European Union Risk Management Plan
BALVERSA (Erdafitinib)

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QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	1.4
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Other RMP Versions Under Evaluation:

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Not Applicable		

Details of the Currently Approved RMP:

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Approved within procedure	
Date of approval (Competent authority opinion date)	

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Erdafitinib
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, protein kinase inhibitors (L01EN01)
Marketing Authorization Applicant	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	1 (BALVERSA)
Invented name(s) in the European Economic Area (EEA)	BALVERSA
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Tyrosine kinase inhibitor
	Summary of mode of action Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor.
	Important information about its composition Not applicable.
Reference to the Product Information	Module 1.3.1 Summary of Product Characteristics, Labelling and Package Leaflet
Indication(s) in the EEA	Current: BALVERSA as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harboring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting.
	Proposed: Not applicable

Dosage in the EEA	Current: The recommended starting dose of BALVERSA is 8 mg orally once daily. This dose should be maintained and serum phosphate level should be assessed between 14 and 21 days after initiating treatment. The dose can be up-titrated to 9 mg once daily if the serum phosphate level is <9.0 mg/dL (<2.91 mmol/L), and there is no drug-related toxicity. If the phosphate level is 9.0 mg/dL or higher, relevant dose modifications should be used. After Day 21, the serum phosphate level should not be used to guide up-titration decision. The dosing regimen allows for stepwise dose reduction to 8, 6, 5 or 4 mg and/or interruption for tolerability. The tablets should be swallowed whole with or without food.	
	Proposed: Not applicable	
Pharmaceutical form(s) and strengths	Current: BALVERSA is formulated as 3 mg, 4 mg, and 5 mg film-coated tablets. • 3 mg: yellow, round biconvex-shaped tablet, 7.6 mm in diameter, debossed with “3” on one side, and “EF” on the other side • 4 mg: orange, round biconvex-shaped tablet, 8.1 mm in diameter, debossed with “4” on one side, and “EF” on the other side • 5 mg: brown, round biconvex-shaped tablet, 8.6 mm in diameter, debossed with “5” on one side, and “EF” on the other side	
	Proposed: Not applicable	
Is/will the product be subject to additional monitoring in the EU?	☑ **Yes**	☐ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: Urothelial Carcinoma

Urothelial carcinoma (UC; formerly known as transitional cell carcinoma) encompass cancers of the bladder, renal pelvis (part of the kidney), ureters (Cancer Network 2016), and the urethra (American Cancer Society 2023). Bladder tumors account for 90% to 95% of UC, while upper tract urothelial cancers (UTUCs) that include UC of the renal pelvis and ureter account for only 5% to 10% of UC (Roupret 2013; Luo 2022). It is estimated that 5% to 8% of UCs originate in the renal pelvis or ureter (Sfakianos 2015).

Incidence:

Globally, the age-standardized incidence of bladder cancer was estimated to be 5.6/100,000 population in 2020 (Ferlay 2020). The incidence of bladder cancer in 2020 was 35.3/100,000 population for the European Union, ranging from 17.3/100,000 population in Austria to 52/100,000 population Greece (ECIS 2023). In Germany, the age-standardized incidence of bladder cancer was 24.4/100,000 in 2019 (German Centre for Cancer Registry Data 2022). The incidence of bladder cancer was 17.3/100,000 population in the United States in 2020 (SEER 2023) and 15.6/100,000 population in the United Kingdom from 2016 to 2018 (Cancer Research UK 2021). The estimated annual incidence of UTUCs in western countries is approximately 2/100,000 population (Roupret 2013; Luo 2022).

Approximately 5% of patients have metastatic disease at the time of diagnosis (Flaig 2020).

Prevalence:

Globally in 2020, the 5-year prevalence of bladder cancer was estimated to be 21.6/100,000 population (Ferlay 2020). In 2020, the 5-year prevalence rate of bladder cancer in the European Union was estimated to be 111.7/100,000 population, ranging from 46.8/100,000 population in Austria to 200.2/100,000 population in Greece (ECIS 2023). In Nordic countries (Denmark, Finland, Iceland, Norway, Sweden, Faroe Islands, and Greenland), the estimated 5-year prevalence rate was 115.4/100,000 population in 2020 (NordCan 2022).

FGFR alterations occur in 10% to 20% of patients with metastatic urothelial carcinoma (mUC) (Necchi 2019, Tully 2021), with the most common being *FGFR3* activating mutations (Casadei 2019).

Demographics of the Population in the Proposed Indication - Age, Sex, Racial and/or Ethnic Origin, and Risk Factors for the Disease

Age: Bladder cancer primarily affects older individuals, with a median age of 73 years at the time of diagnosis (Zheng 2021, Halaseh 2022). According to the Sweden National Registry data from 1997 to 2019, there were a total of 53,298 cases of urinary bladder cancer. The distribution of age at diagnosis is as follows: 64 years and below: 11,469 cases (accounting for 22% of the total); 65-69 years: 7,579 cases (14% of the total); 70-74 years: 9,568 cases (18% of the total);

75-79 years: 9,806 cases (18% of the total); 80-84 years: 8,158 cases (15% of the total); 85 years and above: 6,718 cases (13% of the total) (Häggström 2022).

Sex: UC is more common in men than women, with men having a 3-fold greater risk of developing bladder cancer; it is the fourth most common cancer in men (Lucca 2015). Recent data reports 27% of bladder cancer cases in the United Kingdom are in females, and 73% are in males (Cancer Research UK 2021). However, women tend to have a poorer prognosis and less favorable tumor characteristics at the time of diagnosis due to a delay in diagnosis, as symptoms are often initially attributed to urinary tract infection (Arora 2018).

Race and Ethnicity: Bladder cancer has been observed to have a higher incidence among white individuals compared to the black and Asian population (Delon 2022). In 2020, the highest incidence of bladder cancer in the United States was among the white population (non-Hispanic descent), with a rate of 21.1/100,000 population. The incidence rates for the black (non-Hispanic descent), Asian, and Hispanic population were 11.1/100,000 population, 8.0/100,000 population, and 9.2/100,000 population, respectively (SEER 2023).

Risk factors: Smoking, increasing age, male sex, chronic bladder inflammation, family history of cancer, pelvic radiation therapy, and alkylating agents have been identified as risk factors for UC (Tyson 2022). In addition, exposure to certain medicinal, chemical, and industrial compounds primarily found in the textile, asphalt, petroleum, metallurgy, rubber, dye, leather, dry cleaning, and painting industries (Arora 2018), and germline genetic mutations (National Cancer Institute 2023) have also been identified as risk factors for bladder cancer.

Main Existing Treatment Options:

Management of locally advanced or mUC patients depends primarily on their overall health, age and performance status. For mUC patients who are sufficiently fit for systemic therapy, cisplatin-based combination chemotherapy regimens, such as cisplatin-gemcitabine or dose-dense MVAC (methotrexate-vinblastine-doxorubicin-cisplatin) are the preferred regimens in the first-line setting (Powles 2022, von der Maase 2000). However, even among patients who are fit enough to receive first-line treatment, recent real-world data from Europe (Niegisch 2023) and the United Sates (Geynisman 2022) indicate that only a minority are considered cisplatin eligible, most frequently due to the presence of comorbidities (eg, renal insufficiency or heart failure); a proportion of cisplatin-ineligible patients may be able to receive treatment with carboplatin-based regimens (Dogliotti 2007).

The development of anti-programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1) [anti-PD-(L)1] agents significantly expanded therapeutic options in first and subsequent lines of treatment for patients with mUC. In the first-line setting, survival benefit was demonstrated for avelumab maintenance therapy versus best supportive care in patients who had received platinum-based chemotherapy and had not experienced disease progression. Additionally, pembrolizumab and atezolizumab are approved as a first-line therapy for patients who are not eligible for any platinum-based chemotherapy. Clinical benefit from treatment with anti-PD-(L)1 agents in the second-line setting led to the approval of several such agents. Additionally, clinical benefit for anti-PD-(L)1 agents has also been demonstrated in the adjuvant setting for patients with

muscle-invasive disease, including nivolumab, which was approved as adjuvant therapy for patients with high-risk disease after radical cystectomy.

Therapeutic options beyond platinum-based chemotherapy and/or anti-PD-(L)1 agents are significantly more limited. Single agent chemotherapy (eg, vinflunine) provides limited clinical benefit (Culine 2006). More recently, enfortumab vedotin was approved for patients with progressive disease following prior platinum-based chemotherapy and anti-PD-(L)1 agents (Powles 2021). Importantly, these options are further limited by the presence of comorbidities, patient frailty, or residual toxicities associated with previously administered therapies, such as neuropathy; recent real-world studies indicate that only a minority of patients are offered systemic therapy after receiving an anti-PD-(L)1 agent (Morgans 2022).

In the United States, erdafitinib received approval on 12 April 2019 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma, that has susceptible FGFR3 or FGFR2 alterations, and has progressed during or following at least 1 line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Since that time, marketing authorizations have also been received in additional countries.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Survival in the metastatic setting is 12 to 15 months with cisplatin-based combination chemotherapy, but only 3 to 6 months if left untreated. With the advent of immunotherapy, anti-body-drug conjugates, and targeted agents, the overall survival now approaches 2 years for patients who are able to receive these therapies (Stecca 2021).

Globally, the mortality rate for bladder cancer was 2.7/100,000 population in 2020 (Ferlay 2020). For the European Union the age-standardized mortality rate for bladder cancer in 2020 was 10.1/100,000 population and ranged from 4.4/100,000 population in Finland to 14.7/100,000 population in Slovakia (ECIS 2023). In the Nordic countries, the age-standardized mortality rate was 6.3/100,000 population for men and 2.3/100,000 population for women in 2020 (NordCan 2022). In the United States, the mortality rate for bladder cancer in 2020 was 4.0/100,000 population (SEER 2023).

Important Comorbidities:

Comorbidities associated with UC or bladder cancer include diabetes, renal disease, cardiovascular disease, hypertension, and pulmonary disease (Goossens-Laan 2014, Fisher 2018).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety profile for erdafitinib has been characterized in safety pharmacology studies, single- and repeat-dose pivotal toxicology studies in rats and dogs, genotoxicity studies, embryo-fetal development studies in rats, and in vitro and in vivo studies to evaluate phototoxicity and skin sensitization. All in vivo toxicology studies were performed via oral (gavage) administration.

Absorption and metabolism were studied in vitro and in vivo. Distribution and excretion were studied in vivo. Protein binding and drug interaction potential were evaluated in vitro.

The nonclinical development program adhered to the requirements of the International Council for Harmonisation (ICH) guideline S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. The nonclinical safety data was extended with a standalone cardiovascular study in the dog and mechanistic studies to evaluate onset and pathogenesis of soft tissue mineralization in rats. Consistent with ICH guideline S9, a standalone fertility assessment and carcinogenicity assessment have not been performed. As erdafitinib was considered teratogenic based on the embryo-fetal developmental toxicity study in rats, no additional pre-and postnatal development studies were conducted.

Based on the nonclinical data, the risks for hepatotoxicity, genotoxicity, and effects on the respiratory and immune systems are considered limited. In general, the nature of the toxicity of erdafitinib was consistent with the pharmacological activity of a selective pan-FGFR inhibitor and comparable across species. Target organs or biological processes impacted are phosphate homeostasis, chondroid dysplasia, soft tissue mineralization, glandular and epithelial structures, and tooth and nail changes. Erdafitinib is embryotoxic and teratogenic in rats.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
Repeat-dose toxicology studies were conducted with oral administration up to 3 months in rats and dogs, and for 2 weeks in male mice.	In general, the nature of toxicity of erdafitinib was comparable across species. Interference with the phosphate and vitamin D homeostasis is considered a class effect of FGFR inhibitors in general.
Most toxicities observed in the rat (at ≥4 mg/kg/day) and dog (at ≥0.5 mg/kg/day) were considered related to the pharmacological activity of the compound and occurred below the human exposure at a 9-mg daily dose at steady-state, based on the area under the curve (AUC). Cartilage dysplasia and soft tissue mineralization were observed as primary drug-related toxicities in all species.	Persistent and prolonged serum phosphate elevation is considered a causal factor for soft tissue mineralization; transient and limited serum phosphate increases are not expected to result in such sequelae. Elevated phosphate concentrations can be managed by recommended dose modifications (dose interruption or reduction). For persistently elevated phosphate concentrations, adding a non-calcium containing phosphate binder (eg, sevelamer carbonate) may be considered.
Soft tissue mineralizations were associated with a disturbance of vitamin D and phosphate homeostasis, characterized by elevated levels of fibroblast growth factor (FGF)23, 1,25 dihydroxyvitamin D3, serum phosphate and, to a much lesser extent, calcium and parathyroid hormone. Soft tissue mineralizations were noted in mice (≥12.5 mg/kg/day), rats (≥16 mg/kg/day), and dogs (≥1 mg/kg/day).	Chondroid dysplasia is considered less relevant for an adult population that has stopped growing.
Chondroid dysplasia was characterized by histological widening of the growth plates in mice (≥25 mg/kg/day), rats (≥8 mg/kg/day), and dogs (≥1 mg/kg/day) with additional periostal changes in dogs.	Tooth-related changes were most prominent in the rat, but as the incisors of rodents grow continuously, the findings are considered of little relevance for adult patients. Erdafitinib may impact dentin regularity.
Tooth-related changes (abnormal dentin and incremental lines in the rat/irregular dentin in the dog) were noted in the 1- and 3-month studies.	Erdafitinib may affect glandular and epithelial tissues such as mammary, lacrimal and salivary glands, tongue and oral mucosa, and cornea. In the human clinical trials, keratitis, dry eye and dry mouth observations may be related to these changes.
Mammary gland atrophy was noted in male rats in the 1-month study and in rats and dogs in the 3-month studies.	Erdafitinib may cause changes to the integument. Palmar-plantar dysesthesia noted in the human clinical trials may be related to these changes.
Haircoat and nail changes were observed in the 3-month rat and dog studies and included long, thin or irregular fur, local alopecia, and long or broken nails. This related to histological increases in number but reduction in size of hair follicles. There were no histological changes in nail or nailbed.	The findings noted in clinical trials, such as those impacting glandular and epithelial tissue and the integument, are manageable and/or are not anticipated to impact the overall risk-benefit balance and therefore are not considered important risks. Based on the nonclinical and clinical data, **hyperphosphatemia is considered an important identified risk** with the use of erdafitinib.

Key Safety Findings	Relevance to Human Usage
In the 3-month studies in rats and dogs, at the end of treatment, corneal atrophy was seen in rats and lacrimal gland atrophy in rats and dogs. There were no indications for retinopathy. Chondroid dysplasia and soft tissue mineralization were shown to be slowly and partially reversible in the 1-month studies, except for the aorta mineralization in dogs that did not show recovery after a 1-month treatment-free period. Tooth and mammary gland changes were fully reversible after a 1-month treatment-free period. Reversibility was not assessed in the 3-month studies.	
Reproductive toxicity	
No fertility toxicity studies were conducted with erdafitinib. Separate fertility studies are generally not applicable to therapies for the specific cancer indications (ICH S9). 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 approximately the AUC in patients at the maximum recommended dose of 9 mg once daily.	Based on the nonclinical findings, erdafitinib may impact female fertility. However, no human data are available to determine potential effects of erdafitinib on fertility in males or females.
Developmental toxicity	
Erdafitinib showed a teratogenic potential in a rat embryo-fetal development study, characterized by deformations of the extremities with ectrodactyly, absent/misshapen long bones and thoracic vertebrae, and malformations of the great vessels including the aortic arch. The no observed adverse effect level for embryo-fetal development was 1 mg/kg/day, and erdafitinib was considered teratogenic and embryotoxic at ≥4 mg/kg/day.	Based on the nonclinical findings, erdafitinib is teratogenic and can cause fetal harm when administered to pregnant women. **Reproductive and developmental toxicity is considered an important potential risk** with the use of erdafitinib.
Genotoxicity	
Erdafitinib has no genotoxic properties when tested in bacteria, mammalian cells, or rats.	Erdafitinib is not expected to be genotoxic in humans.

Key Safety Findings	Relevance to Human Usage
Carcinogenicity	
No carcinogenicity studies were conducted with erdafitinib. Routine carcinogenicity studies are generally not applicable to therapies for the specific cancer indications (ICH S9). There were no indications for carcinogenic potential in the general toxicity studies.	Erdafitinib is not expected to be carcinogenic in humans.
Safety pharmacology:	
Cardiovascular system (including potential for QT interval prolongation)	
Erdafitinib is an intrinsic human ether-à-go-go-related gene (hERG) blocker with a proarrhythmic liability which translated into a prolonged repolarization (corrected QT interval [QTc]) after intravenous dosing in the anesthetized dog and guinea pig, and after oral dosing in the conscious dog. In the Good Laboratory Practice (GLP) oral conscious dog cardiovascular study, the total plasma exposure of 90.2 ng/mL (unbound concentration of 12.4 ng/mL) at the no effect level represents a safety margin of 2.4 relative to the clinical steady-state free maximum plasma concentration ($C_{max,u}$) for a 9-mg once daily dose.	Based on nonclinical in vitro and in vivo data, erdafitinib has a potential for inducing a prolonged repolarization (QTc interval). The determined no effect level provides a limited safety margin of 2.4 relative to the unbound C_{max} for a clinical dose of 9 mg once daily. QTc prolongation was observed in a low number of patients during clinical trials. Based on the available nonclinical and clinical data, **QT prolongation is considered an important potential risk** with the use of erdafitinib.
Nervous system	
In a modified Irwin's test in rats, erdafitinib showed minimal neurofunctional aberrations (impaired wire maneuvers and flaccid body tone) which were considered a potential direct effect of treatment, from a mean maximum plasma concentration (C_{max}) of 12.1 ng/mL (unbound concentration of 0.871 ng/mL) which is below the clinical steady-state C_{max} (total or unbound) for a 9-mg once daily dose.	There were no observations in clinical trials related to these nonclinical findings.
Phototoxicity	
Erdafitinib showed phototoxicity in vitro. However, there was no skin phototoxicity in a pigmented rat study.	Based on negative findings in the pigmented rat study, there was no phototoxicity expected for erdafitinib in humans. However, with dry skin being observed with erdafitinib in the clinic, excessive exposure to sunlight and dehydration should be avoided.

Key Safety Findings	Relevance to Human Usage
Nephrotoxicity	
No structural toxicities were noted in the kidneys in the 1- and 3-month rat and dog studies. Erdafitinib impacts renal phosphate handling by increasing phosphate reabsorption, which leads to hyperphosphatemia. Hyperphosphatemia has been seen in all nonclinical studies.	Based on the impact of erdafitinib on renal phosphate handling, the benefit/risk ratio for chronic kidney disease patients with severely impaired renal function should be considered carefully. Acute kidney injury, renal impairment, and renal failure have been observed in clinical trials and are adverse drug reactions (ADRs); however, they are considered to have a minimal clinical impact on patients (in relation to the severity of the indication treated) and therefore are not considered important risks.
Hepatotoxicity	
No hepatotoxicity was identified in the clinical pathology and histopathology assessments for the 1- and 3-month rat and dog studies.	Based on the nonclinical findings, erdafitinib is not expected to be hepatotoxic in humans. Clinically significant hepatotoxicity is not observed in clinical trials. Alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased have been observed in clinical trials and are ADRs; however, they are considered to have a minimal clinical impact on patients (in relation to the severity of the indication treated) and therefore are not considered important risks.
Other toxicity-related information or data	
Mechanisms for drug interactions	
Based on in vitro data, erdafitinib is metabolized by cytochrome P450 (CYP)2C9 and CYP3A4.	Clinical drug-drug interaction study 42756493EDI1007 showed that on average, erdafitinib exposure (C_{max} and AUC) was increased by 5% and 34%, respectively, when co-administered with itraconazole (a strong CYP3A4 inhibitor and P-glycoprotein [P-gp] inhibitor), relative to erdafitinib alone. On average, erdafitinib exposure (C_{max} and AUC) was increased by 21% and 48%, respectively, when co-administered with fluconazole (a moderate CYP2C9 and CYP3A4 inhibitor), relative to erdafitinib alone. Alternative agents with no or minimal enzyme inhibition potential should be considered. If erdafitinib is co-administered with a moderate CYP2C9 or strong CYP3A4 inhibitor, the erdafitinib dose may be reduced to the next lower dose based on tolerability. If the moderate CYP2C9 or strong CYP3A4 inhibitor is discontinued, the erdafitinib dose may be adjusted as tolerated. Grapefruit or Seville oranges should be avoided while taking erdafitinib due to strong CYP3A4 inhibition. Co-administration with carbamazepine, a strong CYP3A4 and weak CYP2C9 inducer leads to decreased erdafitinib exposure. On average,

Key Safety Findings	Relevance to Human Usage
	erdafitinib exposure (C_{max} and AUC) was decreased by 34.6% and 62.3%, respectively, when co-administered with carbamazepine, relative to erdafitinib alone. Co-administration of erdafitinib with strong CYP3A4 inducers should be avoided. If erdafitinib is co-administered with a moderate CYP3A4 inducer, the dose should be cautiously increased by 1 to 2 mg and adjusted gradually every 2 to 3 weeks based on clinical monitoring for adverse reactions, not to exceed 9 mg. If the moderate CYP3A4 inducer is discontinued, the erdafitinib dose may be adjusted as tolerated.
Erdafitinib was shown to inhibit human P-gp in vitro. Relevance of in vitro to in vivo inhibition was assessed based on predictive static models recommended by the Food and Drug Administration (FDA) (FDA Guidance for Industry, In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions 2020) and European Medicines Agency (EMA) (EMA Guideline on the Investigation of Drug Interactions 2012) drug-drug interaction guidelines. These predictions indicated that no P-gp inhibition is expected at systemic level; however, inhibition at intestinal level can be expected in vivo.	Erdafitinib is a P-gp inhibitor in vitro and may be a clinical inhibitor of gut P-gp. Impact of P-gp inhibition by erdafitinib at intestinal level was not clinically studied. Concomitant administration of erdafitinib with P-gp substrates may increase their systemic exposure. Based on the nonclinical observation of P-gp inhibition by erdafitinib, **potential drug toxicity due to accumulation of P-glycoprotein substrates is considered an important potential risk** with the use of erdafitinib. 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, whereas dose staggering by 6 hours could avoid this interaction. Therefore, oral narrow therapeutic index P-gp substrates (such as colchicine, digoxin, dabigatran, and apixaban) should be taken at least 6 hours before or after erdafitinib to minimize the potential for interactions.
Erdafitinib was shown to inhibit organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP)1B1, breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein (MATE)-1, MATE-2 transporters in vitro. Relevance of in vitro to in vivo inhibition was assessed based on predictive static models recommended by the FDA (FDA Guidance for Industry, In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions 2020) and EMA (EMA Guideline on the Investigation of Drug Interactions 2012) drug-drug interaction guidelines. Prediction results indicated that no inhibition is expected in vivo for these transporters, with the exception of OCT2.	Erdafitinib is not an in vitro inhibitor of OATP1B3, organic anion transporter (OAT)1, 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. However, mean ratios of C_{max} and AUC for metformin (a sensitive OCT2 substrate) were increased by 9% and 14%, respectively, when co-administered with erdafitinib, relative to metformin alone. Erdafitinib does not have a clinically meaningful effect on metformin pharmacokinetics (PK).

Key Safety Findings	Relevance to Human Usage
Erdafitinib was not a reversible CYP3A4 inhibitor but showed a weak time-dependent based inhibition of CYP3A4 in vitro. Intrinsic clearance of midazolam (CYP3A4 substrate) in presence of erdafitinib in human liver microsomes was comparable to erythromycin (reference CYP3A4 inhibitor), indicating that erdafitinib has similar potential for CYP3A4 mechanism-based inhibition in vivo.	Co-administration with midazolam, a sensitive CYP3A4 substrate, leads to a slight decrease in midazolam exposure. Erdafitinib does not have a clinically meaningful effect on midazolam PK. Therefore, erdafitinib can be administered with CYP3A4 substrates. However, concomitant administration of other CYP3A4 inducers together with erdafitinib may reduce the efficacy of hormonal contraceptives.
In human hepatocyte CYP induction assays, erdafitinib showed a weak induction of CYP3A4 in vitro. Comparison of slope of concentration-induction analysis with the maximum induction effect (E_{max})/half maximal effective concentration (EC_{50}) of rifampicin (CYP3A4 inducer, positive control) indicated that induction effect by erdafitinib was 2.5% of rifampicin. These results indicate that induction effect by erdafitinib was negligible and not clinically meaningful.	Simulations suggested no clinical relevance of CYP induction effect by erdafitinib. Therefore, erdafitinib can be administered with CYP3A4 substrates.

Summary of Nonclinical Safety Concerns

Important identified risks	Hyperphosphatemia
Important potential risks	Reproductive and developmental toxicity
	Potential drug toxicity due to accumulation of P-glycoprotein substrates
	QT prolongation
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The safety of erdafitinib in the UC population is supported by 4 clinical trials in this EU- RMP: 42756493BLC3001, 42756493BLC2001 (main study and drug-drug interaction [DDI] substudy), 42756493BLC2002, and 42756493EDI1001 (hereafter referred to as BLC3001, BLC2001, BLC2002, and EDI1001, respectively). These trials are described below.

- **Phase 3 Trial BLC3001** is a randomized, controlled, open-label, multicenter trial in adult subjects with advanced urothelial cancer (metastatic or surgically unresectable) and susceptible FGFR gene alterations who have progressed on or after 1 or 2 prior treatments (Cohort 1) or 1 prior treatment (Cohort 2). In Cohort 1, subjects who received prior anti-PD-(L)1 were randomized to erdafitinib or chemotherapy. In Cohort 2, subjects who did not receive prior anti-PD-(L)1 were randomized to erdafitinib or pembrolizumab. Subjects received erdafitinib 8 mg once daily (with a possibility to increase to 9 mg once daily). The primary analysis has been conducted. The trial is ongoing.
- **Phase 2 Trial BLC2001** is an open-label, multicenter trial in adult subjects with metastatic or surgically unresectable UC with susceptible FGFR gene alterations. In the main study, subjects received either erdafitinib 10 mg intermittent, 6 mg once daily, or 8 mg once daily (with a possibility to increase to 9 mg once daily). For subjects benefiting from treatment after the final analysis, Protocol Amendment 6 allowed continued access to erdafitinib and collection of safety data after the final analysis. Per Protocol Amendment 7, a DDI substudy was included, in which subjects received erdafitinib 8 mg once daily (with the possibility to increase to 9 mg once daily) in combination with a single dose of midazolam and metformin. For subjects benefiting from treatment after completing the DDI substudy, Protocol Amendment 9 allowed continued access to erdafitinib and collection of safety data in a long-term extension phase. The main study is completed and the DDI substudy is ongoing.
- **Phase 1b/2 Trial BLC2002** is an open-label, multicenter, 2-part trial in adult subjects with metastatic or locally advanced UC. In Phase 1b (dose escalation), subjects receive erdafitinib 6 mg or 8 mg (with or without up-titration to 9 mg) once daily in combination with cetrelimab or erdafitinib 8 mg once daily in combination with cetrelimab and cisplatin or carboplatin. In Phase 2 (dose expansion), subjects receive erdafitinib 8 mg (with up-titration to 9 mg) once daily alone or erdafitinib 8 mg once daily in combination with cetrelimab. The trial is ongoing.
- **Phase 1 Trial EDI1001** was a first-in-human, open-label, multicenter, 4-part trial in adult subjects with advanced or refractory solid tumors or lymphoma that was metastatic or unresectable. In Part 1 (dose escalation), subjects received erdafitinib 0.5 mg to 12 mg once daily or intermittent. In Part 2 (dose confirmation), subjects received erdafitinib 9 mg once daily. In Parts 3 and 4 (dose expansion), erdafitinib 9 mg once daily and 10 mg intermittent, respectively, was administered. The trial is completed.

In this EU-RMP, only subjects with locally advanced or metastatic UC who received the erdafitinib monotherapy starting dose regimen of 8 mg (with or without individualized up-titration to 9 mg) or 9 mg are included for characterization of exposure and safety.

SIII.2. Clinical Trial Exposure

Exposure in Randomized Clinical Trials

The randomized clinical trials population includes one trial, ie, Trial BLC3001 (Cohorts 1 and 2).

Exposure to erdafitinib in the randomized clinical trials population is summarized in Tables SIII.1 through SIII.4 for all subjects by duration, by age group and sex, by dose, and by variable stratifications relevant to the product (eg, renal impairment at baseline and hepatic impairment at baseline).

Table SIII.1: Duration of Erdafitinib Exposure; All Randomized Trials Population

Duration of Exposure	Patients	Person-Months
Indication: Urothelial Cancer		
0-<3 months	109	194.6
3-<6 months	90	414.7
6-<9 months	46	345.2
9-<12 months	20	211.2
12-<18 months	19	285.0
18-<24 months	14	286.2
24-<30 months	4	109.4
30-<36 months	2	68.7
36-<42 months	3	118.4
>=42 months	1	43.4
Total	308	2076.8

Note: The trial BLC3001 is included.
Note: 1 month equals 30.4375 days.

[TSIEXP01A.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/TSIEXP01A.SAS] 04AUG2023, 00:12

Table SIII.2: Exposure by Age Group and Sex; All Randomized Trials Population

	Men		Women	
Age Group	Patients	Person-Months	Patients	Person-Months
Indication: Urothelial Cancer				
<30 years	0	0.0	0	0.0
30-54 years	25	198.1	8	129.1
55-64 years	68	464.3	25	212.9
65-74 years	98	636.0	23	122.8
75-84 years	42	240.2	14	61.5
>=85 years	3	9.6	2	2.3
Total	236	1548.2	72	528.6

Note: The trial BLC3001 is included.
Note: 1 month equals 30.4375 days.

[TSIEXP02A.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/TSIEXP02A.SAS] 04AUG2023, 00:12

Table SIII.3: Exposure by Dose; All Randomized Trials Population

Dose of exposure	Patients	Person-Months
Indication: Urothelial Cancer		
8 or 9 mg QD	308	2076.8

Note: The trial BLC3001 is included.
Note: 1 month equals 30.4375 days.

[TSIEXP03A.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/TSIEXP03A.SAS] 04AUG2023, 00:12

Table SIII.4: Exposure by Special Populations; All Randomized Trials Population

Population	Patients	Person-Months
Indication: Urothelial Cancer		
Renal impairment at baseline		
Normal (eGFR >= 90 mL/min/1.73m^2)	37	205.3
Mild (eGFR 60 to <90 mL/min/1.73m^2)	123	868.0
Moderate (eGFR 30 to <60 mL/min/1.73m^2)	141	950.1
Severe (eGFR < 30 mL/min/1.73m^2)	7	53.4
Missing	0	0.0
Total	308	2076.8
Hepatic impairment at baseline[a]		
Normal	268	1839.5
Mild	36	230.8
Moderate	1	0.3
Severe	0	0.0
Missing	3	6.2
Total	308	2076.8

[a] Normal: Total bilirubin <= ULN and AST <= ULN; Mild: (Total bilirubin <= ULN and AST > ULN) or (ULN < Total bilirubin <= 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin <= 3 x ULN; Severe: Total bilirubin > 3 x ULN
Key: ULN = upper limit of normal; eGFR = estimated glomerular filtration rate; AST = aspartate aminotransferase.
Note: The trial BLC3001 is included.
Note: 1 month equals 30.4375 days.

[TSIEXP04A.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/TSIEXP04A.SAS] 04AUG2023, 00:12

Exposure in All Clinical Trials

The all clinical trials population includes 4 trials (locally advanced or metastatic UC population only):

- Trial BLC3001
- Trial BLC2001 (main study and DDI substudy)
- Trial BLC2002 (monotherapy arm)
- Trial EDI1001 (mUC subjects)

Exposure to erdafitinib in the all clinical trials population is summarized in Tables SIII.5 through SIII.8 for all subjects by duration, by age group and sex, by dose, and by variable stratifications relevant to the product (eg, renal impairment at baseline and hepatic impairment at baseline).

Table SIII.5: Duration of Erdafitinib Exposure; All Clinical Trials Population

Duration of Exposure	Patients	Person-Months
Indication: Urothelial Cancer		
0-<3 months	161	291.7
3-<6 months	139	643.8
6-<9 months	71	525.9
9-<12 months	35	363.9
12-<18 months	32	483.1
18-<24 months	22	451.2
24-<30 months	7	192.3
30-<36 months	6	199.8
36-<42 months	5	196.6
>=42 months	1	43.4
Total	479	3391.8

Note: The trials of BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001 are included.
Note: 1 month equals 30.4375 days.

[TSIEXP01.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/TSIEXP01.SAS] 04AUG2023, 00:12

Table SIII.6: Exposure by Age Group and Sex; All Clinical Trials Population

	Men		Women	
Age Group	Patients	Person-Months	Patients	Person-Months
Indication: Urothelial Cancer				
<30 years	0	0.0	0	0.0
30-54 years	40	303.7	13	150.9
55-64 years	104	741.4	34	344.5
65-74 years	150	1015.4	41	225.8
75-84 years	65	423.0	20	123.8
>=85 years	6	27.5	6	35.8
Total	365	2511.0	114	880.8

Note: The trials of BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001 are included.
Note: 1 month equals 30.4375 days.

[TSIEXP02.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/TSIEXP02.SAS] 04AUG2023, 00:12

Table SIII.7: Exposure by Dose; All Clinical Trials Population

Dose of exposure	Patients	Person-Months
Indication: Urothelial Cancer		
8 or 9 mg QD	479	3391.8

Note: The trials of BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001 are included.
Note: 1 month equals 30.4375 days.

[TSIEXP03.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/TSIEXP03.SAS] 04AUG2023, 00:12

Table SIII.8: Exposure by Special Populations; All Clinical Trials Population

Population	Patients	Person-Months
Indication: Urothelial Cancer		
Renal impairment at baseline		
Normal (eGFR >= 90 mL/min/1.73m^2)	53	277.5
Mild (eGFR 60 to <90 mL/min/1.73m^2)	188	1410.6
Moderate (eGFR 30 to <60 mL/min/1.73m^2)	228	1630.3
Severe (eGFR < 30 mL/min/1.73m^2)	10	73.3
Missing	0	0.0
Total	479	3391.8
Hepatic impairment at baseline[a]		
Normal	427	3054.6
Mild	47	322.6
Moderate	1	0.3
Severe	0	0.0
Missing	4	14.2
Total	479	3391.8

[a] Normal: Total bilirubin <= ULN and AST <= ULN; Mild: (Total bilirubin <= ULN and AST > ULN) or (ULN < Total bilirubin <= 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin <= 3 x ULN; Severe: Total bilirubin > 3 x ULN
Key: ULN = upper limit of normal; eGFR = estimated glomerular filtration rate; AST = aspartate aminotransferase.
Note: The trials of BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001 are included.
Note: 1 month equals 30.4375 days.

[TSIEXP04B.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/TSIEXP04B.SAS] 09MAY2024, 22:22

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Phosphate level > upper limit of normal (ULN)**
Reason for being an exclusion criterion	Erdafitinib impacts renal phosphate reabsorption, which leads to hyperphosphatemia. Interference with the phosphate homeostasis is considered a class effect of FGFR inhibitors in general. Increases in serum phosphate were observed in nonclinical studies.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Hyperphosphatemia is considered an important identified risk based on nonclinical toxicology studies and clinical trial observations. The SmPC provides instructions and guidelines for hyperphosphatemia management.
Criterion 2	**Women who are pregnant or breastfeeding, or planning to become pregnant and men who plan to father a child during the trial or within 6 months after the last dose of study drug**
Reason for being an exclusion criterion	Per ICH guidelines, pregnant women should normally be excluded from clinical trials. Based on findings in animals, erdafitinib can cause fetal harm when administered to pregnant women. Breastfeeding women are usually excluded from clinical trials. There are no data on the presence of erdafitinib in human milk, or the effects of erdafitinib on the breastfed infant, or on milk production.
Considered to be included as missing information	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	Reproductive and developmental toxicity is an important potential risk. The Summary of Product Characteristics (SmPC) states that BALVERSA should not be used during pregnancy, unless the clinical condition of the women requires treatment with BALVERSA. If BALVERSA is used during pregnancy, or if the patient becomes pregnant while taking BALVERSA, the patient should be advised of the potential hazard to the fetus and be counseled about her clinical and therapeutic options. Patients should be advised to contact their healthcare professional if they become pregnant or if pregnancy is suspected while being treated with BALVERSA and up to 1 month afterwards. Breastfeeding should be discontinued during treatment with BALVERSA and for 1 month following the last dose of BALVERSA. In addition, highly effective contraception should be used prior to and during treatment, and for 1 month after the last dose of BALVERSA.
Criterion 3	**Current central serous retinopathy (CSR) or retinal pigment epithelial detachment of any grade**
Reason for being an exclusion criterion	Reversible retinal pigment epithelial detachment and CSR are considered a class effect of FGFR inhibitors in general.
Considered to be included as missing information	No
Rationale (if not included as missing information)	CSR is considered an important identified risk based on clinical trial observations. The SmPC provides instructions and guidelines for eye disorder management.
Criterion 4	**Total bilirubin >1.5 x institutional ULN or direct bilirubin >ULN** **ALT and AST >2.5 x institutional ULN or >5 x institutional ULN for subjects with liver metastases**
Reason for being an exclusion criterion	Erdafitinib is mainly metabolized in the liver.
Considered to be included as missing information	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	Based on study 42756493EDI1008, PK parameters of free erdafitinib following a single 6-mg dose, based on mean geometric ratio for C_{max} and AUC, were similar in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function. There is limited information for patients with severe hepatic impairment. Erdafitinib was well-tolerated in subjects with normal hepatic function and in subjects with mild, moderate, and severe hepatic impairment. The SmPC states that no clinically meaningful differences in the PK of erdafitinib were observed in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function. No dose adjustment is required for patients with mild or moderate hepatic impairment. The PK of erdafitinib in subjects with severe hepatic impairment is unknown due to limited data. Alternative treatment should be considered in patients with severe hepatic impairment.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Elderly	Of the 479 subjects in the all clinical trials population, 288 subjects were 65 years of age or older, and 97 subjects were 75 years of age or older.
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Population with relevant different ethnic origin	Of the 479 subjects in the all clinical trials population, 308 subjects were white, 82 subjects were Asian, and 6 subjects were black or African American.

Subpopulations carrying relevant genetic polymorphisms	In study 42756493EDI1007, 37 subjects were characterized by CYP2C9 *1/*1 genotype, 13 subjects by *1/*2 genotype, and 4 subjects by *1/*3 genotype (subjects were treated with 4 mg erdafitinib monotherapy or in combination with fluconazole or itraconazole). No data are available in subjects characterized by other genotypes (eg, *2/*2, *2/*3, and *3/*3).
Patients with relevant comorbidities:	
Patients with hepatic impairment	Of the 479 subjects in the all clinical trials population, there were 47 subjects with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or ULN < total bilirubin ≤1.5 x ULN) at baseline exposed to erdafitinib for 322.6 person-months. One subject exposed to erdafitinib for 0.3 person-months had moderate (1.5 x ULN < total bilirubin ≤3 x ULN) hepatic impairment and none had severe (total bilirubin >3 x ULN) hepatic impairment at baseline. In study 42756493EDI1008, 8 subjects with mild hepatic impairment, 8 subjects with moderate hepatic impairment, and 2 subjects with severe hepatic impairment at baseline received 6 mg erdafitinib.
Patients with renal impairment	Of the 479 subjects in the all clinical trials population, there were 188 subjects with mild renal impairment (estimated glomerular filtration rate [eGFR] 60 to <90 mL/min/1.73 m²) at baseline exposed to erdafitinib for 1,410.6 person-months, 228 subjects with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m²) at baseline exposed to erdafitinib for 1,630.3 person-months, and 10 subjects with severe renal impairment (eGFR <30 mL/min/1.73 m²) at baseline exposed to erdafitinib for 73.3 person-months.
Patients with cardiovascular impairment	These patients were excluded from clinical trials.
Immunocompromised patients	These patients were excluded from clinical trials.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable

Summary of Missing Information Due to Limitations of the Clinical Trial Program

None

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

Not applicable for the European Union, as erdafitinib is currently not marketed in the European Union.

The International Birth Date for erdafitinib is 12 April 2019. Worldwide postauthorization exposure data is provided below.

SV.1.1. Method used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

The recommended starting dose of erdafitinib is 8 mg orally once daily. Dose adjustment was made based on serum phosphate concentrations. For simplicity purposes, the Company assumed 8 mg is equivalent to 1 person-day, and 365 person-days is equivalent to 1 person-year.

SV.1.2. Exposure

Based on the total 2,105,483 mg distributed worldwide from launch to 31 March 2023, the estimated exposure to erdafitinib is 263,186 person-days or 721 person-years.

There is no available information on postauthorization use of erdafitinib in special populations.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Erdafitinib is an anticancer medicinal agent which will be prescribed under medical supervision and has no abuse potential. Therefore, there is no concern for potential illegal use.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
Risk 1: Gastrointestinal disorders: diarrhea, stomatitis[a], dry mouth, constipation, nausea, vomiting, abdominal pain, dyspepsia
Risk 2: Skin and subcutaneous tissue disorders: paronychia, onycholysis, onychomadesis, nail dystrophy, nail disorder, nail discoloration, palmar-plantar erythrodysesthesia syndrome, alopecia, dry skin, onychalgia, onychoclasis, nail ridging, skin fissures, pruritus, skin exfoliation, xeroderma, hyperkeratosis, skin lesion, eczema, rash, nail bed bleeding, nail discomfort, skin atrophy, palmar erythema, skin toxicity
Risk 3: Metabolism and nutrition disorders: decreased appetite, hypophosphatemia
Risk 4: Eye disorders: dry eye, ulcerative keratitis, keratitis, conjunctivitis, xerophthalmia, blepharitis, lacrimation increased
Risk 5: Investigations: weight decreased, blood creatinine increased, alanine aminotransferase increased, aspartate aminotransferase increased
Risk 6: Nervous system disorders: dysgeusia
Risk 7: Respiratory, thoracic and mediastinal disorders: epistaxis, nasal dryness
Risk 8: Renal and urinary disorders: acute kidney injury, renal impairment, renal failure
Risk 9: General disorders and administration site conditions: asthenia, fatigue, mucosal dryness
Risk 10: Phototoxicity
Risk 11: Hepatobiliary disorders: hepatic cytolysis, hepatic function abnormal, hyperbilirubinemia
Risk 12: Blood and lymphatic system disorders: anemia

Risks not Included in the List of Safety Concerns in the RMP
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
Risk 1: Metabolism and nutrition disorders: hyponatremia
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Not applicable
Known risks that do not impact the risk-benefit profile:
Risk 1: Drug-drug interactions (excluding inhibition of human P-gp)
Other reasons for considering the risks not important:
Not applicable

[a] Stomatitis includes mouth ulceration.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Important identified risk	
Central serous retinopathy	CSR was identified as an ADR during clinical trials. CSR events, including vision blurred, chorioretinopathy, detachment of retinal pigment epithelium, visual acuity reduced, visual impairment, retinal detachment, retinopathy, subretinal fluid, serous retinal detachment, vitreous detachment, maculopathy, retinal edema, detachment of macular retinal pigment epithelium, macular detachment, chorioretinitis, retinal thickening, and serous retinopathy were reported. Chronic CSR can lead to a decline in visual acuity and a lower vision-related quality of life and therefore, CSR is considered an important identified risk with the use of erdafitinib. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.
Hyperphosphatemia	Hyperphosphatemia and potential sequelae of prolonged hyperphosphatemia were reported in clinical trials, and anemia, hyperphosphatemia, hypercalcemia, hyperparathyroidism, and vascular calcification were identified as ADRs. Persistent and prolonged hyperphosphatemia can lead to cardiovascular,

	musculoskeletal, renal, or metabolic dysfunction and therefore, hyperphosphatemia is considered an important identified risk with the use of erdafitinib. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.
Important potential risks	
Reproductive and developmental toxicity	Teratogenicity is considered a class effect of FGFR inhibitors. In a rat embryo-fetal toxicity study, erdafitinib was embryotoxic and teratogenic at exposures less than the human exposures at all clinical doses. Based on these findings, erdafitinib can cause fetal harm when administered to a pregnant woman and therefore, reproductive and developmental toxicity is considered an important potential risk with the use of erdafitinib. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.
Potential drug toxicity due to accumulation of P-glycoprotein substrates	Drug-drug interactions with human P-gp are derived from nonclinical data. The clinical relevance of these interactions was evaluated by simulation analysis (refer to Section SVII.3.1 for further details). Based on these results, potential drug toxicity due to accumulation of P-glycoprotein substrates is an important potential risk with the use of erdafitinib. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.
QT prolongation	Based on nonclinical in vitro and in vivo data, erdafitinib has a potential for inducing a prolonged repolarization (QTc interval). Events of QT prolongation were observed during clinical trials. Based on these data, QT prolongation is considered an important potential risk with the use of erdafitinib. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.
Missing information	
None	

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks

1. Central serous retinopathy
2. Hyperphosphatemia

Important potential risks

1. Reproductive and developmental toxicity
2. Potential drug toxicity due to accumulation of P-glycoprotein substrates
3. QT prolongation

Missing Information

There is no missing information.

Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 was used to classify the clinical trials adverse event information that is summarized in this Section. MedDRA terms used in the database search are listed in Annex 7.3.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Central Serous Retinopathy

Potential Mechanisms:

Although CSR is considered a class effect of FGFR inhibitors, the potential mechanism is currently not known. Given the clinical and morphological similarities with mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors, it is hypothesized that mitogen-activated protein kinase (MAPK) pathway inhibition is the underlying mechanism for CSR associated with FGFR inhibitor use (Francis 2021).

Evidence Source(s) and Strength of Evidence:

CSR was reported during the clinical development program and was identified as an ADR. This ADR is described in the SmPC for BALVERSA.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Central Serous Retinopathy in Clinical Trials; Randomized Clinical Trials Population and All Clinical Trials Population

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD
Indication: Urothelial Cancer			
Number of subjects treated	308	285	479
Frequency[c]	89 (28.9%)	4 (1.4%)	151 (31.5%)
Seriousness			
Was serious	5 (1.6%)	0	13 (2.7%)
Outcomes*			
Resulted in death	0	0	0
Not recovered/Not Resolved	35 (11.4%)	3 (1.1%)	62 (12.9%)
Recovered/Resolved	50 (16.2%)	1 (0.4%)	84 (17.5%)
Recovered/resolved with sequelae	3 (1.0%)	0	3 (0.6%)
Recovering/Resolving	1 (0.3%)	0	2 (0.4%)
Unknown	0	0	0
Severity (toxicity grade)[d]			
Worst Grade=1	48 (15.6%)	4 (1.4%)	73 (15.2%)
Worst Grade=2	36 (11.7%)	0	65 (13.6%)
Worst Grade=3	5 (1.6%)	0	13 (2.7%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing	0	0	0

[a] Includes randomized trial BLC3001.
[b] Includes trials BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001.
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA terms representative of central serous retinopathy.
[d] Subject was counted once for their CSR event with the worst grade.
* An event outcome of "Not recovered/Not resolved" indicates that the event did not resolve or that information regarding resolution of the event was not available as of the clinical cut-off date.
Note: Adverse Events were coded using MedDRA Version 24.1.
The denominators are total number of subjects in each group.
Resulted in Death= Fatal outcome in CRF

[MSFAE01.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/MSFAE01.SAS] 02MAY2024, 10:47

In the all clinical trials population, 151 (31.5%) of 479 subjects were reported to have treatment-emergent adverse events (TEAEs) of CSR. The most commonly reported events were vision blurred (10.2%), chorioretinopathy (6.3%), detachment of retinal pigment epithelium (4.6%), visual acuity reduced (4.6%), visual impairment (4.6%), retinal detachment (2.5%), retinopathy (2.3%), and subretinal fluid (2.1%). Most CSR events were Grade 1 or 2, with 13 (2.7%) subjects having Grade 3 events and no subjects experiencing Grade 4 events. Thirteen (2.7%) subjects had a serious event of CSR. CSR resolved (ie, resolved, resolved with sequelae, and resolving) in 89 subjects and 62 subjects had unresolved events of which the majority were Grade 1. CSR led to dose interruptions and reductions in 54 (11.3%) and 70 (31.5%) of subjects, respectively. Sixteen (3.3%) subjects discontinued erdafitinib as a result of CSR due to detachment of retinal pigment epithelium (8 [1.7%] subjects), chorioretinopathy (3 [0.6%] subjects), visual acuity reduced (3 [0.6%] subjects), maculopathy (2 [0.4%] subjects), retinal detachment (1 [0.2%] subject), subretinal fluid (1 [0.2%] subject), vision blurred (1 [0.2%] subject), and visual

impairment (1 [0.2%] subject). The majority of CSR events occurred within the first 90 days of treatment. The median (range) time to first onset for any Grade event was 51.0 (2; 666) days.

Similarly, for the BLC3001 combined erdafitinib cohorts, the incidence of CSR was 89 (28.9%) of 308 subjects and the most commonly reported events were vision blurred (7.1%), chorioretinopathy (6.5%), detachment of retinal pigment epithelium (5.2%), visual acuity reduced (3.9%), visual impairment (3.9%), subretinal fluid (2.6%), and retinopathy (2.3%). CSR led to dose interruptions and reductions in 30 (9.7%) and 44 (14.3%) of subjects, respectively. Nine (2.9%) subjects discontinued erdafitinib as a result of CSR. CSR resolved (ie, resolved, resolved with sequelae, and resolving) in 54 subjects and 35 subjects had unresolved events of which the majority were Grade 1.

In the all clinical trials population, the overall incidence of CSR was moderately higher in subjects ≥65 years of age (96 [33.3%] of 288 subjects) compared with subjects <65 years of age (55 [28.8%] of 191 subjects). Events of retinal pigment epithelium detachment were reported more frequently in subjects ≥65 years of age (18 [6.3%] subjects) compared with subjects <65 years of age (4 [2.1%] subjects).

For the BLC3001 combined erdafitinib cohorts, the overall incidence of CSR was similar in subjects ≥65 years of age (54 [29.7%] of 182 subjects) compared with subjects <65 years of age (35 [27.8%] of 126 subjects). Events of retinal pigment epithelium detachment were reported more frequently in subjects ≥65 years of age (13 [7.1%] subjects) compared with subjects <65 years of age (3 [2.4%] subjects).

Retinopathy is reversible upon withholding treatment, and dosing can be resumed when retinopathy is resolved. Patients who experience an event of CSR can be referred to a retinal specialist for further evaluations. Chronic CSR can lead to a decline in visual acuity and a lower vision-related quality of life (Breukink 2017).

No new safety information that impacts the risk-benefit balance of the product has emerged from worldwide postmarketing experience for the important identified risk of CSR.

Risk Factors and Risk Groups:

Retinopathy is recognized as a class effect of FGFR inhibitors and shares clinical and morphological findings with retinopathy associated with the use of MEK inhibitors (Francis 2021). Suppression of the MAPK pathway is hypothesized to be the common pathogenetic mechanism. For retinopathy associated with MEK inhibitors, age, low glomerular filtration rate, and pre-existing ocular disease were identified as risk factors (Booth 2020).

Preventability:

Per the SmPC, a baseline ophthalmological exam should be performed prior to initiating BALVERSA. Subsequently, patients should be examined monthly during the first 4 months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms. If ophthalmological examination reveals keratitis or retinal abnormality (ie, CSR), BALVERSA

should be withheld until resolution. If resolved within 4 weeks, BALVERSA can be resumed at the next lower dose level. Close monitoring including clinical ophthalmological examinations should be performed in patients who have restarted BALVERSA after an ocular adverse event.

Close clinical monitoring is recommended in patients aged 65 years and older as well as with patients that have clinically significant medical eye disorders.

Impact on the Risk-Benefit Balance of the Product:

While events of CSR have been observed in clinical trials with erdafitinib, the majority of the events were mild or moderate in severity. CSR is a known class effect of FGFR inhibitors. The SmPC and Package Leaflet (PL) provide information on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.

Public Health Impact:

No public health impact is anticipated.

Annex 1 MedDRA Term:

Central Serous Retinopathy (PT)

Important Identified Risk: Hyperphosphatemia

Potential Mechanisms:

Hyperphosphatemia is a class effect of FGFR inhibitors; it is an expected and transient pharmacodynamic effect of FGFR inhibitors due to their mechanism of action.

FGF-23 is released from bone during periods of hyperphosphatemia or elevated parathyroid hormone (PTH) or 1,25-hydroxyvitamin D levels. Within the kidney, FGF-23, in conjunction with its critical co-receptor Klotho, decreases reabsorption of phosphate and inhibits conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D by 1a-hydroxylase. It also inhibits PTH release from the parathyroid glands, thereby regulating both PTH and vitamin D. Loss of FGF-23 function on target organs results in increased phosphate reabsorption and decreased excretion from the kidneys, leading to hyperphosphatemia, higher levels of 1,25-hydroxyvitamin D, and low levels of 25-hydroxyvitamin D as a result of consumption caused by unregulated conversion and reduced PTH secretion from the parathyroid gland (Wang 2017).

Evidence Source(s) and Strength of Evidence:

Disturbance of phosphate homeostasis, characterized by elevated serum concentrations of mainly phosphate, FGF-23, and 1,25-dihydroxyvitamin D3 were observed in rats and dogs at exposures less than the human exposures at all doses studied.

Hyperphosphatemia and potential sequelae of prolonged hyperphosphatemia were reported during the clinical development program, and anemia, hyperphosphatemia, hypercalcemia, hyperparathyroidism, and vascular calcification were identified as ADRs. These ADRs are described in the SmPC for BALVERSA. Although a clear pathogenetic mechanism potentially linking hyperphosphatemia induced through FGFR inhibition in patients with locally advanced or mUC and anemia has not been demonstrated, a causal association between hyperphosphatemia and anemia cannot be excluded. Therefore, anemia is also considered an ADR.

Characterization of the Risk:

The risk of hyperphosphatemia is characterized by TEAEs of hyperphosphatemia as well as TEAEs representative of potential sequelae of prolonged hyperphosphatemia. Prolonged hyperphosphatemia can lead to soft tissue mineralization, cutaneous calcinosis, non-uremic calciphylaxis, hypocalcemia, anemia, secondary hyperparathyroidism, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias. TEAEs related to QT prolongation (eg, QT interval prolongation and arrythmias) are not included in the risk tables, as these are described under the separate important potential risk of QT prolongation.

The below 3 tables present the number of subjects with TEAEs of hyperphosphatemia, the number of subjects with any TEAEs considered potential sequelae of prolonged hyperphosphatemia, and the number of subjects with serum phosphate ≥7 mg/dL for >1 month who had TEAEs considered potential sequelae of prolonged hyperphosphatemia, respectively.

Frequency, Seriousness, Outcomes, and Severity of Hyperphosphatemia in Clinical Trials; Randomized Clinical Trials Population and All Clinical Trials Population

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD
Indication: Urothelial Cancer			
Number of subjects treated	308	285	479
Frequency[c]	242 (78.6%)	2 (0.7%)	376 (78.5%)
Seriousness			
Was serious	0	0	0
Outcomes*			
Resulted in death	0	0	0
Not recovered/Not Resolved	42 (13.6%)	1 (0.4%)	60 (12.5%)
Recovered/Resolved	193 (62.7%)	1 (0.4%)	303 (63.3%)
Recovered/resolved with sequelae	1 (0.3%)	0	2 (0.4%)
Recovering/Resolving	6 (1.9%)	0	10 (2.1%)
Unknown	0	0	1 (0.2%)
Severity (toxicity grade)[d]			
Worst Grade=1	169 (54.9%)	2 (0.7%)	249 (52.0%)
Worst Grade=2	65 (21.1%)	0	113 (23.6%)
Worst Grade=3	7 (2.3%)	0	13 (2.7%)
Worst Grade=4	1 (0.3%)	0	1 (0.2%)
Worst Grade=5	0	0	0
Missing	0	0	0

[a] Includes randomized trial BLC3001.
[b] Includes trials BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001.
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA terms representative of hyperphosphatemia.
[d] Subject was counted once for their hyperphosphatemia event with the worst grade.
* An event outcome of "Not recovered/Not resolved" indicates that the event did not resolve or that information regarding resolution of the event was not available as of the clinical cut-off date.
Note: Adverse Events were coded using MedDRA Version 24.1.
The denominators are total number of subjects in each group.
Resulted in Death= Fatal outcome in CRF

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Frequency, Seriousness, Outcomes, and Severity of TEAEs Considered Potential Sequelae of Prolonged Hyperphosphatemia in Clinical Trials; Randomized Clinical Trials Population and All Clinical Trials Population

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD
Indication: Urothelial Cancer			
Number of subjects treated	308	285	479
Frequency[c]	156 (50.6%)	127 (44.6%)	247 (51.6%)
Seriousness			
Was serious	20 (6.5%)	17 (6.0%)	30 (6.3%)
Outcomes*			
Resulted in death	1 (0.3%)	1 (0.4%)	2 (0.4%)
Not recovered/Not Resolved	108 (35.1%)	75 (26.3%)	150 (31.3%)
Recovered/Resolved	47 (15.3%)	44 (15.4%)	93 (19.4%)
Recovered/resolved with sequelae	0	3 (1.1%)	0
Recovering/Resolving	0	4 (1.4%)	2 (0.4%)
Unknown	0	0	0
Severity (toxicity grade)[d]			
Worst Grade=1	54 (17.5%)	37 (13.0%)	93 (19.4%)
Worst Grade=2	69 (22.4%)	54 (18.9%)	97 (20.3%)
Worst Grade=3	31 (10.1%)	35 (12.3%)	53 (11.1%)
Worst Grade=4	1 (0.3%)	0	2 (0.4%)
Worst Grade=5	1 (0.3%)	1 (0.4%)	2 (0.4%)

[a] Includes randomized trial BLC3001.
[b] Includes trials BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001.
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA terms representative of hyperphosphatemia.
[d] Subject was counted once for their hyperphosphatemia event with the worst grade.
* An event outcome of "Not recovered/Not resolved" indicates that the event did not resolve or that information regarding resolution of the event was not available as of the clinical cut-off date.
Note: Adverse Events were coded using MedDRA Version 24.1.
The denominators are total number of subjects in each group.

[MSFAE05.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_FDA_REQUEST/MSFAE05.SAS] 17APR2024, 15:26

Frequency, Seriousness, Outcomes, and Severity of TEAEs Considered Potential Sequelae of Prolonged Hyperphosphatemia in Clinical Trials; Population of Patients with Phosphate>=7 mg/dl for >1 Month

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD
Indication: Urothelial Cancer			
Number of subjects treated	308	285	479
Patients with phosphate>=7 mg/dl for >1 month	13 (4.2%)	0	16 (3.3%)
Subjects with any TEAEs considered potential sequelae of prolonged hyperphosphatemia[c]	8 (2.6%)	0	9 (1.9%)
Seriousness			
Was serious	0	0	0
Outcomes*			
Resulted in death	0	0	0
Not recovered/Not Resolved	6 (1.9%)	0	7 (1.5%)
Recovered/Resolved	2 (0.6%)	0	2 (0.4%)
Recovered/resolved with sequelae	0	0	0
Recovering/Resolving	0	0	0
Unknown	0	0	0
Severity (toxicity grade)[d]			
Worst Grade=1	3 (1.0%)	0	3 (0.6%)
Worst Grade=2	5 (1.6%)	0	5 (1.0%)
Worst Grade=3	0	0	1 (0.2%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0

[a] Includes randomized trial BLC3001.
[b] Includes trials BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001.
[c] Includes all subjects with phosphate>=7 mg/dl for >1 month who had one or more occurrences of an adverse event that coded to the MedDRA terms representative of TEAE Considered Potential Sequelae of Prolonged Hyperphosphatemia.
[d] Subject was counted once for their event with the worst grade.
* An event outcome of "Not recovered/Not resolved" indicates that the event did not resolve or that information regarding resolution of the event was not available as of the clinical cut-off date.
Note: Adverse Events were coded using MedDRA Version 24.1.
The denominators are total number of subjects in each group.

[MSFAE06.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_FDA_REQUEST/MSFAE06.SAS] 17APR2024, 15:26

In the all clinical trials population, 376 (78.5%) of 479 subjects were reported to have TEAEs with the PT of hyperphosphatemia. There was 1 subject with Grade 4 severity of hyperphosphatemia which the investigator considered as very likely related to the study drug. Hyperphosphatemia was managed by dose modification, restriction of dietary phosphate intake, and treatment with phosphate binders. Of the 479 subjects in the all clinical trials population, 48 (10.0%) subjects had dose interruption and 25 (5.2%) subjects had dose reduction due to hyperphosphatemia. One (0.2%) subject discontinued erdafitinib due to hyperphosphatemia. Hyperphosphatemia was reported early during erdafitinib treatment, with Grade 1 to 2 events generally occurring within the first 3 or 4 months and Grade 3 events occurring within the first month. The median time (range) to first onset of any grade hyperphosphatemia was 16 (6; 449) days. Hyperphosphatemia resolved (ie, resolved, resolved with sequela, and resolving) in 315 subjects and 60 subjects had unresolved events of which the majority were Grade 1.

Similarly, for the BLC3001 combined erdafitinib cohorts, hyperphosphatemia TEAEs were reported for 242 (78.6%) of 308 subjects. One subject had a Grade 4 event. Hyperphosphatemia led to dose interruptions and reductions in 14 (4.5%) and 11 (3.6%) of subjects, respectively. No subjects discontinued erdafitinib as a result of hyperphosphatemia. The median time (range) to first onset of any grade event was similar to that reported for all clinical trials population (15.5 [8; 337] days). Hyperphosphatemia resolved (ie, resolved, resolved with sequelae, and resolving) in 200 subjects and 42 subjects had unresolved events of which the majority were Grade 1.

Overall, there was a low incidence of prolonged hyperphosphatemia, ie, 16/479 (3.3%) subjects in the all clinical trials population and 13/308 (4.2%) subjects in the BLC3001 combined erdafitinib cohorts had serum phosphate ≥7 mg/dL for >1 month. In the all clinical trials population, 9 (56.3%) of 16 subjects with serum phosphate ≥7 mg/dL for >1 month experienced any TEAEs that were potential sequelae of prolonged hyperphosphatemia, compared with 247 (51.6%) of 479 subjects in the overall all clinical trials population. Similar proportions were observed in the BLC3001 combined erdafitinib cohorts. The most frequently reported TEAE considered a potential sequela of prolonged hyperphosphatemia was anemia (135 [28.2%] of 479 subjects in the overall all clinical trials population and 7 [43.8%] of 16 subjects with serum phosphate ≥7 mg/dL for >1 month). For BLC3001, an analysis evaluating the relationship between the maximum serum phosphate level and maximum change in hemoglobin while on treatment was performed for subjects on erdafitinib in Cohorts 1 and 2. This analysis did not suggest a relationship between serum phosphate levels and change in hemoglobin indicative of anemia. Other TEAEs considered potential sequelae of prolonged hyperphosphatemia reported in >5% of subjects in the overall all clinical trials population were blood creatinine increased, arthralgia, hypercalcemia, and renal impairment. These TEAEs were reported in 2 subjects, 1 subject, 1 subject, and no subjects, respectively, in the subgroup with serum phosphate ≥7 mg/dL for >1 month. There was 1 event related to soft tissue mineralization (ie, a nonserious event of vascular calcification), reported in a subject without serum phosphate ≥7 mg/dL for >1 month in the BLC3001 combined erdafitinib cohorts.

Serum phosphate level can decrease upon withholding treatment, and dosing can be resumed when serum phosphate level returns to <7.0 mg/dL. Hyperphosphatemia is for the most part clinically asymptomatic. Persistent and prolonged serum phosphate elevation can lead to cardiovascular, musculoskeletal, renal, or metabolic dysfunction, which can negatively impact quality of life. Dietary phosphate restrictions and/or phosphate lowering therapy might be required to lower the phosphate levels.

No new safety information that impacts the risk-benefit balance of the product has emerged from worldwide postmarketing experience for the important identified risk of hyperphosphatemia.

Risk Factors and Risk Groups:

There are currently no risk factors or risk groups identified.

Preventability:

Per the SmPC, phosphate concentrations should be assessed prior to the first dose and then monitored monthly. For elevated phosphate concentrations in patients treated with BALVERSA, dose modification guidelines should be followed. For persistently elevated phosphate concentrations, a non-calcium containing phosphate binder (eg, sevelamer carbonate) should be considered as needed.

Dietary phosphate intake should be restricted and concomitant use of agents that may increase serum phosphate levels should be avoided for serum phosphate levels ≥5.5 mg/dL. Supplementation with vitamin D in patients receiving BALVERSA is not recommended due to potential contribution to increased serum phosphate and calcium levels.

Impact on the Risk-Benefit Balance of the Product:

While events of hyperphosphatemia and potential sequelae of prolonged hyperphosphatemia have been observed in clinical trials with erdafitinib, the majority of the events were mild or moderate in severity. Hyperphosphatemia is a known class effect of FGFR inhibitors. The SmPC and PL provide information on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.

Public Health Impact:

No public health impact is anticipated.

Annex 1 MedDRA Term:

Hyperphosphataemia (PT)

Important Potential Risk: Reproductive and Developmental Toxicity

Potential Mechanisms:

Teratogenicity is considered a class effect of FGFR inhibitors. FGF/FGFR expression and signalling have been shown to be critical in different stages of mammalian embryo development and in fetal development including limb and heart development.

Evidence Source(s) and Strength of Evidence:

Based on the mechanism of action and 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.

There are no available human data informing the erdafitinib-associated risk.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Reproductive and Developmental Toxicity in Clinical Trials; Randomized Clinical Trials Population and All Clinical Trials Population

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD
Indication: Urothelial Cancer			
Number of subjects treated	308	285	479
Frequency[c]	0	0	0
Seriousness			
Was serious	0	0	0
Outcomes*			
Resulted in death	0	0	0
Not recovered/Not Resolved	0	0	0
Recovered/Resolved	0	0	0
Recovered/resolved with sequelae	0	0	0
Recovering/Resolving	0	0	0
Unknown	0	0	0
Severity (toxicity grade)			
Worst Grade=1	0	0	0
Worst Grade=2	0	0	0
Worst Grade=3	0	0	0
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing	0	0	0

[a] Includes randomized trial BLC3001.
[b] Includes trials BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001.
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA terms representative of teratogenicity.
* An event outcome of "Not recovered/Not resolved" indicates that the event did not resolve or that information regarding resolution of the event was not available as of the clinical cut-off date.
Note: Adverse Events were coded using MedDRA Version 24.1.
The denominators are total number of subjects in each group.
Resulted in Death= Fatal outcome in CRF

[MSFAE02.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/MSFAE02.SAS] 11AUG2023, 02:05

There are no clinical trials of erdafitinib in pregnant women.

The potential reproductive and developmental toxicity of erdafitinib was evaluated in pregnant rats administered oral doses of 0, 1, 4, or 8 mg/kg once daily. Based on findings in animal studies, erdafitinib is teratogenic and can cause fetal harm such as post-implantation loss, deformations of the extremities, a decreased ossification related to a decreased fetal weight, and malformation of greater vessels including the aorta.

Teratogenicity could lead to a serious consequence such as a wide range of structural abnormalities as shown in rat fetuses including hand/foot defects and malformations of some major blood vessels such as the aorta. Higher doses of erdafitinib may lead to spontaneous abortion. The potential risk of reproductive and developmental toxicity will impact a patient's fetus.

No new safety information that impacts the risk-benefit balance of the product has emerged from worldwide postmarketing experience for the important potential risk of reproductive and developmental toxicity.

Risk Factors and Risk Groups:

Pregnant women and women of childbearing potential who may become pregnant while on treatment.

Preventability:

Per the SmPC, BALVERSA should not be used during pregnancy unless the clinical condition of the women requires treatment with BALVERSA. If BALVERSA is used during pregnancy, or if the patient becomes pregnant while taking BALVERSA, the patient should be advised of the potential hazard to the fetus and should be counseled about their clinical and therapeutic options. Patients should be advised to contact their healthcare professional if they become pregnant or if pregnancy is suspected while being treated with BALVERSA and up to 1 month afterwards. Female patients of reproductive potential should be advised to use highly effective contraception prior to and during treatment, and for 1 month after the last dose of BALVERSA. Pregnancy testing with a highly sensitive assay is recommended for females of reproductive potential prior to initiating BALVERSA. Male patients should be advised to use effective contraception (eg, condom) and not donate or store semen during treatment with and for 1 month after the last dose of BALVERSA.

BALVERSA alone or concomitant administration of other CYP3A4 inducers with BALVERSA may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative contraceptive not affected by enzyme inducers (eg, non-hormonal intrauterine device) or an additional nonhormonal contraception (eg, condom) during treatment with and for 1 month after the last dose of BALVERSA.

Impact on the Risk-Benefit Balance of the Product:

There has not been any exposure in pregnant women in clinical trials to date. The SmPC and PL provide information on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.

Public Health Impact:

The public health impact is expected to be low.

Annex 1 MedDRA Term:

Teratogenicity (PT)

Important Potential Risk: Potential Drug Toxicity due to Accumulation of P-glycoprotein Substrates

Potential Mechanisms:

Erdafitinib was shown to inhibit human P-gp in vitro. Clinically relevant P-gp inhibition is not expected at systemic level; however, inhibition at intestinal level can be expected in vivo, due to higher local concentrations after an oral dose. Concomitant administration of erdafitinib with P-gp substrates may increase their systemic exposure.

Evidence Source(s) and Strength of Evidence:

Erdafitinib was shown to inhibit human P-gp in vitro. Simulation predicted an increased exposure of digoxin (a P-gp substrate) when erdafitinib was co-administered with digoxin at the same time, whereas dose staggering by 6 hours could avoid this interaction.

No events of drug-drug interactions with human P-gp have been reported from the available clinical trials with erdafitinib.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Potential Drug Toxicity due to Accumulation of P-glycoprotein Substrates in Clinical Trials; Randomized Clinical Trials Population and All Clinical Trials Population

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD
Indication: Urothelial Cancer			
Number of subjects treated	308	285	479
Frequency[c]	0	0	0
Seriousness			
Was serious	0	0	0
Outcomes*			
Resulted in death	0	0	0
Not recovered/Not Resolved	0	0	0
Recovered/Resolved	0	0	0
Recovered/resolved with sequelae	0	0	0
Recovering/Resolving	0	0	0
Unknown	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Potential Drug Toxicity due to Accumulation of P-glycoprotein Substrates in Clinical Trials; Randomized Clinical Trials Population and All Clinical Trials Population

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD
Severity (toxicity grade)			
Worst Grade=1	0	0	0
Worst Grade=2	0	0	0
Worst Grade=3	0	0	0
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing	0	0	0

[a] Includes randomized trial BLC3001.
[b] Includes trials BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001.
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA terms representative of drug-drug interaction.
* An event outcome of "Not recovered/Not resolved" indicates that the event did not resolve or that information regarding resolution of the event was not available as of the clinical cut-off date.
Note: Adverse Events were coded using MedDRA Version 24.1.
The denominators are total number of subjects in each group.
Resulted in Death=Fatal outcome in CRF

Modified from: [MSFAE03.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_ISS_RMP/MSFAE03.SAS] 11AUG2023, 02:05

The potential of erdafitinib for drug-drug interaction with P-gp in vivo was evaluated by physiologically-based PK simulations. 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, whereas dose staggering by 6 hours could avoid this interaction.

The concomitant administration of erdafitinib with oral narrow therapeutic index P-gp substrates without dose staggering as suggested in the SmPC may increase their systemic exposure. This can potentially cause serious and/or life-threatening adverse events for those narrow therapeutic index drugs, which may lead to hospitalization.

No new safety information that impacts the risk-benefit balance of the product has emerged from worldwide postmarketing experience for the important potential risk of potential drug toxicity due to accumulation of P-glycoprotein substrates.

Risk Factors and Risk Groups:

Patients who have to be on narrow therapeutic index P-gp substrates such as colchicine, digoxin, dabigatran, and apixaban.

Preventability:

Recommendations and actions to be taken on narrow therapeutic index P-gp substrates that may interact with erdafitinib are described in the SmPC for BALVERSA.

Per the SmPC, the prescriber is advised that when BALVERSA is administered with oral narrow therapeutic index P-gp substrates (such as colchicine, digoxin, dabigatran, and apixaban), these

medicinal products should be taken at least 6 hours before or after BALVERSA to minimize the potential for interactions.

Impact on the Risk-Benefit Balance of the Product:

No events of drug-drug interactions with human P-gp have been reported from the available clinical trials with erdafitinib to date. A warning for the potential interaction between erdafitinib and oral narrow therapeutic index P-gp substrates was stated in the clinical trial protocols, resulting in minimal exposure data of subjects with concomitant administration of erdafitinib and these medicinal products. The SmPC and PL provide information on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.

Public Health Impact:

No public health impact is anticipated.

Annex 1 MedDRA Term:

Drug-drug interaction (PT)

Important Potential Risk: QT prolongation

Potential Mechanisms:

Erdafitinib is an intrinsic hERG blocker with a potential for prolonged repolarization (QTc interval).

Evidence Source(s) and Strength of Evidence:

Based on nonclinical in vitro and in vivo data, erdafitinib has a potential for inducing a prolonged repolarization (QTc interval). Erdafitinib led to a prolonged repolarization (QTc) after intravenous dosing in the anesthetized dog and guinea pig, and after oral dosing in the conscious dog.

Events of QT prolongation were reported during the clinical development program. The risk of QT prolongation is described in the SmPC for BALVERSA.

Characterization of the Risk:

The risk of QT prolongation is characterized by TEAEs of electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, and long QT syndrome, as well as other TEAEs representative of cardiac disorders.

Frequency, Seriousness, Outcomes, and Severity of QT Prolongation in Clinical Trials, Randomized Clinical Trials Population and All Clinical Trials Population

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD
Indication: Urothelial Cancer			
Number of subjects treated	308	285	479
Frequency[c]	7 (2.3%)	6 (2.1%)	15 (3.1%)
Seriousness			
Was serious	5 (1.6%)	1 (0.4%)	5 (1.0%)
Outcomes[*]			
Resulted in death	3 (1.0%)	1 (0.4%)	3 (0.6%)
Not recovered/Not Resolved	1 (0.3%)	1 (0.4%)	3 (0.6%)
Recovered/Resolved	3 (1.0%)	4 (1.4%)	9 (1.9%)
Recovered/resolved with sequelae	0	0	0
Recovering/Resolving	0	0	0
Unknown	0	0	0
Severity (toxicity grade)[d]			
Worst Grade=1	1 (0.3%)	4 (1.4%)	5 (1.0%)
Worst Grade=2	0	0	1 (0.2%)
Worst Grade=3	1 (0.3%)	1 (0.4%)	4 (0.8%)
Worst Grade=4	2 (0.6%)	0	2 (0.4%)
Worst Grade=5	3 (1.0%)	1 (0.4%)	3 (0.6%)

Frequency, Seriousness, Outcomes, and Severity of QT Prolongation in Clinical Trials, Randomized Clinical Trials Population and All Clinical Trials Population

	All Randomized Trials[a] Population		All Clinical Trials[b] Population
	Erdafitinib 8 or 9 mg QD	Comparator	Erdafitinib 8 or 9 mg QD

[a] Includes randomized trial BLC3001.
[b] Includes trials BLC3001, BLC2001 (main study and DDI substudy), BLC2002 and EDI1001.
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA terms representative of QT prolongation.
[d] Subject was counted once for their QT prolongation event with the worst grade.
* An event outcome of "Not recovered/Not resolved" indicates that the event did not resolve or that information regarding resolution of the event was not available as of the clinical cut-off date.
Note: Adverse Events were coded using MedDRA Version 24.1.
The denominators are total number of subjects in each group.
Resulted in Death= Fatal outcome in CRF

[MSFAE07.RTF] [PROD/JNJ-42756493/Z_ISS/DBR_ISS_EU/RE_FDA_REQUEST/MSFAE07.SAS] 17APR2024, 15:26

In the all clinical trials population, 15 (3.1%) of 479 subjects were reported to have TEAEs of QT prolongation. The most commonly reported events were syncope (1.3%) and electrocardiogram QT prolonged (0.6%). Most events of QT prolongation were Grade 3 or higher, with 5 (1.0%) subjects having Grade 3 events and 2 (0.4%) subjects experiencing Grade 4 events. Five (1.6%) subjects had a serious event of QT prolongation. Of the 479 subjects in the all clinical trials population, none had dose interruption or dose reduction and 3 (0.6%) subjects discontinued erdafitinib as a result of QT prolongation due to cardio-respiratory arrest (1 subject) and sudden death (2 subjects). QT prolongation resolved (ie, resolved, resolved with sequelae, and resolving) in 9 subjects and 3 subjects had unresolved events of which the majority were Grade 1. Fatal TEAEs of QT prolongation were reported for 3 (0.6%) of 479 subjects: sudden death for 2 subjects and cardio-respiratory arrest for 1 subject. The majority of QT prolongation events occurred within the first 60 days of treatment. The median (range) time to first onset for any Grade event was 38.0 (1;943) days.

For the BLC3001 combined erdafitinib cohorts, TEAEs of QT prolongation were reported for 7 (2.3%) of 308 subjects. The most commonly reported events were cardio-respiratory arrest and sudden death (0.6% each). QT prolongation led to dose interruptions and reductions in none of subjects and 3 (1.0%) subjects discontinued erdafitinib as a result of QT prolongation. QT prolongation resolved (ie, resolved, resolved with sequelae, and resolving) in 3 subjects and 1 subject had an unresolved event of Grade 3. All 3 fatal events of QT prolongation from the all clinical trials population occurred in the BLC3001 combined erdafitinib cohorts.

Overall, there was a low incidence of electrocardiogram QT prolonged, ie, 3 (0.6%) of 479 subjects in the all clinical trials population and 1 (0.3%) of 308 subjects in the BLC3001 combined erdafitinib cohorts. No action was taken with regard to erdafitinib for all events. All events occurred within the first 2 months of treatment. The time to first onset of any grade electrocardiogram QT prolonged events ranged from 23 days to 44 days. Electrocardiogram QT prolongation resolved in 2 subjects and 1 subject had an unresolved Grade 1 event.

In the all clinical trials population, the overall incidence of QT prolongation was moderately higher in subjects ≥65 years of age (11 [3.8%] of 288 subjects) compared with subjects <65 years of age

(4 [2.1%] of 191 subjects). For the BLC3001 combined erdafitinib cohorts, all events of QT prolongation occurred in subjects ≥65 years of age (7 [3.8%] of 182 subjects).

QT prolongation can lead to dizziness, syncopal episodes, and in less common instances, ventricular arrhythmia and sudden cardiac death. These events can adversely impact quality of life and can be potentially life-threatening. ECG monitoring can detect cardiac changes suggestive of QT prolongation.

No new safety information that impacts the risk-benefit balance of the product has emerged from worldwide postmarketing experience for the important potential risk of QT prolongation.

Risk Factors and Risk Groups:

For QT prolongation, advanced age, electrolyte imbalances (eg, hypokalemia), drugs, medical conditions, such as diabetes mellitus and epilepsy, a history of heart failure, and structural heart disease were identified as risk factors (Shah 2019).

Preventability:

Caution is advised when administering BALVERSA with medicinal products known to prolong the QT interval or medicinal products with a potential to induce torsades de pointes, such as class IA (eg, quinidine, disopyramide) or class III (eg, amiodarone, sotalol, ibutilide) antiarrhythmic medicinal products, macrolide antibiotics, selective serotonin re-uptake inhibitors (eg, citalopram, escitalopram), methadone, moxifloxacin, and antipsychotics (eg, haloperiodol, thioridazine).

Impact on the Risk-Benefit Balance of the Product:

While events of QT prolongation have been observed in clinical trials with erdafitinib, the overall incidence is low. The SmPC provides information on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the disease treated and the observed efficacy in patients treated with BALVERSA.

Public Health Impact:

The public health impact is expected to be low.

Annex 1 MedDRA Term:

QT prolongation (PT)

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Central serous retinopathy
	Hyperphosphatemia
Important Potential Risks	Reproductive and developmental toxicity
	Potential drug toxicity due to accumulation of P-glycoprotein substrates
	QT prolongation
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities
Not applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates (in DD/MM/YYY format)
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risk	
Central serous retinopathy	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • A recommendation to perform regular ophthalmological examinations is provided in SmPC Sections 4.2 and 4.4, and in PL Section 2 • Advice on the use of BALVERSA in patients developing eye disorders, including CSR, is provided in SmPC Sections 4.2 and 4.4 • A recommendation to perform a baseline ophthalmological examination prior to initiating treatment with BALVERSA and to have close clinical monitoring in patients aged 65 years and older as well as with patients that have clinically significant medical eye disorders is provided in SmPC Section 4.4 • Advice for patients who develop eye problems (ie, to notify their healthcare professional immediately) and recommendations on the management of eye problems and the use of BALVERSA when developing eye problems is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: medical prescription

Hyperphosphatemia	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2 • PL Section 3 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • A recommendation to monitor phosphate concentrations prior to the first dose and during treatment with BALVERSA is provided in SmPC Sections 4.2 and 4.4, and in PL Sections 2 and 3 • Advice on the use of BALVERSA in patients developing elevated phosphate concentrations, is provided in SmPC Sections 4.2 and 4.4 • Advice for patients who develop symptoms due to high phosphate levels (ie, to notify their healthcare professional immediately) and recommendations on the management of high phosphate levels and the use of BALVERSA when developing high phosphate levels is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: medical prescription
Important Potential Risks	
Reproductive and developmental toxicity	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Warnings for the potential fetal harmful effects when BALVERSA is administered during pregnancy and precautions to avoid pregnancy by using highly effective contraception are provided in SmPC Sections 4.4 and 4.6, and in PL Section 2 • Advice for patients using hormonal contraceptives is provided in SmPC Sections 4.4, 4.5, and 4.6, and in PL Section 2

	• A recommendation to do a pregnancy test is provided in SmPC Sections 4.4 and 4.6, and in PL Section 2 • Patients should notify their healthcare professional immediately about a potential or confirmed pregnancy before and during treatment with BALVERSA, as described in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: medical prescription
Potential drug toxicity due to accumulation of P-glycoprotein substrates	**Routine risk communication:** • SmPC Section 4.5 • SmPC Section 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • A recommendation regarding the use of BALVERSA with narrow therapeutic index P-gp substrates is provided in SmPC Section 4.5 • Advice for patients using concomitant medication is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: medical prescription
QT prolongation	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • A warning regarding the use of BALVERSA with medicinal products known to prolong the QT interval or medicinal products with a potential to induce torsades de pointes is provided in SmPC Section 4.4 **Other routine risk minimization measures beyond the Product Information:** • Legal Status: medical prescription

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1. Removal of Additional Risk Minimization Activities

Activity 1	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risk		
Central serous retinopathy	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • A recommendation to perform regular ophthalmological examinations is provided in SmPC Sections 4.2 and 4.4, and in PL Section 2 • Advice on the use of BALVERSA in patients developing eye disorders, including CSR, is provided in SmPC Sections 4.2 and 4.4 • A recommendation to perform a baseline ophthalmological examination prior to initiating treatment with BALVERSA and to have close clinical monitoring in patients aged 65 years and older as well as with patients that have clinically significant medical eye disorders is provided in SmPC Section 4.4 • Advice for patients who develop eye problems (ie, to notify their healthcare professional	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	immediately) and recommendations on the management of eye problems and the use of BALVERSA when developing eye problems is provided in PL Section 2 • Legal status: medical prescription **Additional risk minimization measures:** • None	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hyperphosphatemia	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2 • PL Section 3 • PL Section 4 • A recommendation to monitor phosphate concentrations prior to the first dose and during treatment with BALVERSA is provided in SmPC Sections 4.2 and 4.4, and in PL Sections 2 and 3 • Advice on the use of BALVERSA in patients developing elevated phosphate concentrations, is provided in SmPC Sections 4.2 and 4.4 • Advice for patients who develop symptoms due to high phosphate levels (ie, to notify their healthcare professional immediately) and recommendations on the management of high phosphate levels and the use of BALVERSA when developing high phosphate levels is provided in PL Section 2 • Legal status: medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Important Potential Risks		
Reproductive and developmental toxicity	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • Warnings for the potential fetal harmful effects when BALVERSA is administered during pregnancy and precautions to avoid pregnancy by using highly effective contraception are provided in SmPC Sections 4.4 and 4.6, and in PL Section 2 • Advice for patients using hormonal contraceptives is provided in SmPC Sections 4.4, 4.5, and 4.6, and in PL Section 2. • A recommendation to do a pregnancy test is provided in SmPC Sections 4.4 and 4.6, and in PL Section 2 • Patients should notify their healthcare professional immediately about a potential or confirmed pregnancy before and during treatment with BALVERSA, as described in PL Section 2 • Legal status: medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Potential drug toxicity due to accumulation of P-glycoprotein substrates	**Routine risk minimization measures:** • SmPC Section 4.5 • SmPC Section 5.2 • A recommendation regarding the use of BALVERSA with narrow therapeutic index P-gp substrates is provided in SmPC Section 4.5 • Advice for patients using concomitant medication is provided in PL Section 2 • Legal status: medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
QT prolongation	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 5.3 • A warning regarding the use of BALVERSA with medicinal products known to prolong the QT interval or medicinal products with a potential to induce torsades de pointes is provided in SmPC Section 4.4 • Legal status: medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for BALVERSA (erdafitinib)

This is a summary of the risk management plan (RMP) for BALVERSA. The RMP details important risks of BALVERSA, how these risks can be minimized, and how more information will be obtained about BALVERSA's risks and uncertainties (missing information).

BALVERSA's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how BALVERSA should be used.

This summary of the RMP for BALVERSA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BALVERSA's RMP.

I. The Medicine and What it is Used For

BALVERSA as monotherapy is authorized for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC) (see SmPC for the full indication). It contains erdafitinib as the active substance and it is given as an oral tablet.

Further information about the evaluation of BALVERSA's benefits can be found in BALVERSA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the EPAR summary landing page.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of BALVERSA, together with measures to minimize such risks and the proposed studies for learning more about BALVERSA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of BALVERSA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BALVERSA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Central serous retinopathy Hyperphosphatemia
Important potential risks	Reproductive and developmental toxicity Potential drug toxicity due to accumulation of P-glycoprotein substrates QT prolongation
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Central serous retinopathy	
Evidence for linking the risk to the medicine	Central serous retinopathy (CSR) was reported during the clinical development program and was identified as an adverse drug reaction (ADR). This ADR is described in the SmPC for BALVERSA.
Risk factors and risk groups	Retinopathy is recognized as a class effect of fibroblast growth factor receptor (FGFR) inhibitors and shares clinical and morphological findings with retinopathy associated with the use of mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors. Suppression of the mitogen-activated protein kinase (MAPK) pathway is hypothesized to be the common pathogenetic mechanism. For retinopathy associated with MEK inhibitors, age, low glomerular filtration rate, and pre-existing ocular disease were identified as risk factors.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7

	• SmPC Section 4.8 • PL Section 2 • PL Section 4 • A recommendation to perform regular ophthalmological examinations is provided in SmPC Sections 4.2 and 4.4, and in PL Section 2 • Advice on the use of BALVERSA in patients developing eye disorders, including CSR, is provided in SmPC Sections 4.2 and 4.4 • A recommendation to perform a baseline ophthalmological examination prior to initiating treatment with BALVERSA and to have close clinical monitoring in patients aged 65 years and older as well as with patients that have clinically significant medical eye disorders is provided in SmPC Section 4.4 • Advice for patients who develop eye problems (ie, to notify their healthcare professional immediately) and recommendations on the management of eye problems and the use of BALVERSA when developing eye problems is provided in PL Section 2 • Legal status: medical prescription Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important Identified Risk: Hyperphosphatemia	
Evidence for linking the risk to the medicine	Disturbance of phosphate homeostasis, characterized by elevated serum concentrations of mainly phosphate, FGF-23, and 1,25-dihydroxyvitamin D3 were observed in rats and dogs at exposures less than the human exposures at all doses studied. Hyperphosphatemia and potential sequelae of prolonged hyperphosphatemia were reported during the clinical development program, and anemia, hyperphosphatemia, hypercalcemia, hyperparathyroidism, and vascular calcification were identified as ADRs. These ADRs are described in the SmPC for BALVERSA. Although a clear pathogenetic mechanism potentially linking hyperphosphatemia induced through FGFR inhibition in patients with locally advanced or metastatic UC and anemia has not been demonstrated, a causal association between hyperphosphatemia and anemia cannot be excluded. Therefore, anemia is also considered an ADR.
Risk factors and risk groups	There are currently no risk factors or risk groups identified.

Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2 • PL Section 3 • PL Section 4 • A recommendation to monitor phosphate concentrations prior to the first dose and during treatment with BALVERSA is provided in SmPC Sections 4.2 and 4.4, and in PL Sections 2 and 3 • Advice on the use of BALVERSA in patients developing elevated phosphate concentrations, is provided in SmPC Sections 4.2 and 4.4 • Advice for patients who develop symptoms due to high phosphate levels (ie, to notify their healthcare professional immediately) and recommendations on the management of high phosphate levels and the use of BALVERSA when developing high phosphate levels is provided in PL Section 2 • Legal status: medical prescription Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

Important Potential Risk: Reproductive and Developmental Toxicity	
Evidence for linking the risk to the medicine	Based on the mechanism of action and findings in animal reproduction studies, BALVERSA can cause fetal harm when administered to a pregnant woman. In a rat embryo-fetal toxicity study, BALVERSA was embryotoxic and teratogenic at exposures less than the human exposures. There are no available human data informing the BALVERSA-associated risk.
Risk factors and risk groups	Pregnant women and women of childbearing potential who may become pregnant while on treatment.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4

	• SmPC Section 4.5 • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • Warnings for the potential fetal harmful effects when BALVERSA is administered during pregnancy and precautions to avoid pregnancy by using highly effective contraception are provided in SmPC Sections 4.4 and 4.6, and in PL Section 2 • Advice for patients using hormonal contraceptives is provided in SmPC Sections 4.4, 4.5, and 4.6, and in PL Section 2. • A recommendation to do a pregnancy test is provided in SmPC Sections 4.4 and 4.6, and in PL Section 2 • Patients should notify their healthcare professional immediately about a potential or confirmed pregnancy before and during treatment with BALVERSA, as described in PL Section 2 • Legal status: medical prescription Additional risk minimization measures • None

Important Potential Risk: Potential drug toxicity due to accumulation of P-glycoprotein substrates	
Evidence for linking the risk to the medicine	BALVERSA was shown to inhibit human P-glycoprotein (P-gp) in vitro. Simulation predicted an increased exposure of digoxin (a P-gp substrate) when BALVERSA was co-administered with digoxin at the same time, whereas dose staggering by 6 hours could avoid this interaction. No events of drug-drug interactions with human P-gp have been reported from the available clinical trials with BALVERSA.
Risk factors and risk groups	Patients who have to be on narrow therapeutic index P-gp substrates such as colchicine, digoxin, dabigatran, and apixaban.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.5 • SmPC Section 5.2 • A recommendation regarding the use of BALVERSA with narrow therapeutic index P-gp substrates is provided in SmPC Section 4.5 • Advice for patients using concomitant medication is provided in PL Section 2 • Legal status: medical prescription

	Additional risk minimization measures • None

Important Potential Risk: QT prolongation	
Evidence for linking the risk to the medicine	Based on nonclinical in vitro and in vivo data, erdafitinib has a potential for inducing a prolonged repolarization (corrected QT [QTc] interval). Erdafitinib led to a prolonged repolarization (QTc) after intravenous dosing in the anesthetized dog and guinea pig, and after oral dosing in the conscious dog. Events of QT prolongation were reported during the clinical development program. The risk of QT prolongation is described in the SmPC for BALVERSA.
Risk factors and risk groups	For QT prolongation, advanced age, electrolyte imbalances (eg, hypokalemia), drugs, medical conditions, such as diabetes mellitus and epilepsy, a history of heart failure, and structural heart disease were identified as risk factors.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • SmPC Section 5.3 • A warning regarding the use of BALVERSA with medicinal products known to prolong the QT interval or medicinal products with a potential to induce torsades de pointes is provided in SmPC Section 4.4 • Legal status: medical prescription Additional risk minimization measures • None

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of BALVERSA.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for BALVERSA.

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.