Summary Report of Benefit-Risk Assessment

BALVERSA FILM-COATED TABLETS 3 MG/ 4 MG/ 5 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Erdafitinib
Product Registrant	Johnson & Johnson Pte. Ltd.
Product Registration Number	SIN15986P, SIN15987P, SIN15988P
Application Route	Abridged evaluation
Date of Approval	7 Aug 2020

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A INTRODUCTION

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

The active substance, erdafitinib, is a highly selective and potent oral pan-FGFR tyrosine kinase inhibitor (TKI), with inhibitory activity against FGFR family members, including FGFR 1, 2, 3 and 4.

Balversa is available as film-coated tablets containing 3 mg, 4 mg, and 5 mg of erdafitinib. Other ingredients in the tablet core are croscarmellose sodium, magnesium stearate (from vegetable source), mannitol, meglumine, and microcrystalline cellulose. Ingredients in the film coating (Opadry amb II) include glycerol monocaprylocaprate Type I, polyvinyl alcohol-partially hydrolyzed, sodium lauryl sulfate, talc, titanium dioxide, iron oxide yellow, iron oxide red (for 4 mg and 5 mg strengths only) and ferrosoferric oxide/iron oxide black (for 5 mg strength only).

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, erdafitinib, is manufactured at Cilag AG, Switzerland. The drug products, Balversa Film-Coated Tablets 3 mg, 4 mg and 5 mg are manufactured at Janssen-Cilag SpA, Latina, Italy.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for Cilag AG, Switzerland were adequate to support the approved storage condition and re-test period. The packaging is closed double, low-density polyethylene (LDPE) bags which are then placed in a closed suitable plastic container. The drug substance is approved for storage below 25°C with a re-test period of 36 months.

Drug product:
The tablet is manufactured using a direct compression approach, followed by film-coating. The process is considered to be a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is a clear polyvinyl chloride - polychlorotrifluoroethylene (PVC-PCTFE) foil blister with an aluminium (Alu) push-through foil (aldehyde-free print lacquer).

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of erdafitinib for the treatment of adult patients with locally advanced or metastatic UC with FGFR3 genetic alterations was based on one pivotal study BLC2001 and one supporting study EDI1001.

Study BLC2001 was an ongoing, Phase II, open-label, single-arm study to evaluate the efficacy and safety of erdafitinib in metastatic or surgically unresectable UC patients having specific FGFR2 or FGFR3 genetic alterations and progressed after prior chemotherapy. Study EDI1001 was a Phase I, first-in-human dose escalation study of erdafitinib in adult subjects with advanced or refractory solid malignancies or lymphoma.

In the dose escalation study, EDI1001, two dosing regimens were investigated in UC patients: 9 mg once daily (QD) (N=10) and 10 mg intermittent schedule of 7 days on-treatment and 7 days off-treatment (N=15). The patients who received the 9 mg QD regimen had a higher objective response rate (ORR) (70% [95% CI 34.8%, 93.3%]) and median duration of response (DOR) (7.16 months) compared to those who received the 10 mg intermittent schedule (ORR: 33% [95% CI 11.8%, 61.6%]; median DOR = 5.60 months). However, the 9 mg QD dose was not studied in the pivotal study due to the high proportion of subjects (70%) who required treatment interruption as a result of toxicity.

Study BLC2001 was initiated with two treatment regimens: Regimen 1 (10 mg QD intermittent schedule with uptitration to 12 mg QD intermittent schedule) and Regimen 2 (6 mg QD daily schedule with uptitration to 8 mg QD daily schedule), with study drug administration on 28-day cycles. Based on a pre-planned Interim Analysis and Pharmacokinetic/ Pharmacodynamic (PK/PD) modelling review by the Data Review Committee, Regimens 1 and 2 were closed due to low response rates and Regimen 3 (8 mg QD daily schedule regimen with uptitration to 9 mg QD daily schedule) was started. Dose uptitration was pharmacodynamically guided based on serum phosphate (PO4) levels, which served as a PD marker for the drug activity and the dose regimens were up-titrated if the PO4 level was <5.5 mg/dL between 14 and 21 days after initiating treatment. Treatment was continued until disease progression or unacceptable toxicity occurred.

The primary efficacy endpoint was ORR (complete response [CR] + partial response [PR]) per RECIST v1.1 assessed by investigator or Independent Radiographic Review Committee (IRRC). Secondary endpoints included disease control rate (DCR), DOR, time to response (TTR), progression free survival (PFS), and overall survival (OS). The sample size was estimated to be at least 88 for Regimen 3 to achieve an ORR of more than 25%.

A total of 210 patients received one of the 3 dosing regimens (8 mg QD: 99; 6 mg QD: 78; 10 mg intermittent: 33). The demographics and baseline characteristics were generally balanced across the treatment groups. The median age for subjects in the 8 mg QD group was 68 years and the majority of subjects were Caucasians (74.7%). The majority (88.9%) of patients had received prior systemic therapies, where 45%, 29% and 14% of subjects had one, two, and three or more lines of therapy, respectively. In addition, 12% of subjects were chemotherapy naïve. A total of 22 subjects had received prior immunotherapy, all of whom received prior anti-programmed death (ligand)-1 [PD(L)-1] therapy and 2 of these subjects received other types of immunotherapy in combination with anti-PD(L)-1 therapy.

Summary of key efficacy results from Study BLC2001 and Study EDI1001

	Study BLC2001			Study EDI1001	
	8 mg	6 mg	10 mg	9 mg	10 mg
Total number	87	78	33	10	15
ORR (95% CI)	40.2% (29.9, 50.5)	34.6% (24.1, 45.2)	21.2% (7.3, 35.2)	70% (34.8, 93.3)	33.3% (11.8, 61.6)
DCR (95% CI)	79.3% (70.8, 87.8)	73.1% (63.2, 82.9)	75.8% (61.1, 90.4)	80% (NR, NR)	46.6% (NR, NR)
Complete response	3.4%	3.8%	3.0%	0	0
Partial response	36.8%	30.8%	18.2%	70.0%	33.3%
Stable disease	39.1%	38.5%	54.5%	10.0%	13.3%
Progressive disease	18.4%	20.5%	18.2%	20.0%	46.7%
DOR (months) (range)	5.55 (2.4, 14.3+)	4.90 (2.5, 17.5)	13.37 (4.2, 19.4)	7.16 (NR, NR)	NR
TTR (months) (min, max)	1.41 (1.3, 5.5)	1.41 (0.9. 5.5)	1.41 (1.2, 2.7)	1.41 (1.3, 17.0)	NR
PFS (months) (95% CI)	5.49 (3.98, 5.68)	5.26 (4.14, 5.49)	4.80 (2.73, 5.52)	5.9 (1.4, 10.3)	NR
OS (months) (95% CI)	12.02 (8.64, NE)	8.64 (6.47, 9.72)	7.46 (6.01, 10.71)	NR	NR

Treatment with erdafinitnib 8 mg QD in chemotherapy relapsed/refractory patients resulted in an ORR of 40.2% (95% CI 29.9%, 50.5%) based on investigator assessment, and 32.2% (95% CI 22.4%, 42%) based on IRRC assessment. The investigator-assessed ORR for the 8 mg QD regimen was numerically higher than that observed for patients who received the 6 mg QD regimen (34.6% [95% CI 24.1%, 45.2%]) or the 10 mg intermittent regimen (21.2% [95% CI 7.3%, 35.2%]). Rapid responses were also observed with the 8 mg QD regimen, with a median TTR of 1.41 months. The median DOR was 5.55 months and median PFS was 5.49 months (95% CI 3.98, 5.68). After a median survival follow up of 10.4 months, 38 subjects (44%) had died. The median OS was 12.02 months (95% CI 8.64 months, not evaluable), and the 12-month survival rate was 52% (95% CI 39%, 64%).

Subgroup analyses showed that the response rates to prior platinum-based chemotherapy (N = 65) and anti-PD(L)-1 immunotherapy (N = 22) were approximately 35% and 4.5% in the

respective subgroups of patients. In the subgroup who received prior anti-PD(L)-1 immunotherapy, a higher response rate was observed with erdafitinib compared to the overall population (ORR 59.1% versus 40.2%, respectively). Efficacy outcomes based on FGFR alterations showed that the ORR was 48.6% in the FGFR3 mutations subgroup (N = 74) and 22.2% in the FGFR3 fusions subgroup (N = 18). There were 7 patients with FGFR3-TACC3 V3 (N = 6) and FGFR3-BAIAP2L1 (N=1) gene fusions who failed to respond (ORR = 0%).

Overall, the pivotal study BLC2001 demonstrated the efficacy of 8 mg erdafitinib with an ORR of 40.2% in metastatic or advanced UC patients who progressed following prior systemic therapy and in whom the majority had FGFR3 genetic alterations (N=92/99), which was considered clinically meaningful. The ORR was also noted to be higher in the subgroup which received prior PDL-1 inhibitors (59.1%).

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of erdafitinib was based primarily on safety data derived from the pivotal Phase II Study BLC2001 and Study EDI1001, comprising a total of 164 patients who received at least one dose of 8 mg (N=99) or 9 mg (N=65) erdafitinib treatment, respectively. The median duration of treatment was 3.3 months (range 0.2 to 23.4 months).

Overview of safety profile (8 mg dose in Study BLC2001 and 9 mg dose in Study EDI1001)

AE	Erdafitinib (N=164)
Any treatment-emergent AE (TEAE)	164 (100%)
TEAE related* to erdafitinib	159 (97.0%)
Serious TEAE	67 (40.9%)
Serious TEAE related* to erdafitinib	16 (9.8%)
TEAE leading to discontinuation	30 (18.3%)
TEAE leading to discontinuation related* to erdafitinib	15 (9.1%)
Deaths due to TEAE	3 (1.8%)
Deaths due to TEAE related* to erdafinitib	0

*as determined by the investigator

All subjects experienced at least one treatment-emergent adverse event (TEAE). The most commonly reported TEAEs were hyperphosphatemia (82%), stomatitis (56%), dry mouth (46%), and diarrhoea (42%). A total of 109 subjects (67%) reported Grade 3 or 4 TEAEs with the majority reported as Grade 3 events and ten subjects (6.1%) reported as Grade 4 events.

The most frequent Grade 3-4 TEAEs were stomatitis (10%), hyponatremia (9.8%), asthenia (6.1%), and anaemia (5.5%). These adverse events were managed with temporary dose interruptions or dose reductions, and most of the TEAEs subsequently resolved. Fifteen subjects (9.1%) had adverse events leading to treatment discontinuation that were considered by the investigator to be related to erdafitinib. Three subjects died due to adverse events (intracranial haemorrhage, sepsis, and acute myocardial infarction) and none were considered drug-related. Serious TEAEs occurred in 41% of subjects and 9.8% of these were considered by the investigator to be related to erdafitinib. The most frequently reported serious TEAEs were dyspnoea (6 subjects, 3.7%) and general physical health deterioration (4 subjects, 2.4%). No systemic life-threatening haematological toxicities or immune-related toxicities were observed.

Adverse events of special interest were class effects of FGFR inhibitors and included eye, nail, skin disorders and hyperphosphatemia. Central serous retinopathy occurred in 26 subjects

(16%) in the 8/9 mg QD group and was of Grade 3 severity for 3 subjects, which were subsequently resolved or lessened to Grade1/2 with dose reduction or interruption. Three subjects discontinued erdafitinib as a result of central serous retinopathy: 2 subjects with Grade 2 detachment of retinal pigment epithelium and 1 subject with Grade 1 chorioretinopathy.

The other common eye disorders were dry eyes (18%), for which intense eye lubrication was indicated. Nail and skin disorders were mostly Grade 1 or Grade 2, although 2 subjects discontinued treatment due to nail disorders and 4 subjects discontinued treatment due to skin disorders (3 subjects due to palmar-plantar erythrodysesthesia). Hyperphosphatemia was an expected transient laboratory abnormality and was not associated with any clinical sequelae.

Overall, erdafitinib presented an acceptable safety profile for the intended population given the disease setting. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

There are limited therapeutic options for locally advanced or metastatic UC patients who progress after first-line systemic therapy. Current treatment options included chemotherapy with taxanes or vinflunine or PDL-1 inhibitors. However, the benefits observed with these therapies remained limited, with the ORR ranging from 10% to 20%. New therapeutic options are required to improve outcomes, particularly in terms of overall survival.

In the pivotal study BLC2001, treatment with erdafitinib 8 mg QD in chemotherapy relapsed/refractory patients achieved an ORR of 40.2% and a median TTR and DOR of 1.4 months and 5.55 months, respectively, which signalled a rapid and durable response. These results, taken together with the favourable PFS (5.49 months) and OS (12.02 months) outcomes, the efficacy results were considered clinically meaningful in the target patient population which comprised majority of patients who had FGFR3 genetic alterations. The overall evidence was adequate to support the indication for UC with all FGFR3 genetic alterations.

All subjects experienced at least one TEAE and the most frequent Grade 3-4 TEAEs were stomatitis (10%), hyponatremia (9.8%), asthenia (6.1%), and anaemia (5.5%). Sixteen subjects (9.8%) had serious TEAEs considered by the investigator to be related to erdafitinib. Fifteen subjects (9.1%) had adverse events leading to treatment discontinuation considered by the investigator to be related to erdafitinib. Three subjects (1.8%) died due to adverse events (intracranial haemorrhage, sepsis, and acute myocardial infarction) and none were considered drug-related.

No systemic life-threatening haematological toxicities or immune-related toxicities were observed. The AEs of special interest reported with Balversa included nail, and skin disorders and hyperphosphatemia and these are expected with FGFR inhibitors. Central serous retinopathy occurred in 26 subjects (16%) in the 8/9 mg QD group and was of Grade 3 severity for 3 subjects, which were subsequently resolved or lessened to Grade1/2 with dose reduction or interruption. Three subjects discontinued erdafitinib as a result of central serous retinopathy. These risks have been adequately addressed in the local package insert via the provision of relevant warnings and precautions, as well as PD based dose modification and dose adjustment recommendations in the event of toxicities.

Overall, the benefit-risk profile of Balversa in the treatment of adult patients with locally advanced or metastatic UC, whose tumours have susceptible FGFR 3 genetic alterations, was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Balversa for the treatment of adult patients with locally advanced or metastatic UC, whose tumors have susceptible FGFR 3 genetic alterations, who have disease progression during or following at least one line of prior chemotherapy including within 12 months of neoadjuvant or adjuvant chemotherapy, was deemed favourable and approval of the product registration was granted on 7 Aug 2020.

G APPROVED PACKAGE INSERT AT REGISTRATION

PRODUCT NAME

BALVERSA™ (erdafitinib) film-coated tablets.

DOSAGE FORMS AND STRENGTHS

BALVERSA™ is formulated as 3 mg, 4 mg, and 5 mg tablets for oral use.

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

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

BALVERSA™ is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC), whose tumors have susceptible fibroblast growth factor receptor (FGFR) 3 genetic alterations, who have disease progression during or following at least one line of prior chemotherapy including within 12 months of neoadjuvant or adjuvant chemotherapy (see *Clinical Studies*).

Dosage and Administration

Dosage – Adults (≥18 years)

Recommended dose

The recommended starting dose of BALVERSA™ is 8 mg orally once daily; with pharmacodynamically guided up-titration, based on serum phosphate concentrations and tolerability at 14 to 21 days, to 9 mg daily if criteria are met (see *Dose Modifications*).

Administration

Before taking BALVERSA™, patients must have confirmation of susceptible FGFR3 gene alterations as confirmed by a validated test (see *Pharmacodynamic effects - Clinical studies*).

The tablets should be swallowed 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.

Missed dose

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

Dose modifications

Pharmacodynamically-guided up-titration based on serum phosphate concentrations

Serum phosphate (PO4) concentrations should be assessed between 14 and 21 days after initiating treatment. Up-titrate the dose to 9 mg daily as soon as possible if that serum phosphate (PO4) concentration is <5.5 mg/dL, and there is no drug-related toxicity.

Dose reduction

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	

Hyperphosphatemia is an expected, transient laboratory abnormality of FGFR inhibitors (see Pharmacodynamics). Phosphate concentrations should be monitored monthly. For elevated phosphate concentrations in patients treated with BALVERSA™ follow dose modification guidelines in Table 2. For all patients, phosphate intake should be restricted to 600-800 mg daily. For elevated phosphate concentrations (≥7.0 mg/dL) in patients treated with BALVERSA™, follow the dose modification guidelines in Table 2, and addition of a non-calcium containing phosphate binder (e.g., sevelamer carbonate) should be considered.

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

Serum phosphate concentration	BALVERSA™ Dose Management[a]
<6.9 mg/dL (<2.2 mmol/L)	Continue BALVERSA™ at current dose.
7.0-9.0 mg/dL (2.3-2.9 mmol/L)	Withhold BALVERSA™ for a week, reassess phosphate concentrations weekly until concentration returns to <5.5 mg/dL and then re-start BALVERSA™ at the same dose level. A dose reduction may be implemented for persistent[b] hyperphosphatemia
>9.0 mg/dL (>2.9 mmol/L)	Hold BALVERSA™ for up to 28 days, with weekly reassessments until concentration returns to < 5.5 mg/dL (or baseline). Then restart BALVERSA™ at 1 dose level below.
> 10.0 mg/dL (> 3.2 mmol/L) or significant alteration in baseline renal function or Grade 3 hypercalcemia	Withhold BALVERSA™ with weekly reassessments until level returns to < 5.5 mg/dL (or baseline). Then may restart BALVERSA™ at 2 dose levels lower.

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

[b] Persistent hyperphosphatemia is considered to be more than 1 sequential (at least 1 week apart) phosphate value of >7 mg/dL

Eye disorder management

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).

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 ophthalmologist.

Subsequently examine patients monthly, including an Amsler grid test, and if any abnormality is observed, follow the management guidelines in Table 3.

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 drug-related corneal or retinal pathology on OE, continue BALVERSA™ at same dose level. If diagnosis from OE is keratitis or retinal abnormality (i.e., CSR[a]/RPED[b]), withhold BALVERSA™ until resolution. If reversible in 4 weeks on OE, resume at next lower dose. Monitor for recurrence for a month. Consider 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. If no drug-related corneal or retinal pathology on OE, withhold BALVERSA™ until resolution. Resume BALVERSA™ at the next lower dose level. If diagnosis from OE is keratitis or retinal abnormality (i.e. CSR/RPED), withhold BALVERSA™ until resolution. If resolved (complete resolution and asymptomatic) within 4 weeks on OE, resume BALVERSA™ at the next lower dose level. 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™ and refer for an OE. 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. Consider permanent discontinuation of BALVERSA™ for recurrence.
Grade 4: Sight-threatening consequences; blindness (20/200 or worse).	Permanently discontinue BALVERSA™. Monitor until complete resolution or stabilization.

[a] CSR-central serous retinopathy

[b] RPED-retinal pigment epithelium detachment

Dose modification for other adverse reactions

Skin, mucosal, and nail changes have been observed with BALVERSA™. Follow dose modification guidelines in Table 4.

Table 4: Recommended dose modifications for adverse reactions with use of BALVERSA™

Severity of Adverse Reaction[a]	**BALVERSA™**
Nail Disorder	***BALVERSA™ Dose Management***
Grade 1	Continue at current dose.
Grade 2	Continue at current dose.
Grade 3	Withhold BALVERSA™ until resolves to Grade 1 or baseline, then may resume at 1 dose level lower.
Grade 4	Permanently discontinue.
Skin Disorder	
Grade 1	Continue at current dose.
Grade 2	Continue at current dose. Consider withholding if no improvement in 1 week. When resolves to ≤ Grade 1 or baseline, restart at same or 1 dose level below.
Grade 3	Withhold BALVERSA™ until resolves to Grade 1 or baseline, then may resume at 1 dose level lower.
Grade 4	Permanently discontinue.
Mucositis	
Grade 1	Continue at current dose.
Grade 2	Continue at current dose. Consider withholding if no improvement in 1 week. When resolves to ≤ Grade 1 or baseline, restart at same or 1 dose level below.
Grade 3	Withhold BALVERSA™ until resolves to Grade 1 or baseline, then may resume at 1 dose level lower.
Grade 4	Permanently discontinue.

[a] Dose adjustment graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Special populations

Pediatrics (17 years of age and younger)

The safety and efficacy of erdafitinib in children have not been established. No data are available.

Elderly (65 years of age and older)

Of the 416 patients treated with BALVERSA™ in clinical studies, 45% were 65 years of age or older, and 12% were 75 years of age or older. No overall differences in safety and effectiveness were observed between elderly and younger patients. No specific dose adjustments are considered necessary for elderly patients (see *Pharmacokinetic Properties*).

Renal impairment

Based on population pharmacokinetic (PK) analyses, no dose adjustment is required for patients with mild or moderate renal impairment (see *Pharmacokinetic Properties*). No data are available in patients with severe renal impairment.

Hepatic impairment

Based on population PK analyses, no dose adjustment is required for patients with mild hepatic impairment (see *Pharmacokinetic Properties*). Limited or no data are available in patients with moderate or severe hepatic impairment.

Contraindications

None.

Warnings and Precautions

Ocular disorders

As with other tyrosine kinase inhibitors, ocular disorders may occur with the administration of BALVERSA™. The most commonly reported CSR events were chorioretinopathy (8%), retinal detachment (5%), and detachment of retinal pigment epithelium (RPED, 5%). CSR was observed in 23 patients (23%) treated with BALVERSA™ in study BLC2001 at the 8 mg daily dose, with a median time to first onset of 50 days. An abnormal Amsler grid test result was identified in the majority (70%) of patients who developed CSR, mostly Grade 1 and 2. In study BLC2001, CSR resolved in 12 patients and 11 patients had ongoing events of which many had improved in severity and the majority were Grade 1. Grade 3 CSR/RPED, involving central field of vision, was reported in 3% of patients. CSR/RPED resolved in 13% of patients and was ongoing in 13% of patients at the study cutoff. CSR led to dose interruptions and reductions in 8.1% and 13.1% of patients, respectively and three patients (3%) discontinued BALVERSA™. Ocular disorders other than CSR occurred in 55% of patients, including dry eye (19%) and vision blurred (17%). Dry eye symptoms occurred in 28% of patients during treatment with BALVERSA™ and were Grade 3 in 6% of patients. All patients should receive dry eye prophylaxis with ocular demulcents as needed.

Screen patients for eye disorders prior to initiating treatment with BALVERSA™ using an Amsler grid test, fundoscopy, visual acuity and if available an OCT. 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. Refer severe treatment-related dry eye to an ophthalmologist for evaluation. Examine patients monthly thereafter and if any abnormality is

observed, or at any time a patient reports eye-related events or visual disturbance, follow the management guidelines in Table 3 (see *Dosage and Administration*).

Embryo-fetal toxicity

Based on findings in animal reproduction studies, erdafitinib can cause fetal harm when administered to a pregnant woman. In a rat embryo-fetal toxicity study, erdafitinib was embryotoxic and teratogenic and oral administration of erdafitinib to pregnant rats during the period of organogenesis caused malformations and embryo-fetal death at exposures less than the human exposures at all doses studied (see *Dosage and Administration*). Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use highly effective contraception prior to and during treatment, and for 3 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with BALVERSA™ and for 3 months after the last dose (see *Pregnancy, Breast-feeding, Contraception, and Fertility*).

Hyperphosphatemia

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

Monitor for hyperphosphatemia and follow the dose modification guidelines when required (see *Dosage and Administration*).

Interactions

Effect of Other Drugs on BALVERSA™

Strong CYP2C9 or CYP3A4 inhibitors

Co-administration with a strong CYP2C9 or CYP3A4 inhibitor increased erdafitinib exposure and may lead to increased drug-related toxicity (see *Pharmacokinetics*). Consider alternative agents with no or minimal enzyme inhibition potential. If BALVERSA™ is co-administered with a strong CYP2C9 or CYP3A4 inhibitor, reduce the BALVERSA™ dose based on tolerability (see *Dosage and Administration*). If the strong inhibitor is discontinued, the BALVERSA™ dose may be adjusted as tolerated.

Strong CYP2C9 or CYP3A4 inducers

Co-administration with strong CYP2C9 or CYP3A4 inducers may lead to decreased erdafitinib exposure (see *Pharmacokinetics*). Consider alternative agents with no or minimal enzyme induction potential. If BALVERSA™ is co-administered with a CYP2C9 or CYP3A4 inducer, the dose might be cautiously increased by 1 to 2 mg and adjusted gradually every two to three weeks based on clinical monitoring for adverse reactions. If the strong inducer is discontinued, the BALVERSA™ dose may be adjusted as tolerated.

Moderate CYP2C9 or CYP3A4 inducers

Co-administration with strong CYP2C9 or CYP3A4 inducers may lead to decreased erdafitinib exposure (see Pharmacokinetics). If a moderate CYP2C9 or CYP3A4 inducer must be co-administered at the start of BALVERSA™ treatment, administer BALVERSA™ dose as recommended (8 mg once daily with potential to increase to 9 mg once daily based on serum phosphate levels on Days 14 to 21 and tolerability). If a moderate CYP2C9 or CYP3A4 inducer must be co-administered after the initial dose increase period based on serum phosphate levels and tolerability, increase BALVERSA™ dose up to 9 mg. When a moderate inducer of CYP2C9 or CYP3A4 is discontinued, continue BALVERSA™ at the same dose, in the absence of drug-related toxicity.

Serum Phosphate Level-Altering Agents

Co-administration of BALVERSA™ with other serum phosphate level-altering agents may increase or decrease serum phosphate levels (see *Pharmacodynamic effects*). Changes in serum phosphate levels due to serum phosphate level-altering agents (other than erdafitinib) may interfere with serum phosphate levels needed for the determination of initial dose increased based on serum phosphate levels (see *Dosage and Administration*). Avoid co-administration of serum phosphate level-altering agents with BALVERSA™ before initial dose increase period based on serum phosphate levels (Days 14 to 21) (see *Dosage and Administration*).

Effect of BALVERSA™ on Other Drugs

P-Glycoprotein (P-gp) substrates

Concomitant administration of BALVERSA™ with P-gp substrates may increase their systemic exposure if administered concurrently (see *Pharmacokinetics*). Oral narrow therapeutic index P-gp substrates such as digoxin should be taken at least 6 hours before or after erdafitinib to minimize the potential for interactions.

CYP3A4 substrates

Co-administration of BALVERSA™ with CYP3A4 substrates may alter the plasma concentrations of CYP3A4 substrates. Avoid co-administration of BALVERSA™ with sensitive substrates of CYP3A4 with narrow therapeutic indices.

OCT2 substrates

Co-administration of BALVERSA™ with OCT2 substrates may increase the plasma concentrations of OCT2 substrates. Consider alternative therapies that are not OCT2 substrates or consider reducing the dose of OCT2 substrates (e.g., metformin) based on tolerability.

Pregnancy, Breast-feeding, Contraception, and Fertility

Pregnancy

There are no available human data informing the erdafitinib-associated risk. Based on findings in animal reproduction studies, erdafitinib can cause fetal harm when administered to a pregnant woman. In a rat embryo-fetal toxicity study, erdafitinib was embryotoxic and teratogenic at exposures less than the human exposures at all doses studied (see *Dosage and Administration*). Fetal toxicity was characterized by hand/foot defects and malformations of some major blood vessels, such as the aorta.

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.

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™.

Pregnancy testing

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

Contraception

BALVERSA™ can cause fetal harm when administered to pregnant women. 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™.

Fertility

Based on findings from animal studies, BALVERSA™ may impair fertility in females of reproductive potential. No human data are available to determine potential effects of BALVERSA™ on fertility in males or females.

Effects on Ability to Drive and Use Machines

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

treatment-related symptoms affecting their vision, it is recommended that they do not drive or use machines until the effect subsides (see *Warnings and Precautions*).

Adverse Reactions

Throughout this section, adverse reactions (ARs) are presented. Adverse reactions are adverse events (AEs) that were considered to be reasonably associated with the use of erdafitinib based on the comprehensive assessment of the available adverse event information. A causal relationship with erdafitinib cannot be reliably established in individual cases. Further, 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 clinical practice.

The safety data described below reflect exposure to BALVERSA™ in study BLC2001 a Phase 2 study including 99 patients with locally advanced or metastatic urothelial carcinoma and whose tumors had certain FGFR genetic alterations as detected by a clinical trial assay in a central laboratory, and who have disease progression during or following at least one line of prior chemotherapy including within 12 months of neoadjuvant or adjuvant chemotherapy. Patients were treated with BALVERSA™ at 8 mg orally once daily; with pharmacodynamically guided up-titration to 9 mg in patients with phosphate concentrations <5.5 mg/dL. Median duration of treatment was 5.3 months (range: 0 to 17 months).

The most common ARs ≥15% were hyperphosphatemia (77%), stomatitis (58%), dry mouth (45%), decreased appetite (38%) dry skin (32%), alopecia (29%), palmar-plantar erythrodysesthesia syndrome (23%), dry eye (19%), onycholysis (18%), paronychia (17%) and nail dystrophy (16%). The most common G3 ARs >1% were stomatitis (10%), nail dystrophy (6%), palmar-plantar erythrodysesthesia syndrome (5%), paronychia (3%), nail disorder (3%), keratitis (3%), onycholysis (2%) and hyperphosphatemia (2%). Adverse reactions leading to dose reduction occurred in 52% of patients, including twenty (20%) for eye disorders. Only nine patients (9%) experienced ARs leading to treatment discontinuation, including three (3%) for eye disorders.

Table 5 presents ARs reported in ≥1% of patients treated with BALVERSA™ at 8 mg once daily in study BLC2001.

Table 5: Adverse reactions reported in ≥ 1% of patients treated with BALVERSA™

			8 mg daily (N=99)	
MedDRA system organ class (SOC)	**Adverse reaction**	**All grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Metabolism and nutrition disorders	Hyperphosphatemia	77	2	0
	Decreased appetite	38	0	0
Gastrointestinal disorders	Stomatitis	58	10	0
	Dry mouth	45	0	0
	Diarrhoea	51	4	0
	Constipation	28	1	0
	Nausea	20	1	0
	Vomiting	13	2	0
Skin and subcutaneous tissue disorders	Dry skin	32	0	0

	Alopecia	29	0	0
	Palmar-plantar erythrodysesthesia syndrome	23	5	0
	Onycholysis	18	2	0
	Paronychia	17	3	0
	Nail dystrophy	16	6	0
	Nail discoloration	11	0	0
	Nail disorder	8	3	0
	Onychalgia	5	0	0
	Pruritus	5	0	0
	Skin fissures	4	0	0
	Nail ridging	3	0	0
	Onychoclasis	3	1	0
	Eczema	1	0	0
	Hyperkeratosis	1	0	0
	Skin exfoliation	1	0	0
	Skin lesion	1	0	0
Eye disorders	Dry eye	19	1	0
	Conjunctivitis	13	0	0
	Chorioretinopathy	8	0	0
	Detachment of retinal pigment epithelium	5	1	0
	Keratitis	5	3	0
	Retinal detachment	5	0	0
	Retinal edema	3	1	0
	Xerophthalmia	3	0	0
	Retinopathy	2	1	0
	Ulcerative keratitis	2	0	0
	Vitreous detachment	2	0	0
Respiratory, thoracic and mediastinal disorders	Nasal dryness	9	0	0
	Oropharyngeal pain	10	1	0
General disorders and administration site conditions	Mucosal dryness	2	0	0
	Fatigue*	51	9	0
	Pyrexia	13	0	0
Nervous system disorders	Dysgeusia	37	1	0
Infections and infestations	Paronychia	17	3	0
	Urinary tract infection	16	5	0
	Conjunctivitis	13	0	0
Renal and urinary tract disorders	Hematuria	10	2	0
Musculoskeletal and connective tissue disorders.	Musculoskeletal pain**	18	0	0
	Arthralgia	8	0	0

* Includes asthenia, fatigue, lethargy, and malaise

** Includes back pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal chest pain, neck pain, pain in extremity

Table 6: Laboratory Abnormalities Reported in >= 10% (All Grade) or >= 5% (Grade 3-4); Treated patients (Study 42756493-BLC2001)

	BALVERSA 8 mg daily (N=98[a])	
	All Grades (%)	Grade 3-4 (%)
Laboratory Abnormality		
Hematology		
Anemia	35	3
Leukopenia	17	0
Thrombocytopenia	16	1
Neutropenia	11	2
Chemistry		
Hyperphosphatemia	77	2
Creatinine increased	52	4
Alanine aminotransferase increased	42	2
Hyponatremia	41	16
Alkaline phosphatase increased	39	1
Hypoalbuminemia	34	0
Aspartate aminotransferase increased	32	0
Hypomagnesemia	29	1
Hypophosphatemia	26	8
Hypercalcemia	20	3
Hyperkalemia	14	0

[a] One of the 99 patients had no laboratory tests.

The following ARs were reported with the administration of BALVERSA™ in BLC2001 and other studies:

Central serous retinopathy (CSR)

CSR has been reported with the use of BALVERSA™ as well as with other FGFR inhibitors. Adverse reactions of CSR were reported in 23% of patients; CSR included chorioretinopathy, retinal detachment, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal edema, retinopathy and vitreous detachment (see *Warning and Precautions*).

Nail disorders

Nail disorders were reported in 57% of patients and included onycholysis, paronychia, nail dystrophy, nail discoloration, onychalgia, nail ridging, onychoclasis, nail bed bleeding and nail discomfort. The incidence of nail disorders increased with increased exposure. The median time to onset for any grade nail disorder was 68 days.

Skin disorders

Skin disorders were reported in 51% of patients and included dry skin and palmar-plantar erythrodysesthesia syndrome, pruritus, skin fissures, eczema, hyperkeratosis, skin exfoliation, skin lesion, xeroderma, skin atrophy, eczema nummular and skin toxicity. The median time to onset for any grade skin disorder was 40 days.

Hyperphosphatemia

Increases in phosphate concentrations are an expected and transient laboratory abnormality (see *Pharmacodynamic effects*). Hyperphosphatemia was reported as an adverse event in 77% of patients treated with BALVERSA™. No event of hyperphosphatemia was reported as serious. The median onset time for any grade event of hyperphosphatemia was 20 days. Mean phosphate elevations peaked approximately 6 weeks after the start of BALVERSA™ and subsequently decreased to below 4.5 mg/dL by approximately month 5.

Overdose

Symptoms and signs

There is no information on overdosage with BALVERSA™.

Treatment

There is no known specific antidote for BALVERSA™ overdose. In the event of an overdose, stop BALVERSA™, undertake general supportive measures until clinical toxicity has diminished or resolved.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Tyrosine kinase inhibitor, ATC code: not yet assigned.

Mechanism of action

Erdafitinib is a highly selective and potent oral pan-FGFR tyrosine kinase inhibitor with high affinity and inhibitory activity at low nanomolar levels for all FGFR family members, FGFR 1, 2, 3 and 4. In FGFR pathway activated cancer cell lines, the concentration required for 50% tumor growth inhibition (IC_{50}) 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.

Pharmacodynamic effects

Cardiac electrophysiology

Erdafitinib had no large effects (i.e.,>20 ms) on cardiac repolarization or other electrocardiographic parameters in humans. Exposure-QT analyses were conducted over a dose range from 0.5 to 12 mg from 187 subjects with cancer in a Phase 1, open label, dose escalation study.

Serum phosphate

Erdafitinib increased serum phosphate concentration, a pharmacodynamic biomarker of FGFR inhibition. BALVERSA™ should be increased to the maximum recommended dose to achieve target serum phosphate levels of 5.5–7.0 mg/dL in early cycles with continuous daily dosing.

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

Clinical studies

Urothelial carcinoma tumors with select FGFR genetic alterations

Study BLC2001 was a multicenter, open-label, single arm Phase 2 study to evaluate the efficacy and safety of BALVERSA™ in 99 patients with locally advanced or metastatic urothelial carcinoma, including 12 patients who were chemo-naïve based on ineligibility for cisplatin. 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 pharmacodynamically guided up-titration to 9 mg once daily in patients whose serum phosphate levels between days 14 and 17 were below the target of 5.5 mg/dL; up-titration occurred in 41% of patients. BALVERSA™ was administered until disease progression or unacceptable toxicity.

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. Half of the patients (51%) received one prior line of therapy, 49% received two or more and 79% had visceral metastases. Efficacy results were based on objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Table 7).

Table 7: Efficacy results for study BLC2001

	IRRC[a] assessment	**Investigator assessment**
Endpoint	**N=87**	**N=87**
Objective response rate (ORR) (%) 95% CI (%)	32.2 (22.4, 42.0)	40.2 (29.9, 50.5)
Complete response (CR) (%)	2.3	3.4
Partial response (PR) (%)	29.9	36.8
Stable disease (SD) (%)	46.0	39.1
Progressive disease (PD) (%)	18.4	18.4
Disease control rate (CR+PR+SD) (%) 95% CI (%)	78 (69.5, 86.8)	79.3 (70.8, 87.8)
Median Duration of Response (months) 95% CI (%) (months)	5.4 (4.2, 6.9)	5.6 (4.2, 7.0)
Time to response (months) range (months)	1.4 (1.2, 4.0)	1.4 (1.3, 5.5)
Median Progression Free Survival (months) 95% CI (%) (months)	5.5 (4.0, 5.6)	5.5 (4.0, 5.7)
Median Overall Survival (months) 95% CI (%) (months)	12.0 (8.6, NE)	

[a] IRRC: Independent Radiologic Review Committee
ORR = CR+PR
CI = Confidence Interval

Investigator assessment demonstrated ORRs for patients receiving BALVERSA™ were consistent regardless of the number of lines of prior systemic therapy and ranged from 36% to 60% and Disease Control Rates (DCRs) ranged from 75% to 90%.

ORR by investigator was higher in patients with serum phosphate ≥5.5 mg/dL (43.5% with serum phosphate ≥5.5 mg/dL versus 33.3% with serum phosphate <5.5 mg/dL as obtained within the first 3 months of treatment). Overall survival was longer in patients with serum phosphate ≥ 5.5 mg/dL (median overall survival 13.8 months with serum phosphate ≥ 5.5 mg/dL versus 7.23 months with serum phosphate <5.5 mg/dL).

Table 8: Efficacy Results by FGFR Genetic Alteration

	BIRC[a] assessment
FGFR3 Point Mutation	N=64
ORR (95% CI)	40.6% (28.6, 52.7)
FGFR3 Fusion [b, c]	N=18
ORR (95% CI)	11.1% (0, 25.6)

[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

Pharmacokinetic Properties

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. Following administration of 8 mg once daily, the proposed starting dose, mean (coefficient of variation [CV%]) erdafitinib steady-state C_{max}, AUC_{τ}, and minimum observed plasma concentration (C_{min}) were 1399 ng/mL (50.8%), 29268 ng**.**h/mL (59.9%), and 936 ng/mL (64.9%). Daily fluctuations in erdafitinib plasma concentrations were low, with a mean (CV%) peak-to-trough ratio of 1.47 (23%) at steady state upon daily dosing.

Absorption

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

Effect of food

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 (see *Dosage and Administration*).

Distribution

The mean apparent volume of distribution of erdafitinib in subjects with cancer was 28.8 L.

In patients with cancer, erdafitinib was 99.76% bound to human plasma proteins, preferentially to α1- acid glycoprotein AGP.

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.

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.

Excretion

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

Special populations

No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed based on age (21-88 years), sex, race (Hispanic or Asian), body weight (36-132 kg), mild or moderate renal impairment or mild hepatic impairment.

Pediatrics

Pharmacokinetics of erdafitinib has not been studied in pediatric patients.

Renal impairment

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 30-59 mL/min/1.73 m²). No 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 (see *Dose modifications*).

Hepatic impairment

No clinically meaningful differences in the pharmacokinetics of erdafitinib were observed in subjects with mild hepatic impairment (as defined by the National Cancer Institute criteria) and

subjects with normal hepatic function based on population PK analysis. Limited or no data are available in patients with moderate or severe hepatic impairment; therefore, BALVERSA™ should be administered with caution should be used in these patients. Monitor closely for adverse reactions and reduce the BALVERSA™ dose (see *Dose modifications*).

CYP2C9 poor metabolizer

Erdafitnib exposure was comparable in subjects with CYP2C9 *1/*2 and *1/*3 genotypes relative to subjects with wild type and similar results were obtained in simulations. No data are available in subjects characterized by other genotypes (e.g., *2/*2, *2/*3, and *3/*3). Simulation suggested no clinically meaningful changes of erdafitinib exposure in CYP2C9 *2/*2 and *2/*3 subjects. The exposure of erdafitinib is predicted to increase by 50% in subjects of CYP2C9 *3/*3 genotype, estimated to be 0.4% to 3% of the population among various ethnic groups and representing the worst-case scenario among the various heterogenous 2C9 poor metabolizer populations.

Drug interactions

Effect of other drugs on erdafitinib

Strong CYP2C9 inhibitor

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

Strong CYP3A4 inhibitor

C_{max} of erdafitinib was 105% (90% CI: 86.7, 127) and AUC_{∞} was 134% (90% CI: 109, 164) when co-administered with itraconazole, a strong CYP3A4 inhibitor and P-gp inhibitor, relative to erdafitinib alone.

Strong CYP3A4/2C9 inducer

The effects of CYP3A4 or CYP2C9 inducers on the PK of erdafitinib have not been evaluated *in vivo*. Simulations suggested that rifampicin (a strong CYP3A4/2C9 inducer) may lead to approximately 60% decrease in erdafitinib exposure (AUC and C_{max}).

Acid lowering agents

Erdafitinib is a BCS Class I compound with 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.

Effect of erdafitinib on other drugs

Major CYP isoform substrates

Erdafitinib is not an inhibitor of major CYP isozymes at clinically relevant concentrations; however, it was shown to be a weak time dependent inhibitor towards CYP3A4 activity as well as a weak inducer of CYP3A4. Simulation supported that drug interactions with CYP3A4 substrates are not expected to be clinically relevant.

P-gp transporter

Erdafitinib is a P-gp inhibitor *in vitro* and may be a clinical inhibitor of gut P-gp. Simulation predicted a C_{max} -ratio of 1.45 and an AUC-ratio of 1.18 for digoxin when erdafitinib was co-administered with digoxin at the same time with a C_{max} -ratio of 1.45 and an AUC-ratio of 1.18, whereas dose staggering by 6 hours could avoid this interaction.

Other transporters

Erdafitinib is not an *in vitro* inhibitor of OATP1B3, OAT1, and OAT3. At clinically relevant concentrations, erdafitinib is not considered to be an inhibitor of BCRP, OATP1B, OCT1, MATE-1, and MATE-2K transporters. Erdafitinib is an OCT2 inhibitor *in vitro*. Simulations with metformin, a OCT2 substrate, predicted a lack of clinically relevant interaction with erdafitinib.

NON-CLINICAL INFORMATION

In repeated dose toxicity studies in rats and dogs, disturbance of phosphate homeostasis, characterized by elevated serum concentrations of mainly phosphate, FGF-23 and 1,25 dihydroxyvitamin D_3 were observed at exposures less than the human exposures at all doses studied (see *Dosage and Administration*). Cartilage dysplasia and soft tissue mineralization, associated with hyperphosphatemia, were observed as primary drug-related toxicities in animals. When rats were given a diet supplemented with the phosphate scavenger sevelamer, the soft tissue mineralizations were reduced. Atrophy of gland and epithelial structures (dental changes, thinning of the corneal epithelium lacrimal gland atrophy changes to haircoat and nails) were seen.

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.

Carcinogenicity, Mutagenicity, and Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of erdafitinib. 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. Dedicated animal fertility studies have not been conducted with erdafitinib. However, in the 3-month general toxicity study, erdafitinib showed effects on female reproductive organs (necrosis of the corpora lutea) in rats at an exposure approximating the AUC in patients at maximum recommended dose of 9 mg, QD.

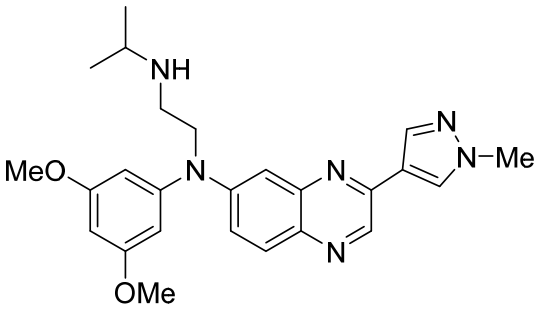
Reproductive Toxicology

Erdafitinib was teratogenic and embryotoxic in rats at ≥ 4 mg/kg/day and exposures less than the human exposures at all doses studied (see *Dosage and Administration*). Fetal malformations and variations included 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.

PHARMACEUTICAL INFORMATION

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:



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 and brown tablets only), Ferrosoferric oxide/iron oxide black (for the brown tablets only).

Shelf Life

See expiry on the outside of the packaging.

Storage Conditions

Store at or below 30ºC. Keep out of the sight and reach of children.

Nature and Contents of Container

Tablets are supplied in child resistant blister packs and bottles.

BALVERSA™ is available in PVC PCTFE foil blisters with an aluminum push through foil sealed inside a wallet pack.

3mg tablets foil blisters come in pack sizes of 56 tablets and 84 tablets.
4mg tablets foil blisters come in pack sizes of 14 tablets (starter pack), 28 tablets, and 56 tablets
5mg tablets foil blisters come in pack sizes of 28 tablets.
Not all pack sizes may be marketed.

BALVERSA™ is available in a white 40 cc HDPE bottle with a child-resistant PP closure and an induction seal liner.

Not all presentations may be available locally.

Instructions for Use and Handling [and Disposal]

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

BATCH RELEASER

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

PRODUCT REGISTRANT

Under licence from Astex Therapeutics Limited.

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