PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrBALVERSA®

Erdafitinib tablets
tablet, 3 mg, 4 mg and 5 mg, oral
Protein Kinase Inhibitor

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RECENT MAJOR LABEL CHANGES

1 Indications	09/2024
1 Indications, 1.2 Geriatrics	09/2024
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	09/2024
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment, Geriatrics	09/2024
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment, Hepatic impairment	03/2023
7 Warnings and Precautions, Endocrine and Metabolism	09/2024
7 Warnings and Precautions, Gastrointestinal	09/2024
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7 Warnings and Precautions, 7.1.4 Geriatrics	09/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BALVERSA® (erdafitinib) is indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible fibroblast growth factor receptor (FGFR)3 genetic alterations, who have disease progression during or following at least one line of prior therapy including within 12 months of neoadjuvant or adjuvant therapy.

BALVERSA® should not be used for the treatment of patients who are eligible for and have not received prior programmed death receptor-1 (PD-1) or programmed death-ligand 1(PD-L1) inhibitor therapy (see 14 CLINICAL TRIALS).

Treatment with BALVERSA® should be initiated following confirmation of a susceptible FGFR genetic alteration using a validated test (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

1.2 Geriatrics

Geriatrics (≥65 years of age): In BALVERSA® clinical studies, patients 65 years of age and older experienced a higher incidence of adverse reactions requiring treatment interruption or discontinuation compared to patients younger than 65 years. No overall differences in efficacy were observed between elderly patients and younger patients.

2 CONTRAINDICATIONS

BALVERSA® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

BALVERSA® (erdafitinib) should be prescribed and managed by a qualified health professional who is experienced in the use of anti-cancer agents.

Before taking BALVERSA®, patients must have confirmation of a susceptible FGFR3 gene alteration by a validated test (see 7 WARNINGS AND PRECAUTIONS**, General** and 14 CLINICAL TRIALS).

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of BALVERSA® is 8 mg orally once daily, with a dose increase to 9 mg once daily based on serum phosphate levels and tolerability, as assessed between 14 and 21 days after initiating BALVERSA® treatment (see 4.4 Administration and Dose Modifications).

Dose increase based on serum phosphate concentrations

Assess serum phosphate concentrations between 14 and 21 days after initiating treatment. Increase the dose of BALVERSA® to 9 mg once daily if that serum phosphate concentration is <9.0 mg/dL and there is no drug-related toxicity. Avoid co-administration of serum phosphate level-altering agents with BALVERSA® before initial dose increase period based on serum phosphate levels.

An increase in serum phosphate concentration is an expected effect of BALVERSA®; therefore, subsequent to the serum phosphate assessment performed between 14 and 21 days after treatment initiation, serum phosphate concentrations in patients should be monitored monthly. (see 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics). For all patients, phosphate intake should be restricted to 600-800 mg daily (see 7 WARNINGS AND PRECAUTIONS, **Hyperphosphatemia and soft tissue mineralization**). For patients with elevated phosphate concentrations (≥7.0 mg/dL), follow the dose modification guidelines in Table 2, and addition of a non-calcium containing phosphate binder (e.g., sevelamer carbonate) should be considered.

Dose Modifications

For possible dose reductions and management of adverse reactions see Tables 1 to 4.

Table 1: BALVERSA® dose reduction schedule

Dose	1st dose reduction	2nd dose reduction	3rd dose reduction	4th dose reduction	5th dose reduction
9 mg →	8 mg	6 mg	5 mg	4 mg	Stop
8 mg →	6 mg	5 mg	4 mg	Stop	

Table 2: Recommended dose modifications based on serum phosphate concentrations with use of BALVERSA® after up-titration

Serum phosphate concentration	BALVERSA® Dose Management[a]
<6.99 mg/dL (<2.24 mmol/L)	Continue BALVERSA® at current dose.

Serum phosphate concentration	BALVERSA® Dose Management[a]
7.00-8.99 mg/dL (2.25-2.90 mmol/L)	Continue BALVERSA® treatment. Start phosphate binder with food until phosphate level is <7.00 mg/dL. A dose reduction should be implemented for a sustained serum phosphate level of ≥7.00 mg/dL for a period of 2 months or if clinically necessary.
9.00-10.00 mg/dL (2.91-3.20 mmol/L)	Withhold BALVERSA® treatment until serum phosphate level returns to ≤7.00 mg/dL (weekly testing recommended). Start phosphate binder with food until serum phosphate level returns to <7.00 mg/dL. Re-start treatment at the same dose level. A dose reduction should be implemented for sustained serum phosphate level of ≥9.00 mg/dL for a period of 1 month or if clinically necessary.
>10.0 mg/dL (>3.2 mmol/L)	Withhold BALVERSA® treatment until serum phosphate level returns to <7.00 mg/dL (weekly testing recommended). Re-start treatment at the first reduced dose level. If serum phosphate level of ≥10.00 mg/dL is sustained for >2 weeks, BALVERSA® should be discontinued permanently. Medical management of symptoms as clinically appropriate.
Significant alteration from baseline renal function or Grade 3 hypocalcemia due to hyperphosphatemia.	BALVERSA® should be discontinued permanently.

[a] For all patients, restrict phosphate intake to 600-800 mg/day.

Eye disorder management

Ocular disorders, including central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED), may occur with the administration of BALVERSA®. Prior to initiating BALVERSA®, perform a baseline ophthalmological exam including an Amsler grid test, fundoscopy, visual acuity and, if available, an optical coherence tomography (OCT). Examine patients monthly thereafter using an Amsler grid test, and if abnormal or if any visual abnormality is observed, follow the management guidelines in Table 3 (see 7 WARNINGS AND PRECAUTIONS, **Monitoring and Laboratory Tests**).

To prevent and treat dry eyes, use artificial tear substitutes, hydrating or lubricating eye gels or ointments frequently, at least every 2 hours during waking hours. Severe treatment-related dry eye should be evaluated by an eye care professional (optometrist or ophthalmologist).

Table 3: Guideline for management of eye disorders with use of BALVERSA®

Severity Grading	BALVERSA® Dose Management
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only, or abnormal Amsler grid test.	Refer for an ophthalmologic examination (OE). If an OE cannot be performed within 7 days, withhold BALVERSA® until an OE can be performed. If no evidence of eye toxicity on OE, continue BALVERSA® at same dose level. If diagnosis from OE is keratitis or retinal abnormality (i.e., CSR[a]), withhold BALVERSA® until resolution. If reversible in 4 weeks on OE, resume at next lower dose. Upon restarting BALVERSA® continue to monitor for recurrence every 1-2 weeks for a month. Consider dose re-escalation if no recurrence.
Grade 2: Moderate; limiting age appropriate instrumental activities of daily living (ADL).	Immediately withhold BALVERSA® and refer for an OE. Resume BALVERSA® at the next lower dose level once signs and symptoms resolve. If diagnosis from OE is keratitis or retinal abnormality (i.e. CSR), withhold BALVERSA® until resolution. If resolved (complete resolution and asymptomatic) within 4 weeks on OE, resume BALVERSA® at the next lower dose level. Upon restarting BALVERSA® continue to monitor for recurrence every 1 to 2 weeks for a month.
Grade 3: Severe or medically significant but not immediate sight-threatening; limiting self-care ADL.	Immediately withhold BALVERSA® until resolution. If resolved (complete resolution and asymptomatic) within 4 weeks, then BALVERSA® may be resumed at 2 dose levels lower. Monitor for recurrence every 1 to 2 weeks for a month. If there is recurrence, consider permanent discontinuation of BALVERSA®.

Severity Grading	BALVERSA® Dose Management
Grade 4: Sight-threatening consequences; blindness (20/200 or worse).	Permanently discontinue BALVERSA®. Monitor until complete resolution or stabilization.

[a] CSR-central serous retinopathy

Dose modification for other adverse reactions

For nail disorders, dry skin and skin toxicity, oral mucositis and dry mouth, follow dose modification guidelines in Table 4.

Table 4: Recommended dose modifications for nail disorder, dry skin and skin toxicity, oral mucositis and dry mouth with use of BALVERSA®

Adverse Reaction	Severity of Adverse Reaction	BALVERSA® Dose Management
Nail Disorder	Grade 1	Continue at current dose.
	Grade 2	Consider holding BALVERSA® with reassessment in 1-2 weeks. If first occurrence and it resolves to ≤ Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes >2 weeks to resolve to ≤ Grade 1 or baseline, then restart at 1 dose level lower.
	Grade 3	Hold BALVERSA®, with reassessment in 1-2 weeks. When resolves to ≤ Grade 1 or baseline, restart at 1 dose level below.
	Grade 4	Discontinue BALVERSA®
Dry Skin and Skin Toxicity	Grade 1	Continue at current dose.
	Grade 2	Continue at current dose.
	Grade 3	Hold BALVERSA® (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤ Grade 1 or baseline, restart at 1 dose level lower.
	Grade 4	Discontinue BALVERSA®
Oral Mucositis	Grade 1	Continue at current dose.

Adverse Reaction	Severity of Adverse Reaction	BALVERSA® Dose Management
	Grade 2	Consider holding BALVERSA® if the subject has other drug related concomitant Grade 2 adverse events. Hold BALVERSA® if the subject was already on symptom management for more than a week. If the BALVERSA® is withheld, reassess in 1-2 weeks. If this is the first occurrence of toxicity and resolves to ≤ Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes >2 weeks to resolve to ≤ Grade 1 or baseline, then restart at 1 dose level below.
	Grade 3	Hold BALVERSA®, with reassessments of clinical condition in 1-2 weeks. When resolves to ≤ Grade 1 or baseline, restart at 1 dose level below.
	Grade 4	Discontinue BALVERSA®
Dry Mouth	Grade 1	Continue at current dose.
	Grade 2	Continue BALVERSA® at current dose.
	Grade 3	Hold BALVERSA® (for up to 28 days), with weekly reassessments of clinical condition. When resolved to ≤ Grade 1 or baseline, restart at 1 dose level lower.
	Grade 4	Discontinue BALVERSA®

For all other adverse reactions, follow the dose modification guidelines in Table 5.

Table 5: Recommended dose modifications for other adverse reactions with use of BALVERSA®

Severity of Adverse Reaction[a]	BALVERSA® Dose Management
Grade 1	Continue at current dose.
Grade 2[b]	Continue at current dose.
Grade 3	Withhold BALVERSA® When resolves to ≤ Grade 1 or baseline, restart BALVERSA® at 1 dose level lower.

Grade 4	Permanently discontinue BALVERSA®.

[a] Dose adjustment graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).
[b] For Grade 2 nail disorders and oral mucositis consider withholding BALVERSA®. Follow dose modification in Table 4.

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): No overall differences in efficacy were observed between elderly patients and younger patients. In BALVERSA® clinical studies, patients 65 years of age and older experienced a higher incidence of adverse reactions requiring treatment interruption or discontinuation compared to patients younger than 65 years; however, no specific dose adjustments are considered necessary for elderly patients (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Renal impairment: Based on population pharmacokinetic (PK) analyses, no dose adjustment is required for patients with mild (eGFR-MDRD 60 to 89 mL/min/1.73 m²) or moderate renal impairment (eGFR-MDRD 30 to 59 mL/min/1.73 m²) (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). Limited data are available in patients with severe renal impairment; therefore, caution should be used in these patients.

Hepatic impairment: No dose adjustment is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). Limited data are available in patients with severe (Child-Pugh C) hepatic impairment; therefore, caution should be used in these patients.

4.4 Administration

The tablets should be swallowed whole with or without food, at approximately the same time every day (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

4.5 Missed Dose

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.

If vomiting occurs any time after taking BALVERSA®, the next dose should be taken at the next scheduled time.

5 OVERDOSAGE

There is no information on overdosage with BALVERSA®. There is no known specific antidote for BALVERSA® overdose. The treatment of overdose of BALVERSA® should consist of general supportive measures.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 6: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 3 mg, 4 mg, 5 mg	**Tablet Core:** Croscarmellose sodium, Magnesium stearate (from vegetable source), Mannitol, Meglumine, and Microcrystalline cellulose. **Film coating:** Ferrosoferric oxide/iron oxide black (for the brown tablets only), Glycerol monocaprylocaprate Type I, Iron oxide yellow, Iron oxide red (for the orange and brown tablets only), Polyvinyl alcohol partially hydrolyzed, Sodium lauryl sulfate, Talc, Titanium dioxide

BALVERSA® 3 mg tablets are yellow, round biconvex shaped, film-coated tablets, debossed with “3” on one side; and “EF” on the other side.
BALVERSA® 4 mg tablets are orange, round biconvex shaped, film-coated tablets, debossed with “4” on one side; and “EF” on the other side.
BALVERSA® 5 mg tablets are brown, round biconvex shaped, film-coated tablets, debossed with “5” on one side; and “EF” on the other side.

Packaging: BALVERSA® (erdafitinib) tablets are supplied in child-resistant blisters packs and bottles in 28 days or 7 days supply as follows:

- 3 mg tablets:
  - Bottle of 56-tablets *[28 days supply of 6 mg daily dose]*
  - Bottle of 84-tablets *[28 days supply of 9 mg daily dose]*
  - Blister packs of 28 tablets, two blisters per box (56 tablets total) *[28 days supply of 6 mg daily dose]*
  - Blister packs of 42 tablets, two blisters per box (84 tablets total) *[28 days supply of 9 mg daily dose]*
- 4 mg tablets:
  - Bottle of 28-tablets *[28 days supply of 4 mg daily dose]*
  - Bottle of 56-tablets *[28 days supply of 8 mg daily dose]*
  - Blister pack of 14 tablets (Starter pack) *[7 days supply of 8 mg daily dose]*
  - Blister pack of 28 tablets *[28 days supply of 4 mg daily dose]*
  - Blister packs of 28 tablets, two blisters per box (56 tablets total) *[28 days supply of 8 mg daily dose]*
- 5 mg tablets:
  - Bottle of 28-tablets *[28 days supply of 5 mg daily dose]*
  - Blister pack of 28 tablets *[28 days supply of 5 mg daily dose]*

7 WARNINGS AND PRECAUTIONS

General

Before taking BALVERSA®, patients must have confirmation of a susceptible FGFR3 gene alteration by a validated test. Patients enrolled in Study BLC3001 had confirmation of at least one of the following genetic alterations in tumour tissues:

- Mutations: FGFR3-S249C, FGFR3-Y373C, FGFR3-R248C, FGFR3-G370C,
- Fusions: FGFR3-TACC3, FGFR3-BAIAP2L1

(see 14 CLINICAL TRIALS)

Driving and Operating Machinery

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 BALVERSA® treatment. If patients experience symptoms affecting their vision, it is recommended that they do not drive or use machines until the effect subsides.

Endocrine and Metabolism

Hyperphosphatemia and soft tissue mineralization

BALVERSA® can cause hyperphosphatemia, which has been reported to lead to soft tissue mineralization, cutaneous calcinosis, non-uremic calciphylaxis and vascular calcification. Increases in phosphate levels are a pharmacodynamic effect of BALVERSA® (see 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics). Hyperphosphatemia was reported as an adverse event in 79% of patients, and vascular calcification has been observed in 0.3% of patients treated with BALVERSA®. The median time to onset for any grade event of hyperphosphatemia was 16 days (range: 6-449 days) after initiating BALVERSA®. Hyperphosphatemia was managed by dose modifications and treatment with phosphate binders. Dose interruption was reported for 10% of patients, dose reduction for 5.2% of patients, and 24% of patients received phosphate binders during treatment with BALVERSA®.

Patients should adhere to a low phosphate diet (600 to 800 mg/day) while taking BALVERSA®, and the use of drugs that can increase serum phosphate levels (such as potassium phosphate supplements, vitamin D supplements, antacids, and phosphate-containing enemas and laxatives) should be avoided. Serum phosphate concentrations in patients should be monitored monthly. Follow the dose modification guidelines when required (see 4.2 Recommended Dose and Dosage Adjustment, Dose Modifications and 4.4 Administration).

Gastrointestinal

Stomatitis

Stomatitis was reported by 53% of patients treated with BALVERSA®, with Grade 3 events reported by 11% of patients. Dose interruptions and dose reductions were reported for 19% and 15% of patients, respectively. If stomatitis is experienced, follow 4.2 Recommended Dose and Dosage Adjustment, Dose Modifications and 4.4 Administration.

Monitoring and Laboratory Tests

Serum Phosphate

Phosphate concentrations should be assessed 14 to 21 days after initiating BALVERSA® treatment and monitored monthly thereafter. For elevated phosphate concentrations in patients treated with BALVERSA®, follow dose modification guidelines in Table 2 (see 4.2 Recommended Dose and Dosage Adjustment, Dose Modifications and 4.4 Administration).

Ocular Monitoring

Prior to initiating BALVERSA®, perform a baseline ophthalmological exam. 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 OCT. For ocular adverse reactions, follow the management guidelines in Table 3 (see 4.2 Recommended Dose and Dosage Adjustment, Dose Modifications and 4.4 Administration). Patients should also be provided instructions to self-administer the Amsler grid test to detect visual abnormalities between physician visits.

Ophthalmologic

Ocular disorders, including central serous retinopathy (CSR) (a grouped term including retinal pigment epithelial detachment [RPED]) resulting in visual field defect, have been reported in patients receiving BALVERSA®.

CSR was reported in 22% patients treated with BALVERSA®, with a median time to first onset of 45 days. Grade 3 or 4 CSR was reported in 2.3% of patients. At the time of data cutoff, CSR had resolved for 65 of 103 (63%) of patients, while the remaining 38 (37%) patients had unresolved events. The most commonly reported CSR events among patients treated with BALVERSA® were chorioretinopathy (6%), detachment of retinal pigment epithelium (RPE) (5%), retinal detachment (3%), retinopathy (2%) and subretinal fluid (2%). In clinical studies, CSR was primarily managed by dose modification, and led to dose interruptions and reductions in 9% and 12% of patients, respectively. There were 3% of patients who discontinued BALVERSA® due to CSR; most commonly due to detachment of RPE (1.7%).

Eye disorders other than CSR were reported in 43% of patients treated with BALVERSA®. The most commonly reported events were dry eye and vision blurred. Of subjects treated with BALVERSA®, 7.5% had dose reductions, 9.2% had dose interruptions, and 2.1% discontinued BALVERSA® due to eye disorders. The median time to first onset for eye disorders was 49 days. Dry eye symptoms occurred in 17% of patients during treatment with BALVERSA®. 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 OCT.

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 management

guidelines in Table 3 (see 4.2 Recommended Dose and Dosage Adjustment, 4.4 Administration and 7 WARNINGS AND PRECAUTIONS**, Monitoring and Laboratory Tests**).

Reproductive Health: Female and Male Potential

- **Fertility**

  No human data on the effect of BALVERSA® on fertility are available. Based on findings from animal studies, BALVERSA® may impair fertility of females of reproductive potential (see 16 NON-CLINICAL TOXICOLOGY, **Reproductive and Developmental Toxicology**).

- **Teratogenic Risk**

  BALVERSA® can cause fetal harm when administered to pregnant women (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations). Advise female patients of reproductive potential to use highly effective contraception prior to and during treatment, and for 3 months after the last dose of BALVERSA®. Male patients must use effective contraception (e.g., condom) and not donate or store semen during treatment and for 3 months after the last dose of BALVERSA®.

  Pregnancy testing with a highly sensitive assay is recommended for females of reproductive potential prior to initiating BALVERSA®.

7.1 Special Populations

7.1.1 Pregnant Women

There are no available human data informing the erdafitinib-associated risk. In a study with pregnant rats, erdafitinib was embryo-fetal toxic and teratogenic in the absence of maternal toxicity (see 16 NON-CLINICAL TOXICOLOGY**, Reproductive and Developmental Toxicology**). Based on findings in animal studies and its mechanism of action, BALVERSA® can cause fetal harm when administered to a pregnant woman.

BALVERSA® should not be used during pregnancy and in women of childbearing potential not using effective contraception. If BALVERSA® is used during pregnancy, or if the patient becomes pregnant while taking BALVERSA®, advise the patient of the potential hazard to the fetus and counsel the patient about her clinical and therapeutic options. Advise patients to contact their healthcare professional if they become pregnant or pregnancy is suspected while being treated with BALVERSA® and up to 3 months afterwards.

7.1.2 Breast-feeding

There are no data on the presence of erdafitinib in human milk, or the effects of BALVERSA® on the breast-fed infant, or on milk production. Because of the potential for serious adverse reactions from BALVERSA® in breast-fed infants, advise women not to breast-feed during treatment with BALVERSA® and for 3 months following the last dose of BALVERSA®.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

In repeat-dose toxicology studies in rats and dogs, toxicities in bone and teeth were observed at exposures less than the human exposures at the maximum recommended clinical dose (see 16 NON-CLINICAL TOXICOLOGY**, General Toxicology**). Chondroid dysplasia/metaplasia were reported in multiple bones in both species, and tooth abnormalities included abnormal/irregular dentin in rats and dogs and discoloration and degeneration of odontoblasts in rats.

7.1.4 Geriatrics

In BALVERSA® clinical studies, patients 65 years of age and older experienced a higher incidence of adverse reactions requiring treatment interruption or discontinuation compared to patients younger than 65 years. In Study BLC3001, the incidence of treatment discontinuations of BALVERSA® due to adverse events was 8.5% (5/59) for patients <65 years, 12% (6/50) for patients ≥65 to <75 years, and 31% (8/26) for patients ≥75 years of age.

No overall differences in efficacy were observed between elderly patients and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile is based on pooled data from 479 patients with locally advanced unresectable or metastatic urothelial carcinoma and FGFR alterations who were treated with BALVERSA® at the recommended dose (8 to 9 mg daily) in clinical studies, with a median duration of treatment of 4.8 months (range: 0.1 to 43 months).The most commonly reported TEAEs (≥20%) were hyperphosphatemia, diarrhea, stomatitis, dry mouth, decreased appetite, anemia, constipation, dry skin, dysgeusia, palmar-plantar erythrodysesthesia syndrome, alopecia, asthenia, ALT increased, onycholysis, and fatigue. Serious TEAEs occurred in 43% of patients, including eye disorders in 5% of patients. Other serious TEAEs (≥2%) in patients treated with BALVERSA® included urinary tract infection (3.8%), hematuria (2.9%), intestinal obstruction (2.5%), and acute kidney injury (2.3%).

Grade 3-4 TEAEs were experienced by 67% of patients. The most common Grade 3-4 adverse reactions (≥2%) were: stomatitis, hyponatremia, palmar-plantar erythrodysesthesia syndrome, anaemia, onycholysis, asthenia, urinary tract infection, diarrhea, hyperphosphatemia, decreased appetite, nail dystrophy, hematuria, intestinal obstruction, aminotransferase increased and fatigue.

Dose interruptions and dose reductions due to TEAEs occurred in 72% and 60% of patients, respectively. Stomatitis was the most common adverse event leading to both dose interruption (19%) and dose reduction (15%), followed by palmar-plantar erythrodysesthesia syndrome (10% for both dose interruption and dose reduction). TEAEs leading to treatment discontinuation occurred in 19% of patients. Detachment of retinal pigment epithelium (1.7%) was the most common adverse event leading to treatment discontinuations.

An adverse event with a fatal outcome, acute myocardial infarction, occurred in 1 patient.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety data described below reflect exposure to BALVERSA® in Cohort 1 of Study BLC3001. This was a Phase 3 study that included patients with locally advanced unresectable or metastatic urothelial carcinoma harbouring susceptible FGFR3 genetic alterations who had progressed after 1 or 2 prior treatments, at least 1 of which included a PD-1 or PD-L1 inhibitor. Patients were treated either with BALVERSA® (8 mg orally once daily with individualized up-titration to 9 mg) or chemotherapy (docetaxel 75 mg/m^2 once every 3 weeks or vinflunine 320 mg/m^2 once every 3 weeks). The median duration of treatment for patients receiving BALVERSA® was 4.9 months (range: 0.2 to 39 months).

Table 7 presents TEAEs reported in ≥10% of patients treated with BALVERSA® 8 or 9 mg once daily versus chemotherapy in Study BLC3001 Cohort 1.

Table 7: Treatment Emergent Adverse Events Reported in ≥ 10% of Patients Treated with BALVERSA® in Study BLC3001 Cohort 1

System organ class Preferred Term	Erdafitinib (N=135)		Chemotherapy (N=112)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Blood and lymphatic system disorders				
Anemia	26	7	32	8
Eye disorders				
Dry eye[a]	25	0.7	3.6	0
Central Serous Retinopathy[b]	18	2.2	0	0
Gastrointestinal disorders				
Diarrhea[c]	63	3	17	2.7
Stomatitis[d]	56	10	18	1.8
Dry mouth	39	0	3.6	0
Constipation	27	0	28	1.8
Nausea	15	1.5	24	1.8
General disorders and administration site conditions				
Fatigue[e]	29	1.5	42	7
Pyrexia	15	0.7	13	1.8
Infections and infestations				
Urinary tract infection	11	4.4	7	2.7
Investigations				

System organ class Preferred Term	Erdafitinib (N=135)		Chemotherapy (N=112)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Alanine aminotransferase increased	27	3	3.6	0.9
Weight decreased	22	2.2	2.7	0
Aspartate aminotransferase increased	22	2.2	2.7	0
Blood creatinine increased	14	0	6	0
Blood alkaline phosphatase increased	10	2.2	3.6	0.9
Metabolism and nutrition disorders				
Hyperphosphatemia	80	5	0	0
Decreased appetite	27	3	21	2.7
Hyponatremia	12	7	3.6	1.8
Musculoskeletal and connective tissue disorders				
Arthralgia	10	1.5	8	0.9
Nervous system disorders				
Dysgeusia[f]	30	0.7	7	0
Renal and urinary disorders				
Haematuria	12	2.2	9	1.8
Respiratory, thoracic and mediastinal disorders				
Epistaxis	13	0	2.7	0
Skin and subcutaneous tissue disorders				
Nail disorders[g]	70	12	5	0
Palmar-plantar erythrodysaesthesia syndrome	30	10	0.9	0
Dry skin[h]	27	1.5	6	0
Alopecia	25	0.7	24	0

Key: AE = adverse event

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.1.

[a] includes dry eye, lacrimation increased and xerophthalmia.
[b] includes choroidal effusion, chorioretinitis, chorioretinopathy, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, macular detachment, maculopathy, retinal detachment, retinal function test abnormal, retinal oedema, retinal thickening, retinopathy, serous retinal detachment, serous retinopathy, subretinal fluid and vitreous detachment.
[c] includes colitis, colitis microscopic, diarrhoea, diarrhoea haemorrhagic, enteritis, enterocolitis and frequent bowel movements.
[d] includes angular cheilitis, aphthous stomatitis, aphthous ulcer, cheilitis, gingival erosion, gingival pain, gingivitis, gingival ulceration, glossitis, glossodynia, mouth ulceration, mucosal hyperaemia, mucosal inflammation, oral mucosal blistering, oral mucosal erythema, oral pain, oropharyngeal pain, pharyngeal inflammation, pharyngitis, stomatitis, tongue discomfort and tongue ulceration.

System organ class Preferred Term	Erdafitinib (N=135)		Chemotherapy (N=112)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)

[e] includes fatigue and asthenia.
[f] includes dysgeusia and ageusia.
[g] includes onycholysis, onychomadesis, nail discolouration, nail disorder, nail dystrophy, paronychia, nail ridging, nail infection, nail toxicity, onychalgia, onychoclasis, nail discomfort and nail injury.
[h] includes dry skin, xerosis and xeroderma.

8.3 Less Common Clinical Trial Adverse Reactions

The following are adverse reactions reported in less than 10% of patients receiving BALVERSA®:

Eye Disorders: Conjunctivitis, Keratitis, Ulcerative keratitis
Gastrointestinal disorders: Abdominal pain
General disorders and administration site conditions: Mucosal dryness
Renal and urinary disorders: Acute kidney injury
Respiratory, thoracic and mediastinal disorders: Nasal dryness
Skin and subcutaneous tissue disorders: Nail bed bleeding, Pruritus, Skin fissures, Hyperkeratosis, Skin exfoliation, Eczema, Skin lesion, Skin toxicity, Palmar erythema, Skin atrophy

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 8 presents laboratory abnormalities observed in ≥ 10% (All Grades) of subjects in BLC3001 Cohort 1 who received at least 1 dose of BALVERSA®.

Table 8: Laboratory Abnormalities Reported in ≥ 10% (All Grades) of Patients Treated with BALVERSA® in BLC3001 Cohort 1

	Erdafitinib[a]		Chemotherapy[b]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Laboratory Abnormality				
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
Decreased albumin	29	0	33	6
Increased calcium(corrected)	27	8	9	0
Increased potassium	24	0	21	0
Decreased magnesium	24	0	17	0

Hematology				
Decreased hemoglobin	50	12	57	12
Decreased white blood cell	26	0	40	20
Decreased platelet count	17	1.5	18	1
Decreased neutrophil count	16	0.8	40	26

[a]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.
[b]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.

Note: Severity graded per NCI CTCAE v4.03.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Erdafitinib is primarily metabolized in humans by CYP2C9 and CYP3A4 to form the O-demethylated major metabolite. 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.

CYP2C9 or CYP3A4 inhibitors
Co-administration of moderate CYP2C9 or strong CYP3A4 inhibitors is predicted to increase the steady-state exposure of erdafitinib. Co-administration of BALVERSA® with moderate CYP2C9 or strong CYP3A4 inhibitors should be avoided.

CYP3A4 / CYP2C9 inducers
Co-administration with carbamazepine, a strong CYP3A4 and weak CYP2C9 inducer leads to decreased erdafitinib exposure. Avoid co-administration of dual CYP2C9 and strong CYP3A4 inducers with BALVERSA®.

Acid lowering agents
Erdafitinib exhibits adequate solubility across the pH range of 1 to 7.4. Acid lowering agents (e.g., antacids, H_2-antagonists, or proton pump inhibitors) are not expected to affect the bioavailability of erdafitinib.

Drugs affecting transporters
Erdafitinib is a substrate for P-gp but not for BCRP, OATP1B1, and OATP1B3. P-gp inhibitors are not expected to affect the PK of erdafitinib in a clinically relevant manner.

Sevelamer
No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed in patients taking sevelamer (non-calcium, phosphate scavenger).

Drug metabolizing enzymes
Erdafitinib is a time dependent inhibitor and inducer of CYP3A4 *in vitro*. Erdafitinib does not have a clinically meaningful effect on midazolam (a sensitive CYP3A4 substrate). Erdafitinib is not an inhibitor of other major CYP isozymes at clinically relevant concentrations.

Drug transporters

Erdafitinib is an inhibitor of OCT2 and P-Glycoprotein (P-gp) *in vitro*. Erdafitinib does not have a clinically meaningful effect on metformin (a sensitive OCT2 substrate). Erdafitinib does not inhibit BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, MATE1 or MATE-2K at clinically relevant concentrations.

9.4 Drug-Drug Interactions

The drugs listed in Table 9 below are based on either drug interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 9: Established or Potential Drug-Drug Interactions

Drug name	Source of Evidence	Effect	Clinical comment
Effect of moderate CYP2C9 or strong CYP3A4 inhibitors on erdafitinib such as:			
Fluconazole (moderate CYP2C9 and CYP3A4 inhibitor)	CT	↑ erdafitinib exposure • mean ratio (90% CI) for C_{max} was 121% (100, 147) • mean ratio (90% CI) for AUC_{∞} was 148% (120, 182) May lead to increased drug-related toxicity	Co-administration of BALVERSA® with moderate CYP2C9 or strong CYP3A4 inhibitors should be avoided. If co-administration of a moderate CYP2C9 or strong CYP3A4 inhibitor is unavoidable, monitor closely for adverse reactions, and reduce the BALVERSA® dose as recommended in Table 5 (see 4.2 Recommended Dose and Dosage Adjustment, Dose Modifications and 4.4 Administration). If the moderate CYP2C9 or strong CYP3A4 inhibitor is discontinued, the BALVERSA® dose may be adjusted, in the absence of drug-related toxicity.
Itraconazole (strong CYP3A4 inhibitor and P-gp inhibitor)	CT	↑ erdafitinib exposure • mean ratio (90% CI) for C_{max} was 105% (87, 127) • mean ratio (90% CI) for AUC_{∞} was 134% (109, 164) May lead to increased drug-related toxicity	

Drug name	Source of Evidence	Effect	Clinical comment
Effect of CYP2C9 or CYP3A4 inducers on erdafitinib such as:			
Rifampin (strong CYP3A4 inducer and moderate CYP2C9 inducer)	T	↓ erdafitinib exposure May lead to decreased activity	Avoid co-administration of dual CYP2C9 and strong CYP3A4 inducers with BALVERSA®. If BALVERSA® is co-administered with a CYP2C9 or CYP3A4 inducer, the dose might be cautiously increased up to 9 mg based on clinical monitoring for adverse reactions and serum phosphate. If the inducer is discontinued, the BALVERSA® dose may be adjusted as tolerated.
Carbamazepine (strong CYP3A4 inducer and weak CYP2C9 inducer)	CT	↓ erdafitinib exposure • mean ratio (90% CI) for C_{max} was 78% (73, 83) • mean ratio (90% CI) for AUC_{∞} was 45% (40, 52) May lead to decreased activity.	
Effect of erdafitinib on substrates of CYP3A4 such as:			
Midazolam	CT	No clinically meaningful effect • mean ratio (90% CI) for C_{max} was 86% (74, 101) • mean ratio (90% CI) for AUC_{∞} was 82% (71, 95)	No dose adjustment is required when co-administering with BALVERSA®.
Effect of erdafitinib on substrates of OCT2 such as:			
Metformin	CT	No clinically meaningful effect • mean ratio (90% CI) for C_{max} was 109% (90, 131) • mean ratio (90% CI) for AUC_{∞} was 114% (93, 139)	No dose adjustment is required when co-administering with BALVERSA®.
Effect of erdafitinib on substrates of P-Glycoprotein(P-gp) such as:			
Digoxin	T	P-gp substrates systemic exposure may be increased.	Oral narrow therapeutic index P-gp substrates should be taken at least 6 hours before or after erdafitinib to minimize the potential for interactions.

Legend: CT = Clinical Trial; T = Theoretical (simulation)

9.5 Drug-Food Interactions

BALVERSA® can be administered with or without food (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Drug-herb interactions have not been studied (see 9.4 Drug-Drug Interactions). Avoid concomitant use of St. John's Wort, as this herb is a strong inducer of CYP3A.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory test have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Erdafitinib is an oral pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor that binds to and inhibits all FGFR family members, FGFR 1, 2, 3 and 4. Erdafitinib inhibited FGFR phosphorylation and signaling and decreased cell viability in cancer cell lines expressing activating FGFR genetic alterations, including point mutations, amplifications, and fusions. In FGFR pathway activated cancer cell lines, the concentration required for 50% tumor growth inhibition (IC50) is in the low nanomolar range 0.1 to 129.2 nM.

Erdafitinib demonstrated antitumor activity in FGFR-driven cell lines and xenograft models derived from multiple tumor types, including bladder cancer.

10.2 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.

In vitro, erdafitinib was demonstrated to be an intrinsic human ether-a-go-go-related gene (hERG) blocker with an IC50 of 183 ng/mL, and to have a potential to induce arrhythmia in rabbit ventricular wedge preparations starting at 44.7 ng/mL. In animal studies, erdafitinib increased QTc intervals after single intravenous dosing in anesthetized dogs and guinea pigs and after single oral dosing in conscious dogs. Idioventricular rhythm, ventricular escape rhythm, and decreased heart rate were also observed in conscious dogs. The unbound C_{max} values for erdafitinib after single doses in animals were at least 2.4 times higher than the human unbound exposures at the maximum recommended clinical dose.

Serum phosphate

A population pharmacokinetic/pharmacodynamic (Pop PK/PD) model demonstrated that erdafitinib increased serum phosphate concentration, a pharmacodynamic biomarker of FGFR inhibition. Continuous daily dosing of BALVERSA® within the recommended dose range should be used to achieve target serum phosphate concentrations of 7 mg/dL to 9 mg/dL, as assessed between 14 and 21 days after initiation of therapy (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

10.3 Pharmacokinetics

Table 10: Arithmetic Mean (SD) Pharmacokinetic Parameters of Erdafitinib at Steady-State Following Administration of 8 mg QD BALVERSA® in Patients with Cancer

Moiety	C_{max} (µg/mL)	AUC_{tau} (µg.h/mL)	t_{max} (h) [a]	Peak-to-trough ratio	Vd/F (L)	CL/F (L/h)	Effective $t_{1/2}$ (h)
Erdafitinib	1.4 (0.71)	29 (18)	2.5 (2-6)	1.47 (0.34)	28.8	0.362	58.9

[a] Median and range for t_{max}, under fasting conditions

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 in a dose-proportional manner across the dose range of 0.5 to 12 mg. Steady state was achieved after 2 weeks with once daily dosing and the mean accumulation ratio was 4-fold relative to a single dose.

Food Effect

Administration of erdafitinib to healthy subjects under fasting conditions and with a high-fat meal did not result in clinically relevant changes in C_{max} and AUC. Median time to reach t_{max} was delayed about 1.5 hours with food.

Absorption

After single dose oral administration, median time to achieve peak plasma concentration (t_{max}) was 2.5 hours (range: 2 to 6 hours).

Distribution

The mean apparent volume of distribution of erdafitinib in subjects with cancer was 28.8 L, demonstrating limited distribution outside the extravascular space. In patients with cancer, erdafitinib was 99.7% bound to human plasma proteins, preferentially to α1-acid glycoprotein AGP.

Metabolism

Metabolism is the main route of elimination for erdafitinib. Erdafitinib is primarily metabolized in human by CYP2C9 and CYP3A4 to form the O-demethylated major metabolite. 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.

Elimination

Mean total apparent clearance (CL/F) of erdafitinib was 0.362 L/h in patients. The mean effective half-life of erdafitinib in patients was 58.9 hours.

Up to 16 days following a single oral administration of radiolabeled [14C]-erdafitinib, 69% of the dose was recovered in feces (14-21% as unchanged erdafitinib) and 19% in urine (13% as

unchanged erdafitinib).

Special Populations and Conditions

No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed based on age (21 to 92 years), sex, race (White, Hispanic or Asian), body weight (36 to 166 kg), mild or moderate renal impairment and mild or moderate hepatic impairment.

- **Pediatrics (<18 years of age)**

  Pharmacokinetics of erdafitinib has not been studied in pediatric patients.

- **Geriatrics (≥65 years of age)**

  In the population PK analysis, age was identified as a significant covariate on erdafitinib clearance. Erdafitinib clearance was lower by 15% in the 65 to 75 years old group, and lower by 21% in the >75 years old group as compared to the <65 years old group. This decreased clearance with increasing age did not lead to a clinically meaningful effect on erdafitinib exposure.

- **Sex**

  In the population PK analysis, no clinically meaningful differences in the pharmacokinetics of erdafitinib were observed based on sex.

- **Genetic Polymorphism**

  CYP2C9 poor metabolizer
  Simulation suggested that the exposure of erdafitinib is predicted to increase in subjects of CYP2C9 *3/*3 genotype. Patients known to have this genotype should be monitored for increased adverse reactions.

- **Ethnic Origin**

  The potential effects of race/ethnicity on the PK of erdafitinib were investigated as part of the population PK analysis and in clinical studies. In the population PK analysis dataset, most erdafitinib-treated subjects were White (Caucasian, Hispanic or Latino, 58.5%). Hispanic accounted for 4.3%, and Asian 25.6%. No statistically significant association between race/ethnicity (White, Hispanic, Asian) and PK parameters of erdafitinib was observed.

- **Hepatic Insufficiency**

  No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function. Limited data are available in patients with severe (Child-Pugh C) hepatic impairment; therefore, BALVERSA® should be administered with caution when used in these patients. Monitor closely for adverse reactions and reduce the BALVERSA® dose as recommended in Table 5 (see 4 DOSAGE AND ADMINISTRATION, 4.4 Administration).

- **Renal Insufficiency**

  Based on population PK analysis, no clinically meaningful differences in the pharmacokinetics of erdafitinib were observed between subjects with normal renal function (eGFR-MDRD [estimated glomerular filtration rate modification of diet in renal disease] ≥90 mL/min/1.73 m²), and subjects with mild (eGFR-MDRD 60 to 89 mL/min/1.73 m²) and moderate renal impairment (eGFR-MDRD 30 to 59 mL/min/1.73 m²). Limited data are available in patients with severe renal impairment; therefore BALVERSA® should be administered with caution in these patients. Monitor closely for adverse reactions and reduce the BALVERSA® dose as recommended in Table 5 (4 DOSAGE AND ADMINISTRATION, 4.4 Administration).

- **Obesity**

  In population PK analysis, no clinically meaningful differences in the pharmacokinetics of erdafitinib were observed based on body weight (range 36 to 166 kg).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15ºC - 30ºC).
Keep out of sight and reach of children.

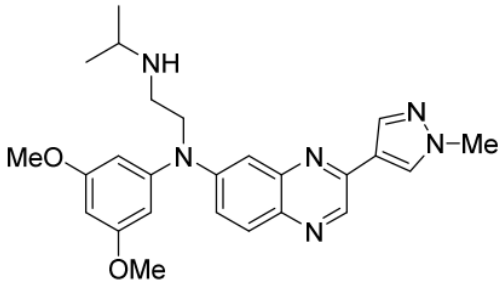
12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance
Proper/Common name: erdafitinib
Chemical name: N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl) quinoxalin-6-yl]ethane-1,2-diamine
Molecular formula and molecular mass: $C_{25}H_{30}N_6O_2$; 446.56
Structural formula:



Physicochemical properties: The drug substance is a yellow powder. It is in a crystalline form and does not exhibit polymorphism. The drug substance is practically insoluble, or insoluble to freely soluble in organic solvents and slightly soluble to practically insoluble, or insoluble in aqueous media over the physiological pH range. The drug substance has 2 dissociation constants, a pKa_1 of 9.2 (basic amine moiety) and a pKa_2 of 1.9 (basic pyrazole moiety).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Locally Advanced or Metastatic Urothelial Carcinoma with Select FGFR3 Alterations

The efficacy of BALVERSA® was evaluated in Study BLC3001 Cohort 1, a phase 3, randomized, open-label, multicenter study in patients with advanced urothelial cancer harboring selected FGFR alterations. Patients who had progressed after 1 or 2 prior treatments, at least 1 of which included a PD-1 or PD-L1 inhibitor, were randomized 1:1 to receive BALVERSA® or chemotherapy (docetaxel or vinflunine). Patients who received neoadjuvant or adjuvant chemotherapy and showed disease progression within 12 months of the last dose were considered to have received systemic therapy in the metastatic setting (Table 11).

Supportive efficacy of BALVERSA was evaluated in Study BLC2001, a multicentre Phase 2 study in patients with locally advanced or metastatic urothelial carcinoma whose disease progressed on or after at least one prior chemotherapy (Table 11).

Table 11: Summary of Patient Demographics for Clinical Trials in Patients with Urothelial Carcinoma

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
BLC3001 (Cohort 1)	Randomized (1:1), multi-centre, open-label, active-controlled Phase 3 study in patients with advanced urothelial carcinoma harbouring select FGFR alterations.	BALVERSA®: 8 mg orally once daily, with individualized up-titration to 9 mg orally once daily.	136	66 (32-85)	M: 71% F: 29%
		Chemotherapy: Docetaxel 75 mg/m^2 once every 3 weeks *or* Vinflunine 320 mg/m^2 once every 3 weeks	130	69 (35-86)	M: 72% F: 28%
BLC2001	Multi-centre Phase 2 study in patients with locally advanced or metastatic urothelial carcinoma harbouring select FGFR alterations.	BALVERSA®: 8 mg orally once daily, with individualized up-titration to 9 mg orally once daily.	87	67 (36-87)	M: 79% F: 21%

BLC3001 Cohort 1

A total of 266 patients previously treated with an anti-PD-(L)1 agent were randomized to receive either erdafitinib or chemotherapy (docetaxel or vinflunine). 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 presence or absence of visceral or bone metastases. Patients were treated until disease progression, intolerable toxicity, withdrawal of consent, decision by the investigator to discontinue treatment, or the end of the study, whichever occurred first.

FGFR3 genetic alterations were identified by a Polymerase Chain Reaction (PCR) test at the central laboratory for 74% of patients, and by local next generation sequencing (NGS) tests in 25% of patients. Two subjects (1%) did not have FGFR alterations.

Eighty-one percent of patients had FGFR3 mutations, 17% had FGFR3 fusions, and 2% had both FGFR3 mutations and fusions. No patients had FGFR2 alterations.

The summary of key patient demographics and baseline disease characteristics is provided in Table 12 below.

Table 12: Key Demographics and Baseline Disease Characteristics – Study BLC3001: Cohort 1

Patient Demographics and Baseline Disease Characteristics	BALVERSA®	Chemotherapy
N	136	130
Age (years)		
Mean	65	68
Median (range)	66 (32, 85)	69 (35, 86)
< 65	59 (43.4%)	45 (34.6%)
≥ 65	77 (56.6%)	85 (65.4%)
Sex		
Female	40 (29.4%)	36 (27.7%)
Male	96 (70.6%)	94 (72.3%)
Type of histology		
Transitional Cell Carcinoma	128 (94.1%)	124 (95.4%)
Transitional Cell Carcinoma with minor components (<50% overall) of variant histology	8 (5.9%)	6 (4.6%)
Primary tumor location		
Upper tract (Renal Pelvis, Ureter)	41 (30.1%)	48 (36.9%)
Lower tract (Bladder, Urethra, Prostate)	95 (69.9%)	82 (63.1%)
ECOG		
0	63 (46.3%)	51 (39.2%)
1	61 (44.9%)	66 (50.8%)
2	12 (8.8%)	13 (10.0%)
Prior Anti-PD-(L)1 therapy		
Pembrolizumab	47 (34.6%)	47 (36.2%)
Avelumab	31 (22.8%)	28 (21.5%)
Atezolizumab	26 (19.1%)	26 (20.0%)
Prior Chemotherapy		
Platinum-based therapy	122 (89.7%)	111 (85.4%)
No platinum-based therapy	1 (0.7%)	3 (2.3%)

The primary efficacy endpoint was Overall Survival (OS). Assessment of radiographic response was performed by investigators according to RECIST (Response Evaluation Criteria in Solid

Tumours Version 1.1). Progression-Free Survival (PFS) and Objective Response Rate (ORR) were included as secondary efficacy endpoints.

The key efficacy is based on data from 136 patients who were treated with the BALVERSA® 8-9 mg daily regimen in Study BLC3001 Cohort 1. A statistically significant improvement in OS was demonstrated for patients treated with BALVERSA® compared to chemotherapy (HR=0.64; 95% CI: 0.47, 0.88; p-value=0.0050). Statistically significant improvements in the key secondary endpoints of PFS and ORR were also demonstrated for BALVERSA® compared with chemotherapy.

Efficacy results are summarized in Table 13.

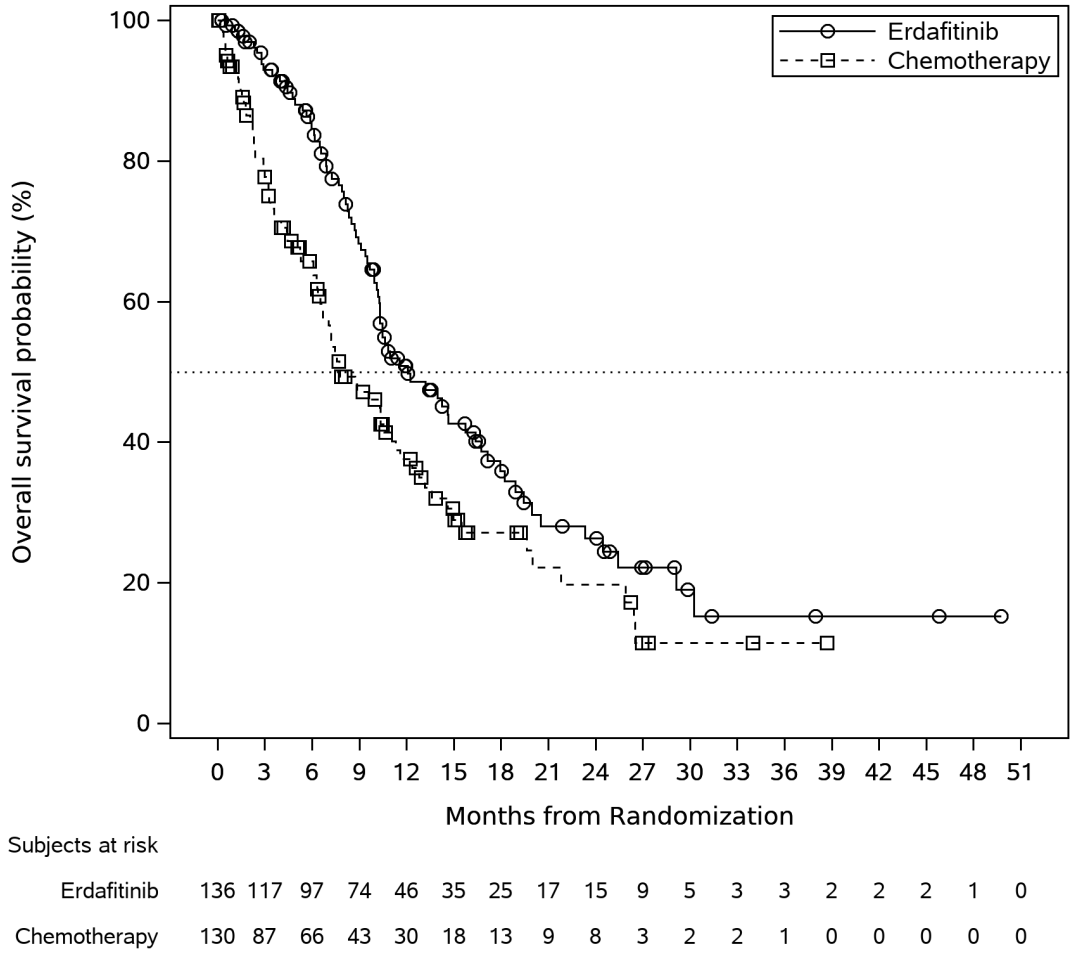
Table 13: Efficacy Results for Study BLC3001, Cohort 1

	Erdafitinib (N=136)	**Chemotherapy (N=130)**
Overall Survival (OS)		
Number of events (%)	77 (56.6%)	78 (60.0%)
Median, months (95% CI)	12.06 (10.28, 16.36)	7.79 (6.54, 11.07)
HR (95% CI)	0.64 (0.47, 0.88)	
P-value	0.0050	
Progression-free survival (PFS)		
Number of events (%)	101 (74.3%)	90 (69.2%)
Median, months (95% CI)	5.55 (4.40, 5.65)	2.73 (1.81, 3.68)
HR (95% CI)	0.58 (0.44, 0.78)	
P-value	0.0002	
Objective response rate (ORR), confirmed		
ORR (95% CI)	35.3% (27.3, 43.9)	8.5% (4.3, 14.6)
P-value	< 0.001	
Complete response, CR (%)	7 (5.1%)	1 (0.8%)
Partial response, PR (%)	41 (30.1%)	10 (7.7%)

All p-values reported are 2-sided.

The Kaplan-Meier OS curve for the two treatment arms is presented in Figure 1.

Figure 1: Kaplan-Meier Plot of Overall Survival for Study BLC3001, Cohort 1



BLC3001 Cohort 2

Study BLC3001 had a Cohort 2, which enrolled patients who had progressed on or after 1 prior treatment not containing an anti-PD-(L)-1 agent. In Cohort 2, a total of 351 patients were randomized to BALVERSA® (8 mg with individualized guided up-titration to 9 mg) versus pembrolizumab (200 mg every 3 weeks).

The pre-specified final analysis of Cohort 2 did not meet its primary efficacy endpoint for superiority of OS of BALVERSA® compared to pembrolizumab. In subjects with locally advanced unresectable or metastatic bladder cancer who had progressed on or after 1 prior line of systemic therapy and no prior PD-1 or PD-L1 inhibitor, the OS hazard ratio (HR) was 1.18 (95% CI: 0.92, 1.51; p-value=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.

Study BLC2001

Study BLC2001 was a multicenter, open-label Phase 2 study designed to evaluate the efficacy and safety of BALVERSA® in patients with locally advanced or metastatic urothelial carcinoma. All patients were enrolled based on investigator assessment of measurable disease and were

required to have tumor tissues with at least 1 of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C or 1 of the following FGFR gene fusions: FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR2-BICC1, FGFR2-CASP7, as determined by a clinical trial assay performed at a central laboratory.

The efficacy analysis was based on 87 patients whose disease progressed on or after at least one prior chemotherapy. 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, measured between days 14 and 17, were below the target of 5.5 mg/dL. This dose increase occurred in 41% of patients. BALVERSA® was administered until disease progression or unacceptable toxicity.

The summary of key patient demographics and baseline disease characteristics is provided in Table 14 below.

Table 14: Key Demographics and Baseline Disease Characteristics: Chemo-relapsed/refractory Urothelial Carcinoma Patients in the 8-mg Daily Regimen in Study BLC2001

Patient Demographics and Baseline Disease Characteristics	**BALVERSA®**
N	87
Age (years)	
Mean	65
Median (range)	67 (36, 87)
< 65	34 (39.1%)
≥ 65	53 (60.9%)
Sex	
Female	18 (20.7%)
Male	69 (79.3%)
Race	
White	64 (73.6%)
Non-white	7 (8.0%)
Unknown/Not reported	16(18.4%)
ECOG Performance Status Score	
0	44 (50.6%)
1	36 (41.4%)
2	7 (8.0%)
Hemoglobin Level	
< 10 g/dL	14 (16.1%)
>= 10 g/dL	73 (83.9%)
Creatinine Clearance (mL/min)	
< 60	41 (47.1%)
>= 60	46 (52.9%)
Primary Tumour Location	
Upper tract (renal pelvis, ureter)	22 (25.3%)

Patient Demographics and Baseline Disease Characteristics	BALVERSA®
N	87
Lower tract (bladder, urethra, prostatic urethra)	65 (74.7%)
Visceral Metastases (lung, liver and bone)	
Present	69 (79.3%)
Liver	18 (20.7%)
Lung	49 (56.3%)
Bone	18 (20.7%)
Absent	18 (20.7%)
Number of Lines of Prior Systemic Therapies*	
1	44 (50.6%)
2	29 (33.3%)
>=3	14 (16.0%)

Note: * Prior therapies include gemcitabine/gemcitabine HCl, cisplatin, carboplatin, anti-PD-(L)1's.

Study Results

The major efficacy outcome measures were objective response rate (ORR) and duration of response (DoR), as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Efficacy outcomes were also assessed by independent radiologic review committee (IRRC).

The median duration of therapy was 5.3 months, and the median duration of efficacy follow-up was 11.3 months.

The reported efficacy results are summarized in Table 15 and Table 16 below.

Table 15: Efficacy Results for Study BLC2001

	Investigator assessment
Endpoint	**N=87**
Objective response rate (ORR) (%) 95% CI (%)	40.2 (29.9, 50.5)
Complete response (CR) (%)	3.4
Partial response (PR) (%)	36.8
Median Duration of Response (months) 95% CI (months)	5.6 (4.2, 7.0)

ORR = CR+PR
CI = Confidence Interval

IRRC assessment was supportive, with an ORR of 32.2% (95% CI: 22.4, 42.0), including CRs in 2.3% of patients. IRRC-assessed DoR was determined to be 5.4 months (95% CI: 4.2, 6.9).

Table 16: Efficacy Results by FGFR Genetic Alteration

	Investigator assessment
FGFR3 mutation[a] (N=64) **ORR (95% CI)**	48.4% (36.2, 60.7)
FGFR3 fusion[b] (N=18) **ORR (95% CI)**	22.2% (3, 41.4)
FGFR2 fusion[c] (N=6) **ORR (95% CI)**	0

[a] FGFR3-S249C, FGFR3-Y373C, FGFR3-R248C, FGFR3-G370C
[b] FGFR3-TACC3_V1, FGFR3-TACC3_V3, FGFR3-BAIAP2L1, FGFR2-CASP7/FGFR3_TACC3_V3
[c] FGFR2-CASP7, FGFR2-BICC1, FGFR2-CASP7/FGFR3_TACC3_V3

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology
Repeated-dose toxicity studies were conducted in rats and dogs for up to 3 months. The highest doses tested in rats (32 mg/kg, intermittent dosing schedule 7 days on/7 days off) and dogs (1.5 mg/kg, intermittent dosing schedule 7 days on/7 days off) were approximately 1.4 and 1.3 times the maximum recommended clinical dose based on unbound AUC comparisons, respectively. In both species, disturbance of phosphate homeostasis, characterized by elevated serum concentrations of mainly phosphate, FGF-23 and 1,25 dihydroxyvitamin D3 were observed. Chondroid dysplasia/metaplasia and soft tissue mineralization, associated with hyperphosphatemia, were observed as primary drug-related toxicities in rats and dogs.

Chondroid dysplasia/metaplasia was evident in growth plates or synchondroses of multiple bones (sternum, femur) causing clinical signs of limping and sternum/tail deformations (rats). Soft tissue mineralizations were observed in multiple organs and tissues, including heart, aorta, and stomach. The death of a male rat at 32 mg/kg (intermittent dosing schedule 7 days on/7 days off) was due to aorta and myocardial mineralizations.

Tooth abnormalities were observed, including abnormal/irregular dentin in rats and dogs and discoloration and degeneration of odontoblasts in rats. Eye-related findings notably atrophy (thinning) of the corneal epithelium (rats) and lacrimal gland atrophy (rats and dogs) were seen. Additional atrophy of glandular tissues (mammary, salivary, and Harderian gland) and epithelial structures (tongue and oral mucosa) and changes in haircoat (piloerection, rough, thin or local hair loss) and nails (malformed, discolored or broken) were observed in rats or dogs.

Soft tissue mineralizations (except for the aorta mineralization in dogs) and chondroid dysplasia in rats and dogs and mammary gland atrophy in rats were partially to fully recovered at the end of a 4-week drug-free recovery period. In a mechanistic study, when rats were given a diet supplemented with the phosphate scavenger sevelamer, the soft tissue mineralizations were reduced.

In a 1-month rat oral toxicity study that included assessment of neurofunctional integrity by the modified Irwin's test after single dose, erdafitinib induced minimal neurofunctional aberrations (impaired wire maneuvers and flaccid body tone) at ≥8 mg/kg. At the dose level of 8 mg/kg, the C_{max} of erdafitinib was less than the human exposures at the recommended clinical dose.

Carcinogenicity
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of erdafitinib.

Genotoxicity
Erdafitinib did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either in vitro micronucleus or the in vivo rat bone marrow micronucleus assay.

Reproductive and Developmental Toxicology
Fertility
Dedicated animal fertility studies have not been conducted with erdafitinib. However, in the 3-month repeat-dose rat toxicity study, erdafitinib showed effects on female reproductive organs (necrosis of the corpora lutea) in rats at an exposure approximating 7.3 times the unbound AUC in patients at the maximum recommended clinical dose.

Embryo-fetal toxicity
Erdafitinib was teratogenic and embryo-fetal toxic in rats, in the absence of maternal toxicity. Pregnant rats were administered erdafitinib at oral doses of 1, 4, or 8 mg/kg/day during the period of organogenesis. No maternal toxicity was observed, but a significant decrease in fetal survival and reduced fetal weight were observed at 8 mg/kg/day. Doses ≥ 4 mg/kg/day were associated with increased fetal malformations and variations, including limb/paw defects (ectrodactyly, absent or misshapen long bones), malformed thoracic and lumbar vertebrae, great blood vessel abnormalities (high arched/retroesophageal aorta, retroesophageal subclavian artery), and retarded ossifications. At 4 mg/kg/day and 8 mg/kg/day in rats, the maternal systemic exposures were less than human exposures at the recommended clinical dose based on unbound AUC.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrBALVERSA®
erdafitinib tablets

Read this carefully before you start taking **BALVERSA®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BALVERSA®**.

What is BALVERSA® used for?

BALVERSA® is used to treat a type of bladder cancer called urothelial carcinoma (cancer in the bladder and urinary tract organs). It is used in adults whose cancer:

- has spread to other parts of the body or cannot be removed by surgery; and
- has worsened after treatment with at least one other therapy; and
- has changes in certain genes called FGFR3 (known as fibroblast growth factor receptors).

Your healthcare professional will determine if you are eligible for treatment with BALVERSA®.

How does BALVERSA® work?

Fibroblast growth factor receptors (FGFRs) are proteins found on cells that help them grow and divide. Some people with bladder cancer have FGFRs that are abnormally active. BALVERSA® works by blocking the activity of FGFRs to slow down the growth and spread of bladder cancer cells.

What are the ingredients in BALVERSA®?

Medicinal ingredients: erdafitinib
Non-medicinal ingredients: croscarmellose sodium, ferrosoferric oxide/iron oxide black (for the brown tablets only), glycerol monocaprylocaprate Type I, iron oxide red (for the orange and brown tablets only), iron oxide yellow, magnesium stearate (from vegetable source), mannitol, meglumine, microcrystalline cellulose, polyvinyl alcohol partially hydrolyzed, sodium lauryl sulfate, talc, titanium dioxide

BALVERSA® comes in the following dosage forms:

Tablets (film-coated): 3 mg (yellow), 4 mg (orange) and 5 mg (brown)

Do not use BALVERSA® if:

- you are allergic to erdafitinib or to any other ingredient in the medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BALVERSA®. Talk about any health conditions or problems you may have, including if you:

- have vision or eye problems.

- have or have had kidney problems.
- have or have had liver problems.

Other warnings you should know about:

- **General:**
  - Only a healthcare professional who has experience treating cancer should treat you with this drug.
  - Before prescribing you BALVERSA®, your healthcare professional will do a test. This test will confirm that your disease is suitable for treatment with this drug.

- **BALVERSA® may cause:**
  - **Eye problems**, which are common and can be serious.
    - Eye problems include dry eyes, disorders of the cornea (front part of eye) and disorders of the retina (an internal part of the eye).
    - Tell your healthcare professional right away if you develop any eye problem or if your vision changes while taking BALVERSA®.
    - Use a lubricating eye ointment or a tear replacement therapy at least every 2 hours while awake to prevent and treat dry eyes.
  - **High phosphate levels in the blood (hyperphosphatemia)**, which are common and can be serious.
    - Adhere to a low phosphate diet. Ask your healthcare professional for dietary advice. Avoid the use of medicines that can increase the levels of phosphate in your blood. This includes potassium phosphate supplements, vitamin D supplements, antacids, and phosphate-containing enemas and laxatives.
    - If you develop increased levels of phosphate in your blood, you may be prescribed another medicine to manage this side effect.

- **Stomatitis (mouth sores, inflammation of the mouth):**
  Stomatitis is common with BALVERSA®.

- **Female patients:**
  - **Pregnancy and birth control**
    - If you are able to become pregnant:
      - A pregnancy test should be done before you start to take BALVERSA®.
      - Avoid becoming pregnant while taking BALVERSA®. It may harm your unborn child or make you lose the pregnancy.
      - Use an effective method of birth control while taking BALVERSA®. Talk to your healthcare professional about birth control methods that may be right for you.
      - Keep using birth control for 3 months after stopping BALVERSA®.
    - If you become pregnant while taking BALVERSA®, tell your healthcare professional right away.
    - If you plan to get pregnant after taking your last dose of BALVERSA®, ask your healthcare professional for advice. This is because BALVERSA® may remain in your body after the last dose.
  - **Breastfeeding**
    - BALVERSA® may pass into breast milk. Do **NOT** breast-feed while you are

taking it and for 3 months after taking your last dose of BALVERSA®.
- Talk to your healthcare professional about the best way to feed your baby.

- **Male patients:**
  - **Pregnancy and birth control**
    - Avoid fathering a child while taking BALVERSA®. It may harm your unborn child.
    - If your partner becomes pregnant while you are taking BALVERSA®, tell your partner's healthcare professional right away.
    - Use an effective method of birth control while taking BALVERSA®. Talk to your healthcare professional about birth control methods that may be right for you.
    - Men taking BALVERSA® must use a condom. Do **NOT** donate or store semen while taking it. This is because the drug may pass into the sperm.
    - Keep using birth control and do **NOT** donate or store semen for 3 months after stopping BALVERSA®.

- **Fertility – information for women and men:**
  BALVERSA® may affect your fertility. Talk to your healthcare professional if this is a concern for you.

- **Children and adolescents:**
  BALVERSA® is **NOT** recommended for use in patients under the age of 18 years.

- **Adults (65 years and older):**
  You may be at a higher risk of side effects if you are 65 years of age and older.

- **Check-ups and testing:**
  You will have regular visits with your healthcare professional during treatment with BALVERSA®. They will:

  - Do blood tests to monitor your phosphate levels, and check your liver and kidney health. The tests will be done:
    - before you start on BALVERSA®,
    - about 2 weeks after starting treatment, and
    - once a month thereafter during treatment with BALVERSA®.

    Your healthcare professional will tell you if your blood test results are abnormal.
  - Check your eyes.
    - You will be sent to see an eye specialist to examine and monitor your eyes. This will be done before you start on BALVERSA® and if you develop eyes or vision problems while taking BALVERSA®.
    - Your healthcare professional will also check your eyes once a month during treatment using an Amsler grid test. They may give you instructions on using the grid so you can monitor your vision at home between visits.

- **Driving and using machines:**
  Eye problems are common in patients taking BALVERSA®. Give yourself time after taking BALVERSA® to see how you feel before driving a vehicle or using machinery. If

you develop symptoms affecting your vision, do **NOT** drive or use machines as long as these last.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BALVERSA®:

- clarithromycin, ciprofloxacin, rifampin – used to treat bacterial infections
- itraconazole, fluconazole, miconazole – used to treat fungal infections
- atazanavir, darunavir/ritonavir, cobicistat – used to treat viral infections, primarily HIV
- enzalutamide, apalutamide – used to treat prostate cancer
- mitotane – used to treat adrenal cancer
- carbamazepine and phenytoin – used to prevent seizures or to treat epilepsy or to treat a painful condition of the face called trigeminal neuralgia
- St. John's Wort (Hypericum perforatum) – an herbal medicine used for depression
- digoxin – used for heart problems

How to take BALVERSA®:

- Take BALVERSA® exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Your healthcare professional will tell you how much BALVERSA® to take. It is important that you take the recommended daily dose.
- Do **NOT** change your dose or stop taking BALVERSA® without first talking with your healthcare professional.
- Take BALVERSA® with or without food at about the same time each day.
- If you take digoxin, your healthcare professional may adjust the time that you take your medications.
- Swallow BALVERSA® tablets whole.
- If you vomit after taking your dose, do **NOT** take another one. Take your next dose the next day at the normal time.

Usual dose:

Usual adult starting dose:
8 mg: Take two 4 mg tablets by mouth once a day.
Your healthcare professional may adjust your dose, temporarily stop or completely stop your treatment. This may happen:

- based on your blood test and eye exam results.
- if you are taking medicines that may interact with BALVERSA®.
- if you have certain side effects while taking BALVERSA®.

Increased adult dose:
9 mg: Take three 3 mg tablets by mouth once a day.

Reduced adult dose:
6 mg: Take two 3 mg tablets by mouth once a day.
5 mg: Take one 5 mg tablet by mouth once a day.
4 mg: Take one 4 mg tablet by mouth once a day.

Overdose:

If you think you, or a person you are caring for, have taken too much BALVERSA®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

- If you forget to take your dose of BALVERSA®, take it as soon as you remember if it is on the same day. Continue with taking the next scheduled dose the next day at the normal time.
- If you miss a day's dose, do NOT take a double dose to make up for the missed dose. Instead, wait until it is time and take your regular dose at the normal time.

What are possible side effects from using BALVERSA®?

These are not all the possible side effects you may feel when taking BALVERSA®. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- decreased appetite
- mouth sores
- diarrhea
- constipation
- nausea
- vomiting
- stomach (abdominal) pain
- dry mouth
- dry skin
- hair loss
- nasal dryness
- vagina dryness
- feeling tired
- feeling weak
- fever
- muscle pain
- change in sense of taste
- weight loss
- sore throat
- nose bleeds

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Nail or skin problems which may include: nails separating from the bed, infected skin around the nail, poor nail formation, discolored nails, nail pain, breaking of the nails, ridging of nails, nail bleeding		✓	
Skin problems which may include: itching, itching skin rash (eczema), crack in the skin		✓	
Palmar-Plantar erythrodysesthesia syndrome (hand-foot syndrome): swelling, peeling or tenderness, mainly on the hands or feet		✓	
Eye (vision) problems: dry eyes, inflamed eyes, watering eyes, disorders of the retina (an internal part of the eye), blurred vision, vision loss		✓	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): burning feeling when you urinate		✓	
Hematuria: blood in urine		✓	
Anemia (low red blood cells): feeling tired, looking pale and you may feel your heart pumping		✓	
COMMON			
Acute kidney injury (sudden decrease in kidney function): less urination, confusion, puffiness in your face and hands, swelling in your feet or ankles		✓	
Intestinal obstruction (blockage of intestine): nausea, vomiting, stomach (abdominal) pain, diarrhea, constipation.	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store BALVERSA® at room temperature between 15ºC - 30ºC.
- **Keep out of reach and sight of children.**
- Do **NOT** throw away any medicines via wastewater or household waste. Ask your healthcare provider or pharmacist about the right way to throw away outdated or unused BALVERSA®. These measures will help protect the environment.

If you want more information about BALVERSA®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.janssen.com/canada), or by calling Janssen Inc. at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc.
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