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Summary of the Risk Management Plan (RMP) for BALVERSA® (Erdafitinib)

Marketing Authorisation Holder (MAH): Janssen-Cilag AG

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of BALVERSA® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of BALVERSA® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of BALVERSA®.

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.