weeks, discontinue BALVERSA permanently. • Medical management of symptoms as clinically relevant.

Serum phosphate with life-threatening consequences; urgent intervention indicated (e.g., dialysis)	• Discontinue BALVERSA permanently.
Central Serous Retinopathy (CSR)	
Any	Withhold BALVERSA and perform an ophthalmic evaluation within 2 weeks: • If improving within 14 days, restart BALVERSA at the current dose. • If not improving within 14 days, withhold BALVERSA until improving; once improving, may resume at the next lower dose level. Upon restarting BALVERSA, monitor for recurrence every 1 to 2 weeks for a month. If recurs or has not improved after 4 weeks of withholding BALVERSA, consider permanent discontinuation.
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 CTCAEv5.0).

4.2.4 Use in Specific Populations

Females and Males of Reproductive Potential

BALVERSA can cause fetal harm when administered to a pregnant woman *[see Pregnancy and lactation (4.6)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with BALVERSA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with BALVERSA and for one month after the last dose.

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.

Infertility

Females

Based on findings from animal studies, BALVERSA may impair fertility in females of reproductive potential *[see Preclinical Safety data (5.3)]*.

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.

Geriatric Use

Of the 479 patients treated with BALVERSA in clinical studies, 40% of patients were less than 65 years old, 40% of patients were 65 years to 74 years old, and 20% were 75 years old and over.

Patients 65 years of age and older treated with BALVERSA experienced a higher incidence of adverse reactions requiring treatment discontinuation than younger patients. In clinical trials, the incidence of treatment discontinuations of BALVERSA due to adverse reactions was 10% in patients younger than 65 years, 20% in patients ages 65-74 years, and 35% in patients 75 years or older.

No overall difference in efficacy was observed between these patients and younger patients *[see Clinical Studies].*

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 (5.2.1)].*

4.3 Contraindication

None.

4.4 Special Warnings and Precautions for use

4.4.1 Ocular Disorders

BALVERSA can cause ocular disorders, including central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) resulting in visual field defect.

In the pooled safety population *[see Undesirable effects (4.8)]* CSR/RPED occurred in 22% of patients treated with BALVERSA, with a median time to first onset of 46 days. In 104 patients with CSR, 40% required dose interruptions and 56% required dose reductions; 2.9% of BALVERSA-treated patients required permanent discontinuation for CSR. Of the 24 patients who restarted BALVERSA after dose interruption with or without dose reduction, 67% had recurrence and/or worsening of CSR after restarting. CSR was ongoing in 41% of the 104 patients at the time of last evaluation.

Dry eye symptoms occurred in 26% of BALVERSA-treated 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 or permanently discontinue BALVERSA based on severity and/or ophthalmology exam findings *[see Posology and method of administration (4.2.3)]*.

4.4.2 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 (5.1)].*

In the pooled safety population *[see Undesirable effects (4.8)]*, increased phosphate occurred in 73% of BALVERSA-treated patients. The median onset time of increased phosphate was 16 days (range: 8-421) after initiating BALVERSA. Twenty-four percent of patients received phosphate binders during treatment with BALVERSA. Vascular calcification was observed in 0.2% of patients treated with BALVERSA.

Monitor for hyperphosphatemia throughout treatment. Restrict dietary phosphate intake (600-800 mg daily) and avoid concomitant use of agents that may increase serum phosphate levels.

If serum phosphate is above 7.0 mg/dL, consider adding an oral phosphate binder until serum phosphate level returns to <7.0 mg/dL. Withhold, dose reduce, or permanently discontinue BALVERSA based on duration and severity of hyperphosphatemia according to Table 2 *[see Posology and method of administration (4.2.3)]*.

4.4.3 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 Pregnancy and Lactation (4.6), Use in Specific populations (4.2.4) and Pharmacological Properties (5)]*.

4.5 Interaction with other medicinal products and other forms of interactions

4.5.1 Effect of Other Drugs on BALVERSA

Table 3 summarizes drug interactions that affect the exposure of BALVERSA or serum phosphate level and their clinical management.

Table 3: 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 Pharmacokinetic Properties (5.2)].* • Increased erdafitinib plasma concentrations may lead to increased drug-related toxicity *[see Special Warning and Precautions for use (4.4)].*
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 Posology and method of administration (4.2.3)]* If the moderate CYP2C9 or strong CYP3A4 inhibitor is discontinued, resume the BALVERSA dose before dose modifications in the absence of drug-related toxicity.
Strong CYP3A4 Inducers	
Clinical Impact	• Co-administration of BALVERSA with strong CYP3A4 inducers decreased erdafitinib plasma concentrations *[see Pharmacokinetic Properties (5.2)].* • Decreased erdafitinib plasma concentrations may lead to decreased activity.
Clinical Management	• Avoid co-administration of strong CYP3A4 inducers with BALVERSA.
Moderate CYP3A4 Inducers	
Clinical Impact	• Co-administration of BALVERSA with moderate CYP3A4 inducers may decrease erdafitinib plasma concentrations *[see Pharmacokinetic Properties (5.2)].* • Decreased erdafitinib plasma concentrations may lead to decreased activity.
Clinical Management	• If a moderate CYP3A4 inducer must be co-administered at the start of BALVERSA treatment, administer BALVERSA at a dose of 9 mg daily. • When a moderate 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 (5.1)].* • • 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 Posology and method of administration (4.2.3)]*
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 Posology and method of administration (4.2.3)]*

4.5.2 Effect of BALVERSA on Other Drugs

Table 4 summarizes the effect of BALVERSA on other drugs and their clinical management.

Table 4: 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 Pharmacokinetic Properties (5.2)].* • 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.

4.6 Pregnancy and lactation

4.6.1 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 Pharmacological Properties (5)]*.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.

4.6.2 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.

4.7 Effects on ability to drive and use machine

No studies to establish the effects of erdafitinib on the ability to drive and use machines have been conducted. However, eye disorders such as central serous retinopathy or keratitis have been noted with FGFR inhibitors and with TRADENAME treatment. If patients experience treatment related symptoms affecting their vision, it is recommended that they do not drive or use machines until the effect subsides (*see Special Warning and Precautions for use (4.4)].*

4.8 Undesirable effects

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

- Ocular Disorders *[see Special Warning and Precautions for use (4.4.1)]*.
- Hyperphosphatemia *[see Special Warning and Precautions for use (4.4.2)]*.

4.8.1 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 pooled safety population described in the Special Warning and Precautions reflects exposure to BALVERSA as a single agent at the recommended dose (8 to 9 mg orally daily) in 479 patients with advanced urothelial cancer and *FGFR* alterations in 42756493BLC3001 (NCT03390504), 42756493BLC2001 (NCT02365597), 42756493BLC2002 (NCT 03473743), and 42756493EDI1001 (NCT01703481). Among 479 patients who received BALVERSA, the median duration of treatment was 4.8 months (range: 0.1 to 43 months). In this pooled safety population, the most common

(>20%) adverse reactions, including laboratory abnormalities, were increased phosphate, nail disorders, stomatitis, diarrhea, increased creatinine, increased alkaline phosphatase, increased alanine aminotransferase, decreased hemoglobin, decreased sodium, increased aspartate aminotransferase, fatigue, dry mouth, dry skin, decreased phosphate, decreased appetite, dysgeusia, constipation, increased calcium, dry eye, palmar-plantar erythrodysesthesia syndrome, increased potassium, alopecia, and central serous retinopathy.

BLC3001

The safety of BALVERSA was evaluated in Cohort 1 of the BLC3001 study that included patients with locally advanced unresectable or metastatic urothelial carcinoma which had susceptible *FGFR3* genetic alterations and were previously treated with a PD-1 or PD-L1 inhibitor *[see Clinical Studies]*. Patients received either BALVERSA (8 mg orally once daily with individualized up-titration to 9 mg) (n=135) or chemotherapy (docetaxel 75 mg/m^2 once every 3 weeks or vinflunine 320 mg/m^2 once every 3 weeks) (n=112). Among patients who received BALVERSA, median duration of treatment was 4.8 months (range: 0.2 to 38 months).

Serious adverse reactions occurred in 41% of patients who received BALVERSA. Serious reactions in >2% of patients included urinary tract infection (4.4%), hematuria (3.7%), hyponatremia (2.2%), and acute kidney injury (2.2%). Fatal adverse reactions occurred in 4.4% of patients who received BALVERSA, including sudden death (1.5%), pneumonia (1.5%), renal failure (0.7%), and cardiorespiratory arrest (0.7%).

Permanent discontinuation of BALVERSA due to an adverse reaction occurred in 14% of patients. Adverse reactions which resulted in permanent discontinuation of BALVERSA in >2% of patients included nail disorders (3%) and eye disorders (2.2%).

Dosage interruptions of BALVERSA due to an adverse reaction occurred in 72% of patients. Adverse reactions which required dosage interruption in >4% of patients included nail disorders (22%), stomatitis (19%), eye disorders (16%), palmar-plantar erythrodysesthesia syndrome (15%), diarrhea (10%), hyperphosphatemia (7%), increased aspartate aminotransferase (6%), and increased alanine aminotransferase (5%).

Dose reductions of BALVERSA due to an adverse reaction occurred in 69% of patients. Adverse reactions which required dose reductions in >4% of patients included nail disorders (27%), stomatitis (19%), eye disorders (17%), palmar-plantar erythrodysesthesia syndrome (12%), diarrhea (7%), dry mouth (4.4%), and hyperphosphatemia (4.4%).

Table 5 presents adverse reactions reported in ≥15% of patients treated with BALVERSA at 8 or 9 mg once daily versus chemotherapy.

Table 5: Adverse Reactions Reported in ≥15% of Patients Who Received BALVERSA Versus Chemotherapy (Study BLC3001)

	BALVERSA (N=135)		Chemotherapy (N=112)	
Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders				
Nail disorders[a]	70	12	5	0

Palmar-plantar erythrodysesthesia syndrome	30	10	0.9	0
Dry skin[a]	27	1.5	6	0
Alopecia	25	0.7	24	0
Gastrointestinal disorders				
Diarrhea[a]	63	3	17	2.7
Stomatitis[a]	56	10	18	1.8
Dry Mouth	39	0	3.6	0
Constipation	27	0	28	1.8
Nervous system disorders				
Dysgeusia[a]	30	0.7	7	0
General disorders				
Fatigue[a]	29	1.5	42	7
Metabolism and nutrition disorders				
Decreased appetite	27	3	21	2.7
Eye disorders				
Dry eye[a]	25	0.7	3.6	0
Central serous retinopathy[a]	18	2.2	0	0
Investigations				
Decreased weight	22	2	2.7	0

[a] Includes multiple terms

Clinically relevant adverse reactions in <15% of patients who received BALVERSA included nausea (15%), pyrexia (15%), epistaxis (13%), vomiting (10%), and arthralgia (10%).

Table 6 presents laboratory abnormalities reported in ≥15% of patients treated with BALVERSA at 8 or 9 mg once daily versus chemotherapy.

Table 6: Selected Laboratory Abnormalities Reported in ≥15% of Patients Who Received BALVERSA Versus Chemotherapy; Cohort 1 Safety Analysis Set (Study BLC3001)

	BALVERSA (N=135[1])		**Chemotherapy (N=112[2])**	
Laboratory Abnormality	**All Grades[3] (%)**	**Grade 3-4[3] (%)**	**All Grades[3] (%)**	**Grade 3-4[3] (%)**
Chemistry				
Increased phosphate	76	5	0	0
Increased alkaline phosphatase	54	4.7	29	1
Increased alanine aminotransferase	46	3.8	15	1
Increased aspartate aminotransferase	44	3.1	13	0
Decreased sodium	44	16	25	6
Increased creatinine	43	1.5	17	0
Decreased phosphate	34	8	25	3.6

Increased calcium	27	8	9	0
Increased potassium	24	0	21	0
Hematology				
Decreased hemoglobin	50	12	57	12
Decreased platelet count	17	1.5	18	1
Decreased neutrophil count	16	0.8	40	26

[1] The denominator used to calculate the rate varied from 52 to 131 based on the number of patients with a baseline value and at least one post-treatment value.
[2] The denominator used to calculate the rate varied from 11 to 102 based on the number of patients with a baseline value and at least one post-treatment value.
[3] Severity graded per NCI CTCAE v4.03

BLC2001

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* and other *FGFR* 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).

Serious adverse reactions occurred in 41% of patients. The most frequent (>3%) serious adverse reactions were central serous retinopathy (4.6%), urinary tract infection (3.4%), and general physical health deterioration (3.4%).

Fatal adverse reactions occurred in 8% of patients, including acute myocardial infarction (1.1%).

Permanent discontinuation of BALVERSA due to an adverse reaction occurred in 21% of patients. The most frequent (≥ 2%) reasons for permanent discontinuation included central serous retinopathy (4.6%), general physical health deterioration (3.4%), palmar-plantar erythrodysesthesia syndrome (2.3%), acute kidney injury (2.3%), and fatigue (2.3%).

Dosage interruptions of BALVERSA occurred in 68% of patients. The most frequent (≥ 5%) adverse reactions requiring dosage interruption included hyperphosphatemia (24%), stomatitis (17%), nail disorders (16%), central serous retinopathy (9%), palmar-plantar erythro-dysesthesia syndrome (8%), and fatigue (8%).

Dose reductions of BALVERSA occurred in 53% of patients. The most frequent (≥ 5%) adverse reactions for dose reductions included nail disorders (21%), stomatitis (15%), central serous retinopathy (14%), hyperphosphatemia (7%), palmar-plantar erythro-dysesthesia syndrome (7%), fatigue (6%), and blurred vision (6%).

Table 7 presents adverse reactions reported in ≥15% of patients treated with BALVERSA at 8 mg or 9 mg once daily.

Table 7: Adverse Reactions Reported in ≥15% of Patients (Study BLC2001)

Adverse Reaction	BALVERSA 8 mg daily (N=87)	
	All Grades (%)	Grade 3-4 (%)
Gastrointestinal disorders		
Stomatitis[a]	62	11
Diarrhea[a]	48	4.6
Dry mouth	45	0
Constipation	28	1.1
Nausea	21	1.1
Skin and subcutaneous tissue disorders		
Nail disorders[a]	62	14
Dry skin[a]	37	0
Alopecia	26	0
Palmar-plantar erythrodysesthesia syndrome	26	6
General disorders and admin. site conditions		
Fatigue[a, b]	54	8
Decreased weight	16	0
Metabolism and nutrition disorders		
Decreased appetite	38	0.0
Nervous system disorders		
Dysgeusia[a]	38	1.1
Eye disorders		
Dry eye[a]	29	1.1
Central serous retinopathy[a]	28	4.6
Blurred vision	17	0
Infections and Infestations		
Urinary tract infection	17	6

[a] Includes multiple terms
[b] Includes fatal adverse reactions (n=2)

Clinically relevant adverse reactions in <15% of patients who received BALVERSA included pyrexia (14%), extremity pain (13%), vomiting (13%), and peripheral edema (10%).

Table 8 presents laboratory abnormalities reported in ≥15% of patients treated with BALVERSA at 8 mg or 9 mg once daily.

Table 8: Selected Laboratory Abnormalities Reported in ≥ 15% of Patients

Laboratory Abnormality	BALVERSA 8 mg daily (N=87[1])	
	All Grades (%)	Grade 3-4 (%)

Chemistry		
Increased phosphate	76	1.2
Increased creatinine	52	4.7
Increased alanine aminotransferase	41	1.2
Increased alkaline phosphatase	41	1.2
Decreased sodium	40	16
Decreased magnesium	31	1.2
Increased aspartate aminotransferase	30	0
Decreased phosphate	24	9
Increased calcium	22	3.5
Hematology		
Decreased hemoglobin	35	3.5
Decreased platelets	19	1.2
Decreased leukocytes	17	0

[1] The denominator used to calculate the rate varied from 83 to 86 based on the number of patients with a baseline value and at least one post-treatment value.

4.9 OVERDOSE

There is no clinical experience with overdoses of erdafitinib and no known specific antidote for erdafitinib overdose. The highest single dose of erdafitinib studied in healthy subjects was 12 mg. In the event of an overdose, erdafitinib should be stopped and general supportive measures undertaken until clinical toxicity has diminished or resolved.

5 Pharmacological Properties

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 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.

5.1 Pharmacodynamic Properties

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

FGFR inhibition by BALVERSA increases serum phosphate level *[see Posology and method of administration (4.2.3) and Interaction with other medicinal products and other forms of interactions (4.5)].*

5.2 Pharmacokinetic Properties

Following administration of BALVERSA 8 mg once daily, the mean (coefficient of variation [CV%]) erdafitinib steady-state maximum plasma concentration (C_{max}), area under the curve (AUC_{tau}), and minimum 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 of BALVERSA, erdafitinib exposure (C_{max} and 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 with a 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 in erdafitinib exposure was observed following administration of BALVERSA with 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).

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 effects on erdafitinib exposure were observed based on age (21-92 years), sex, race (White, Hispanic or Asian), body weight (36-166 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 and in patients with severe renal impairment. The pharmacokinetics of erdafitinib in patients with renal impairment requiring dialysis is unknown.

Drug Interaction Studies

Clinical Studies

Effect of Other Drugs on Erdafitinib

Moderate CYP2C9 Inhibitors

Erdafitinib mean ratios for C_{max} and AUC_{inf} were 121% and 148%, respectively, when BALVERSA was co-administered with fluconazole, a moderate CYP2C9 and CYP3A4 inhibitor, relative to BALVERSA administered alone.

Strong CYP3A4 Inhibitors

Erdafitinib mean ratios for C_{max} and AUC_{inf} were 105% and 134%, respectively, when BALVERSA was co-administered with itraconazole (a strong CYP3A4 inhibitor and P-gp inhibitor) relative to BALVERSA alone.

CYP3A4/2C9 Inducers

Erdafitinib mean ratios for C_{max} and AUC_{inf} were 78% and 45%, respectively, when BALVERSA was co-administered with carbamazepine (a strong CYP3A4 and weak CYP2C9 inducer) relative to BALVERSA alone.

Effect of Erdafitinib on Other Drugs

CYP3A4 Substrates:

No clinically meaningful effect on the exposure of midazolam (a CYP3A4 substrate) was observed following coadministration with BALVERSA.

OCT2 Substrates:

No clinically meaningful effect on the exposure of metformin (an OCT2 substrate) was observed following coadministration with BALVERSA.

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 (including antacids, H_2-antagonists and proton pump inhibitors) are not expected to affect the bioavailability of erdafitinib.

5.2.1 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.

5.3 Preclinical Safety data

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.

CLINICAL STUDIES

Urothelial Carcinoma with Susceptible *FGFR3* Genetic Alterations

The efficacy of BALVERSA was evaluated in Study BLC3001 (NCT03390504) Cohort 1, a randomized, open-label, multicenter study in which 266 patients with advanced urothelial cancer harboring selected *FGFR3* alterations were randomized 1:1 to receive BALVERSA (8 mg with titration up to 9 mg) versus chemotherapy (docetaxel 75 mg/m^2 once every 3 weeks or vinflunine 320 mg/m^2 once every 3 weeks) until unacceptable toxicity or progression. Randomization was stratified by region (North America vs. Europe vs. rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2) and visceral or bone metastases (yes vs. no). All

patients needed to have had disease progression after 1 or 2 prior treatments, at least 1 of which included a PD-1 or PD-L1 inhibitor. *FGFR3* genetic alterations were identified from tumor tissue in a central laboratory by the QIAGEN *therascreen*® *FGFR* RGQ RT-Polymerase Chain Reaction (PCR) kit in 75% of patients while the remainder (25%) were identified by local next generation sequencing (NGS) assays.

The major efficacy outcome measures were overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) assessed by investigator using RECIST (Response Evaluation Criteria in Solid Tumors) Version 1.1.

The median age was 67 years (range: 32 to 86 years) and 71% were male; 54% were White, 29% Asian, 0.4% Black, 0.4% multiple races, 16% not reported; 2% were Hispanic/Latino; and baseline ECOG performance status was 0 (43%), 1 (48%), or 2 (9%). Eighty-one percent of patients had *FGFR3* mutations, 17% had fusions, and 2% had both mutations and fusions. Ninety-five percent of patients had pure transitional cell carcinoma (TCC) and 5% had TCC with other histologic variants. The primary tumor location was the upper tract for 33% of subjects and lower tract for 67%; 74% of patients had visceral or bone metastases. Eighty-eight percent of patients received platinum-containing chemotherapy previously. PD-1 or PD-L1 inhibitor therapy was received only in the neoadjuvant or adjuvant setting in 7% of patients.

Statistically significant improvements in OS, PFS, and ORR were demonstrated for BALVERSA compared with chemotherapy.

Table 9 and Figures 1 and 2 summarize the efficacy results for BLC3001 Cohort 1.

Table 9: Efficacy Results for Study BLC3001 Cohort 1

	BALVERSA N=136	**Chemotherapy N=130**
Overall Survival (OS)		
Number of events (%)	77 (56.6%)	78 (60.0%)
Median[a], months (95% CI)	12.1 (10.3, 16.4)	7.8 (6.5, 11.1)
Hazard ratio[b] (95% CI)	0.64 (0.47, 0.88)	
p-value[c]	0.0050	
Progression-free survival (PFS)		
Number of events (%)	101 (74.3%)	90 (69.2%)
Median[a], months (95% CI)	5.6 (4.4, 5.7)	2.7 (1.8, 3.7)
Hazard ratio[b] (95% CI)	0.58 (0.44, 0.78)	
p-value[c]	0.0002	
Objective response rate (ORR)		
ORR (95% CI)	35.3% (27.3, 43.9)	8.5% (4.3, 14.6)
p-value[d]	<0.001	
Complete response, CR (%)	5.1%	0.8%
Partial response, PR (%)	30.1%	7.7%

All p-values reported are 2-sided and compared with 0.019 of the allocated alpha for the interim analysis.

[a] Based on Kaplan-Meier estimates

[b] Based on an unstratified Cox proportional hazard model

[c] Based on an unstratified log-rank test

[d] p-value is estimated using Cochran-Haenszel (CMH) test with ECOG performance status (0 or 1 vs 2) as a stratification factor.

ORR = confirmed objective response (CR + PR)

CI = Confidence Interval

Figure 1: Kaplan-Meier Plot of Overall Survival (Study BLC3001 Cohort 1)

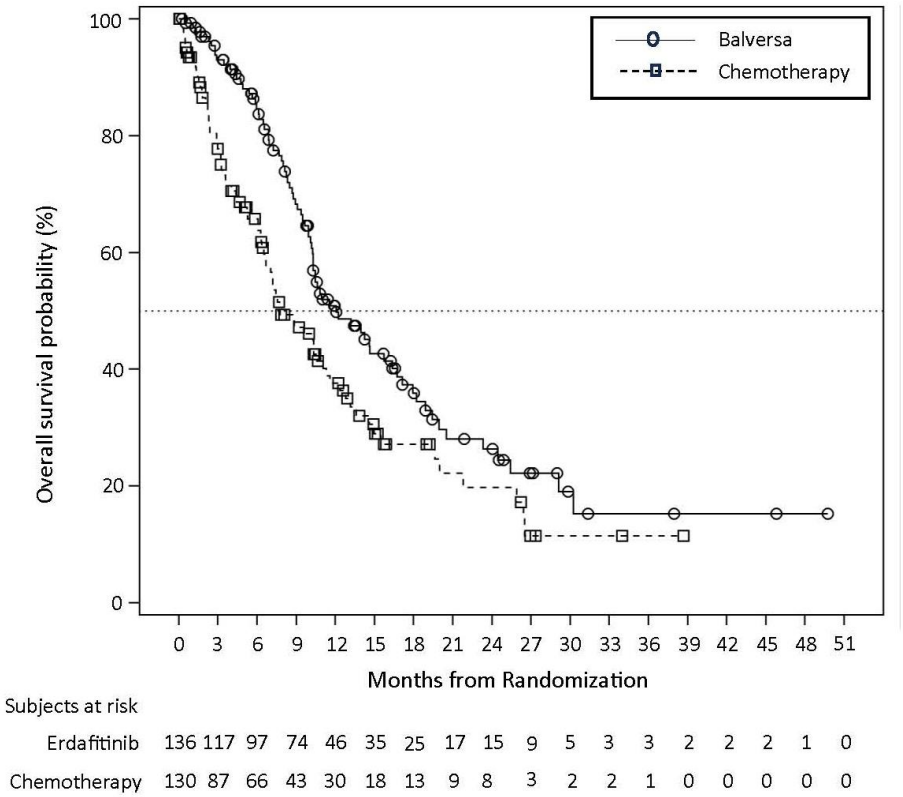
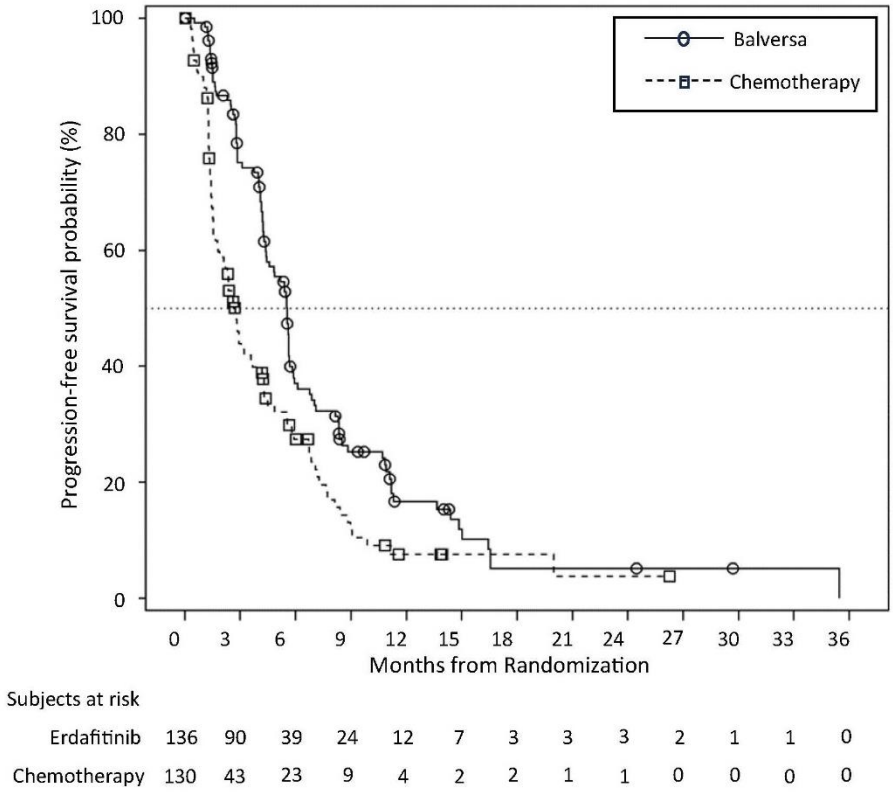


Figure 2: Kaplan-Meier Plot of Progression-free Survival (Study BLC3001 Cohort 1)



Study BLC3001 Cohort 2

Study BLC3001 (NCT03390504) Cohort 2 was a multicenter, open-label, randomized study in 351 patients with locally advanced or metastatic urothelial carcinoma with selected *FGFR3* alterations who received 1 prior line of systemic therapy and no prior PD-1 or PD-L1 inhibitor. Patients were randomized 1:1 to receive BALVERSA (8 mg with titration up to 9 mg) or pembrolizumab 200 mg every 3 weeks. The study did not meet its major efficacy outcome measure for superiority of OS at the pre-specified final analysis. The OS hazard ratio (HR) was 1.18 (95% CI: 0.92, 1.51; p=0.18), median 10.9 (95% CI: 9.2, 12.6) months for BALVERSA versus 11.1 (95% CI: 9.7, 13.6) months for pembrolizumab *[see Therapeutic indication (4.1)]*.

Study BLC2001

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). *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 validated 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 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 10 and Table 11. ORR was 32.2%. Responders included patients who had previously not responded to anti PD-L1/PD-1 therapy.

Table 10: 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 11: 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

6 Pharmaceutical Particulars

6.1 List of excipients

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 tablets only).

6.2 Incompatibilities

No information in USPI

6.3 Shelf-Life

See expiry date on the outer pack.

6.4 Special precautions for storage

Do not store above 30°C.

Keep out of reach of children.

6.5 Nature and contents of container

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.
  - Two dose pack wallets of 28-tablets each in a box of 56-tablets.
  - Two dose pack wallets of 42-tablets each in a box of 84-tablets.

- Bottle of 56 tablets with child resistant closure and 2 x 1g silica gel desiccant pouches.
- Bottle of 84 tablets with child resistant closure and 2 x 1g silica gel desiccant pouches.

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

  - One starter pack wallet of 14-tablets in a box.
  - One starter pack wallet of 28-tablets in a box.
  - Two dose pack wallets of 28-tablets each in a box of 56-tablets.
  - Bottle of 28 tablets with child resistant closure and 2 x 1g silica gel desiccant pouches.
  - Bottle of 56 tablets with child resistant closure and 2 x 1g silica gel desiccant pouches.

7 Marketing Authorization Holder

Manufactured by:

Janssen-Cilag S.p.A. Latina, Italy

Imported by

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

For any product information, please contact us at medinfosea@its.jnj.com

8 Marketing Authorization Numbers and Date of Authorization

Product name	Market Authorization Number	Date of Authorization
Balversa 3 mg	1C 15179/63 (NC)	25-NOV-2020
Balversa 4 mg	1C 15180/63 (NC)	25-NOV-2020

9. Date of revision of the text

USPI THOR V. OCT 2024,effect on ability to drive follow CCDS

WARNING ACCORDING TO THE ANNOUNCEMENT FROM MINISTRY OF PUBLIC HEALTH

This medicinal product may cause serious harm. It must be used only under physician's supervision.