Swiss Summary of the Risk Management Plan (RMP)

for

Steglatro®

(Ertugliflozin 5mg)

Film-coated tablets

Version 2.0 (November2020)
based on RMP V4.0 (core)

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 Steglatro® 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 authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Steglatro® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

MSD Merck Sharp & Dohme AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Steglatro®.

1 Safety Specification

1.1 Non-Clinical Part of the Safety Specification

Table 1 Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings with Ertugliflozin (from non-clinical studies)	Relevance to Human Usage
Toxicity	
• In repeat-dose toxicity studies in rats and dogs target organs included gastrointestinal tract, kidney, endocrine system, and bone. • Gastrointestinal tract findings in rat (erosions/ulcers, foveolar hyperplasia and/or crypt degeneration in pylorus) at ≥77x exposure margin based on the human steady state area under the concentration-time curve (AUC) at the maximum clinical dose of 15 mg. Findings considered rat specific. • Kidney (see nephrotoxicity below). • Endocrine (hypertrophy of adrenal glomerulosa, attributed to increased natriuresis, not adverse). • Bone (hyperostosis) in 6-month rat at ≥77x exposure margin based on the human steady state AUC at the maximum clinical dose of 15 mg. Findings considered rat specific.	Nonclinical gastrointestinal tract, endocrine system and bone findings are not considered relevant to human usage. Ertugliflozin is more selective for human SGLT2 over human SGLT1 relative to rat SGLT2 over rat sodium-glucose co-transporter 1 (SGLT1). The GI findings are attributed to inhibition of SGLT1 due to the high concentration of ertugliflozin in the rat GI tract which is not expected to occur in humans. Additionally, these findings were observed at very high exposures relative to the maximum human clinical exposure. The hypertrophy of the adrenal glomerulosa is an adaptive finding to the SGLT2 mediated osmotic diuresis and not considered adverse. There is a large exposure margin for the rat specific finding of hyperostosis. The hyperostosis was attributed to gastrointestinal SGLT1 inhibition resulting in altered calcium homeostasis likely due to carbohydrate malabsorption.
Reproductive	
• Ertugliflozin was not teratogenic in rats and rabbits at maternal exposures that were 239 and 1069x, respectively, the human steady state AUC at the maximum clinical dose of 15 mg. At a maternally toxic dose in rats (250 mg/kg/day), lower fetal viability, lower maternal body weight, a higher incidence of a visceral malformation (membranous ventricular septal defect) and skeletal variations (variations of the centrum, unossified seventh cervical centrum, incomplete ossification of lumbar centrum, and incomplete ossification, unossified and misaligned thoracic centrum), vertebrae (twenty seventh presacral), limb (unossified metatarsal), and ribs (full and short supernumerary ribs) were observed at maternal exposure that was 510x the 15 mg maximum clinical dose.	Findings are not relevant to human usage due to very large safety margins.

Key Safety Findings with Ertugliflozin (from non-clinical studies)	Relevance to Human Usage
Developmental toxicity	
• In the pre-and postnatal development (PPND) study, decreased postnatal growth and delayed sexual maturation were observed in rats administered ertugliflozin from gestation Day 6 through lactation Day 21 at ≥100 mg/kg/day (>300x the maximum recommended human dose [MRHD]).	Findings in the PPND rat study are not relevant to human usage due to very large safety margins.
• Ertugliflozin was orally administered to juvenile rats from postnatal day (PND) 21 to PND 90, a period of renal development corresponding to the late second and third trimesters of human pregnancy, at doses of 5, 25, and 250 mg/kg/day with a non-dosing recovery phase to PND 118 (control and 250 mg/kg/day groups). Doses □25 mg/kg/day (55 times human exposure at the maximum clinical dose of 15 mg), resulted in lower body weight and body weight gain, and delayed sexual maturation. These changes recovered by PND 118. Increased kidney weights, dilatation of the renal pelvis and tubules, and renal mineralization occurred at doses □5 mg/kg/day (13x human exposure at the maximum clinical dose of 15 mg). These renal findings did not fully reverse within the 1-month recovery period). • The lacteal excretion of radiolabeled ertugliflozin in lactating rats was evaluated 10 to 12 days after parturition. Ertugliflozin derived radioactivity exposure in milk and plasma were similar, with a milk/plasma ratio of 1.07, based on AUC.	The renal findings in the juvenile toxicity study did not fully reverse within the 1-month recovery period, a period of renal development corresponding to the late second and third trimesters of human pregnancy. Possibly relevant during the second and third trimesters of pregnancy or with exposure during breastfeeding.
Nephrotoxicity	
• Renal tubular dilatation noted at all doses in repeat-dose rat and mouse studies. Renal tubular dilatation associated with increased incidence and severity of chronic progressive nephropathy in rats was considered adverse at the highest dose level tested but not considered human relevant. Some rats had evidence of ascending urinary tract infections. Housing the animals on bedding may have contributed to this finding.	Renal tubular dilation was considered secondary to diuresis. There is a large exposure margin for the rat specific finding of exacerbation of chronic progressive nephropathy, a common background finding in older rats. The ascending urinary tract infection finding may possibly be relevant to humans.
Hepatotoxicity	
No evidence of hepatotoxicity in repeat-dose rat and dog studies.	No evidence of hepatoxicity in nonclinical studies, therefore not a risk to humans.

Key Safety Findings with Ertugliflozin (from non-clinical studies)	Relevance to Human Usage
Genotoxicity	
Negative genotoxicity (microbial reverse mutation, in vitro cytogenetic (human lymphocyte), and in vivo rat micronucleus assays).	No evidence of genotoxicity, therefore not a risk to humans.
Carcinogenicity	
In the 2-year rat carcinogenicity study, ertugliflozin-related neoplastic findings included an increased incidence of benign adrenal medulla pheochromocytoma in male rats at 15 mg/kg/day. There were no findings in the 2-year mouse carcinogenicity study.	This finding was attributed to gastrointestinal SGLT1 inhibition resulting in altered calcium homeostasis. Ertugliflozin is more selective for human SGLT2 over human SGLT1 relative to rat SGLT2 over rat SGLT1. This finding was not considered relevant to human risk. The no-observed-effect level (NOEL) was 5 mg/kg/day (approximately 16 times human exposure at the MRHD of 15 mg/day).
General Safety Pharmacology	
CV (including potential for QT interval prolongation) – IC_{50} for inhibition of human ether-a- go-go-related gene (hERG) current amplitude was 1465 × the human unbound maximum observed concentration (C_{max}) MRHD of 15 mg. No risk for QT prolongation. No hemodynamic or electrocardiographic changes noted in dog CV study. Rat safety pharmacology studies: no biologically relevant effects on the central nervous or respiratory systems.	No CV, central nervous system or respiratory system risks to humans.
Mechanisms for Drug Interactions	
• Mechanisms for perpetrator drug-drug interactions (DDI): The potential for ertugliflozin and primary circulating glucuronide metabolites M5c and M5a to inhibit or induce drug metabolism or drug transport were evaluated. • Ertugliflozin, M5c and M5a, did not significantly inhibit the major drug-metabolizing cytochrome P (CYP)450 (IC_{50} >30 μM) or uridine diphosphate- glucuronosyltransferase (UGT) (IC_{50} >100μM) enzymes in vitro, indicating a low potential for drug interactions with compounds that are metabolized by these enzymes. The in vitro potential of ertugliflozin, M5c, or M5a to induce CYP3A4, CYP1A2, or CYP2B6 was low based on mRNA and enzyme activity changes in hepatocyte studies.	The risk of ertugliflozin causing metabolism or transporter DDIs is low.

Key Safety Findings with Ertugliflozin (from non-clinical studies)	Relevance to Human Usage
• Ertugliflozin or glucuronide metabolites do not inhibit P-gp, breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)1, organic anion transporter (OAT)1, OAT3, and OCT2 transporters in vitro, indicating a low risk of clinical interactions with compounds that are substrates of these transporters.	
• Mechanisms for victim DDIs: The potential for interactions following co-administration of ertugliflozin with inhibitors and inducers of drug metabolism and drug transport were evaluated.	The risk of victim DDIs following co-administration of ertugliflozin with inhibitors or inducers of metabolism or transporters is low.
• In humans, glucuronidation on the hydroxy groups of the modified glucose moiety was the major elimination pathway (86%), with minor contributions from oxidative metabolism (12%) and renal excretion (2%) of unchanged ertugliflozin. The primary UGT enzymes involved in the glucuronidation of ertugliflozin were UGT1A9 (□81%) and UGT2B7 (□19%).	
• The potential for a DDI after co-administration of ertugliflozin with a UGT inhibitor was evaluated using physiologically-based pharmacokinetic (PBPK) modeling. PBPK simulated ertugliflozin co-administration with multiple doses of the UGT inhibitor mefenamic acid predicted an ertugliflozin AUC ratio and maximum concentration ratio (C_{max},R) of 1.51 and 1.19, respectively, compared to ertugliflozin administered alone. Clinically relevant DDIs with ertugliflozin in the presence of UGT inhibitors are not anticipated.	
• Multiple-dose administration of rifampin 600 mg qd x 10 days with ertugliflozin 15 mg was associated with a 39% decrease in ertugliflozin area under the concentration –time curve from time zero to infinity (AUC_{inf}). Based on the ertugliflozin dose vs A1C response model, the 5 mg dose following co-administration with rifampin is predicted to maintain clinically meaningful glycemic efficacy; therefore, the decrease in ertugliflozin exposure with rifampin (a UGT and CYP inducer) is not considered clinically relevant.	

Key Safety Findings with Ertugliflozin (from non-clinical studies)	Relevance to Human Usage
• Ertugliflozin is a substrate for P-gp and BCRP efflux transporters, but is not a substrate for OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1, OAT3, and OCT2 uptake transporters. However, no clinically relevant interaction is expected with inhibitors of these transporters based on the oral bioavailability of ertugliflozin of ~100%, and dose-proportional increases in exposure over the dose range of 0.5 mg to 300 mg, indicating that P-gp and BCRP do not limit the oral absorption of ertugliflozin. Therefore, clinically relevant DDIs with ertugliflozin in the presence of inhibitors of these transporters are not anticipated.	

1.2 Summary of the Safety Concerns

Table 2 Summary of Safety Concerns

Important identified risks	DKA with atypical presentation
Important potential risks	None
Missing information	Use in pregnancy and breastfeeding Use in patients with CHF Class IV

2 Pharmacovigilance Plan (including post-authorisation safety studies)

2.1 Summary Table of Additional Pharmacovigilance Activities

Table 3 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 authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				
Study P004/1021 and P007/1017 which were ongoing, additional PV activities in the previous version of the RMP, have since completed, refer to Annex 2.				

3 Plans for Post-Authorisation Efficacy Studies

There are no ongoing or proposed post-authorization efficacy studies (PAES) for ertugliflozin.

4 Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

4.1 Summary of Risk Minimisation Measures

Table 4 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
DKA with atypical presentation	Routine risk minimisation measures: Text in product circular including: Warnings and Precautions Adverse Reactions Additional risk minimisation measures: None	Routine pharmacovigilance activities including: Target follow-up questionnaire Additional pharmacovigilance activities: None
Use in pregnancy and breastfeeding	Routine risk minimisation measures: Text in product circular including: Use in Specific Populations Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Use in patients with CHF Class IV	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: None

5 Summary of the Risk Management Plan by Product

5.1 Summary of risk management plan for ertugliflozin

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

The Company Core Data Sheet (CCDS) and Company Core Patient Product Information (CCPPI) for ertugliflozin give essential information to healthcare professionals and patients on how ertugliflozin should be used.

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

5.2 The Medicine and What It is Used For

Ertugliflozin is authorised for adults aged 18years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control. It contains ertugliflozin as the active substance and it is given orally.

Ertugliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease.

5.3 Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the CCPPI and CCDS addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

If important information that may affect the safe use of ertugliflozin is not yet available, it is listed under 'missing information' below.

5.4 List of Important Risks and Missing Information

Important risks of ertugliflozin are risks that need special risk management activities to further investigate or minimise 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 ertugliflozin. 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 (e.g. on the long-term use of the medicine);

Table 5 List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	DKA with atypical presentation
Important potential risks	None
Missing information	Use in pregnancy and breastfeeding Use in patients with CHF Class IV

5.5 Summary of Important Risks

Table 6 Important Identified Risk: DKA with Atypical Presentation

Evidence for linking the risk to the medicine	Review of ertugliflozin clinical trial data regarding DKA with Atypical Presentation and recognition of this as an SGLT2 inhibitor class effect represents sufficient evidence of a causal association with ertugliflozin exposure.
Risk factors and risk groups	Factors predisposing patients to DKA include situations of decreased insulin and/or increase glucagon such as T1DM, pancreatic insulin deficiency, decreased caloric intake, insulin dose reduction, or increased insulin requirements due to acute medical illness or surgery, and alcohol abuse.
Risk minimisation measures	Routine risk minimisation measures: Text in product circular including: Warnings and Precautions Adverse Reactions Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 7 Important Missing Information: Use in Pregnancy and Breastfeeding

Risk minimisation measures	Routine risk minimisation measures: Text in product circular including: Use in Specific Populations Additional risk minimisation measures: None

Table 8 Important Missing Information: Use in Patients with CHF Class IV

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

5.6 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ertugliflozin.

5.7 Other Studies in Post-Authorisation Development Plan

Not applicable

6 Summary of Changes to the Risk Management Plan Over Time

Major changes to the RMP over time are shown in Table 9.

Table 9 Major Changes to the Risk Management Plan

RMP Version	Date	Safety Concerns	Comment
1.0	Dec 2016	**Identified Risks** Genital mycotic infections Volume depletion Hypoglycemia in combination with insulin and/or an insulin secretagogue Diabetic ketoacidosis with atypical presentation **Potential Risks** Hypoglycemia in the absence of insulin and/or an insulin secretagogue Urinary tract infections Renal impairment Bone fracture **Missing information** Use in pediatric patients Use in elderly patients (≥75 years) Use in pregnancy Use in breastfeeding Use in patients with severe renal impairment (including ESRD requiring hemodialysis or undergoing peritoneal dialysis) Use in patients with severe hepatic impairment Use in patients with CHF Class II-IV Long-term CV Safety	This is the first RMP which has been submitted for ertugliflozin.
2.0	Sep 2017	**Identified Risks** Volume depletion DKA with atypical presentation **Potential Risks** Renal impairment Lower limb amputations Bone fracture **Missing information** Use in pediatric patients Use in elderly patients (≥75 years) Use in pregnancy and breastfeeding Use in patients with CHF Class II-IV Long-term CV Safety	Risks and missing information were removed based on the updated (Mar 2017) EMA Guideline on good pharmacovigilance practices (GVP) Module V (Rev 2). The important potential risk of lower limb amputations was added as a new safety concern for the SGLT2 inhibitor class.
2.1	Dec 2017	**Identified Risks** Volume depletion DKA with atypical presentation **Potential Risks** Renal impairment Lower limb amputations Bone fracture **Missing information** Use in pediatric patients Use in elderly patients (≥75 years) Use in pregnancy and breastfeeding Use in patients with CHF Class II-IV Long-term CV Safety	No change in the safety concerns. In section, SIV.3.5 Patients with Renal Impairment, editorial revisions were made to align with the product labeling.

3.0	Dec 2017	**Identified Risks** Volume depletion DKA with atypical presentation **Potential Risks** Renal impairment Lower limb amputations Bone fracture **Missing information** Use in elderly patients (≥75 years) Use in pregnancy and breastfeeding Use in patients with CHF Class II-IV Long-term CV Safety	Missing information was removed based on the updated (Mar 2017) EMA Guideline on good pharmacovigilance practices (GVP) Module V (Rev 2).
4.0	Nov 2020	Clinical Trial Exposure Population not studied in clinical trials Post-authorization Experience New safety concerns and reclassification with a submission of an updated RMP Presentation of important identified risks and important potential risks Summary of the safety concerns Routine and additional pharmacovigilance activities Summary table of additional pharmacovigilance activities Routine and additional risk minimization measures Summary of risk minimization measures List of important risks and missing information Summary of important risks	This RMP was updated following completion of VERTIS-CV trial for ertugliflozin and to align with the new GVP Module V (Rev.2) guidance.