Swiss Summary of the Risk Management Plan (RMP)

for

Steglujan®

(Ertugliflozin 5mg / Sitagliptin 100mg)

Film-coated tablets

Version 1.0 (November 2018)
based on RMP V3.0 (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 Steglujan® 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 Steglujan® 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 Steglujan®.

1 Elements for Summary Tables in the EPAR

1.1 Summary Table of Safety Concerns

Table 1 Summary of Safety Concerns

Important identified risks	• Volume depletion • DKA with atypical presentation • Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson syndrome • Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis) • Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (eg, arthralgia, myalgia, myopathy) • Acute Pancreatitis • Bullous pemphigoid
Important potential risks	• Impaired renal function, including acute renal failure (sometimes requiring dialysis) • Lower limb amputations • Bone fracture • Malignancy • Infections: URTI, nasopharyngitis, and elated terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis) • Neurotoxicity: tremor, ataxia, and balance disorders • Skin reactions: contact dermatitis • Pancreatic cancer
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

1.2 Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

Table 2 Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)

Study / Activity	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim / Final Reports (target dates)
Study 8835-004/B1521021 / Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study To Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK-8835/PF-04971729) in Subjects with T2DM and Established Vascular Disease / Category 3	To continue monitoring and gain further information on 1) the characteristics of ertugliflozin use in patients with CHF Class II-III 2) the long-term CV safety profile in patients treated with ertugliflozin. 3) the frequency and characteristics of volume depletion events in patients treated with ertugliflozin 4) the frequency and characteristics of events of DKA in patients treated with ertugliflozin 5) the frequency and characteristics of events of renal impairment in patients treated with ertugliflozin 6) the frequency and characteristics of events of lower limb amputation in patients treated with ertugliflozin 7) the frequency and characteristics of events of bone fracture in patients treated with ertugliflozin, 8) the frequency and characteristics of events of malignancy in patients treated with ertugliflozin and 9) the characteristics of ertugliflozin use in elderly patients (≥75 years)	Use in patients with CHF Class II-IV, long-term CV safety, volume depletion, DKA with atypical presentation, renal impairment, lower limb amputations, bone fracture, malignancy and use in elderly patients (≥75 years)	Started	2020

1.3 Summary of Post-Authorisation Efficacy Development Plan

There are no ongoing or proposed PAES for ertugliflozin.

1.4 Summary Table of Risk Minimisation Measures

Table 3 Summary of Safety Concerns and Risk Minimisation Activities

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Volume depletion	Text in product circular including: Dosage and Administration Warnings and Precautions Use in Specific Populations Adverse Reactions	None
DKA with atypical presentation	Text in product circular including: Warnings and Precautions Adverse Reactions	None
Hypersensitivity reactions: anaphylactic reaction, angioedema, rash, urticaria, skin exfoliation, and Stevens-Johnson syndrome	Text in product circular including: Contraindications Warnings and Precautions Adverse Reactions	None
Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis)	Text in product circular including: Adverse Reactions	None
Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (eg, arthralgia, myalgia, myopathy)	Text in product circular including: Adverse Reactions	None
Acute pancreatitis	Text in product circular including: Warnings and Precautions Adverse Reactions	None
Bullous pemphigoid	Text in product circular including: Warnings and Precautions Adverse Reactions	None
Important Potential Risks		
Impaired renal function, including acute renal failure (sometimes requiring dialysis)	Text in product circular including: Dosage and Administration Warnings and Precautions Use in Specific Populations Adverse Reactions	None
Lower limb amputations	None	None
Bone fracture	None	None
Malignancy	Text in product circular including: Adverse Reactions	None
Infections: URTI, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis	Text in product circular including: Adverse Reactions	None
Neurotoxicity: tremor; ataxia; and balance disorders	None	None
Skin reactions: contact dermatitis	None	None
Pancreatic cancer	None	None
Missing Information		
Use in elderly patients (≥75 years)	Text in product circular including: Warnings and Precautions Use in Specific Populations	None
Use in pregnancy and breastfeeding	Text in product circular including: Use in Specific Populations	None
Use in patients with CHF Class II-IV	None	None
Long-term CV safety	None	None

2 Elements for a Public Summary

2.1 Overview of Disease Epidemiology

T2DM is a condition in which the pancreas does not make enough insulin to control the level of sugar in the blood or when the body is unable to use insulin effectively. Insulin is a hormone produced by your pancreas (an organ behind the stomach) and it is released to help your body store and use sugar from the food you eat. Diabetes is a lifelong disease which affects approximately 1 out of every 11 adults worldwide. T2DM is more likely to develop with increasing age and in those who have a family history, smoke, have high blood pressure, are overweight, do not exercise, or have an ethnic background known to be associated with the disease (eg, American Indians, Hispanics, Asians or Africans). People with diabetes have a greater chance of developing CVD, kidney disease or diabetic eye disease.

2.2 Summary of Treatment Benefits

Ertugliflozin/sitagliptin contains 2 different medications, ertugliflozin and sitagliptin. Ertugliflozin is a type of medication called an SGLT2 inhibitor being developed for the treatment of patients with T2DM whose blood glucose levels are not satisfactorily controlled on diet and exercise. Ertugliflozin works in the kidneys where it increases the amount of sugar being released into the urine, thereby lowering and helping to control blood sugar levels.

Sitagliptin is another T2DM medication, called a DPP-4 inhibitor, that enhances the body's own ability to control blood sugar levels. Sitagliptin helps the body increase insulin production and reduce the amount of sugar made by the liver when blood sugar is high, especially after eating. By itself, sitagliptin works only when blood sugar levels are high.

In clinical studies, treatment with ertugliflozin 5 mg or 15 mg once daily taken together with sitagliptin showed a benefit in reducing A1C, a substance that measures how well blood sugar is controlled. In addition, ertugliflozin produced meaningful reductions in body weight and systolic blood pressure. These studies included 990 subjects randomly assigned to treatment with ertugliflozin and sitagliptin.

1. Study P005/1019, in which ertugliflozin, sitagliptin, or both sitagliptin and ertugliflozin was added to the treatment of patients with T2DM who had poor control of blood sugar with diet and exercise while taking metformin. This study showed that ertugliflozin and sitagliptin given together resulted in significant and clinically meaningful improvement in control of blood sugar compared to ertugliflozin or sitagliptin alone.

2. Study P017/1047, in which ertugliflozin and sitagliptin together or placebo were added to the treatment of patients with T2DM who had poor control of blood sugar with diet and exercise. This study demonstrated that the addition of ertugliflozin and sitagliptin together resulted in a significant and clinically meaningful improvement in control of blood sugar compared to placebo.

3. Study P006/1015, in which ertugliflozin or placebo was added to the treatment of patients with T2DM who had poor control of blood sugar with diet and exercise while taking metformin and sitagliptin. This study demonstrated that the addition of ertugliflozin resulted in a significant and clinically meaningful improvement in control of blood sugar compared to placebo.

2.3 Unknowns Relating to Treatment Benefits

Ertugliflozin/sitagliptin has not been studied in and is not recommended for use in individuals who:

- Have T1DM (insulin dependent or juvenile diabetes, such as usually develops in children and teenagers)
- Are below 18 years of age
- Are pregnant
- Are breastfeeding
- Have severe liver problems

It is not known if the effects of ertugliflozin/sitagliptin on blood pressure and body weight reduction will, if sustained, provide a significant additional reduction in the risk of conditions such as heart attacks and strokes.

2.4 Summary of Safety Concerns

Important Identified Risks

Table 4 Summary of Important Identified Risks

Risk	What is Known	Preventability
Volume depletion (water loss)	Ertugliflozin/sitagliptin can cause dehydration which means losing too much water from your body. Symptoms of dehydration are feeling dizzy, light-headed, or weak, especially when you stand up, and fainting or near fainting.	You are more likely to get dehydrated if you have kidney problems, take water pills (diuretics) or are 65 years or older. Your doctor can help determine if you are at higher risk for dehydration and provide guidance to prevent dehydration.
DKA with atypical presentation (increased levels of "ketone bodies" in your blood)	Ertugliflozin/sitagliptin can cause a rare but serious condition called DKA (increased levels of "ketone bodies" in your blood) that can lead to death. Diabetic ketoacidosis is a medical emergency and must be treated in the hospital. Symptoms of DKA include nausea, vomiting, loss of appetite, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness, or tiredness.	You may be more likely to develop DKA with prolonged fasting, excessive alcohol consumption, sudden reductions in insulin dose, or a higher need for insulin due to major surgery or serious illness. Avoid sudden prolonged fasting and excessive alcohol consumption and tell your doctor if you are planning to have a surgery or you become very ill.
Hypersensitivity (allergic reactions)	Symptoms of serious allergic reactions to sitagliptin, one of the medicines in ertugliflozin/sitagliptin, including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty breathing or swallowing, can occur. Compared to patients receiving sitagliptin alone, ertugliflozin/sitagliptin does not increase the risk of allergic reactions.	Individuals with known allergic reactions to the active substance or components are not recommended to use ertugliflozin/sitagliptin. Individuals who have any symptoms of a serious allergic reaction should stop taking ertugliflozin/sitagliptin and call their doctor right away.
Gastrointestinal disorders (stomach upset, vomiting, diarrhea, abdominal pain, and loss of appetite)	Stomach upset, vomiting, diarrhea, abdominal pain, and loss of appetite may occur with sitagliptin, one of the medicines in ertugliflozin/sitagliptin, most often during initiation of therapy, and resolve spontaneously in most cases. Compared to patients receiving sitagliptin alone, ertugliflozin/sitagliptin does not increase the risk of gastrointestinal disorders.	Preventability is unknown. No specific action is recommended.
Musculoskeletal disorders (muscle and joint disorders)	In a study in dogs with sitagliptin, one of the medicines in ertugliflozin/sitagliptin, slight muscle cell breakdown was seen with daily doses of sitagliptin far above the recommended daily dose for humans. In humans, symptoms such as muscle and joint pain have been reported with sitagliptin. Compared to patients receiving sitagliptin alone, ertugliflozin/sitagliptin does not increase the risk of muscle and joint disorders.	Preventability is unknown. No specific action is recommended.

Acute pancreatitis (inflammation of the pancreas)	Patients with diabetes are at increased risk of acute pancreatitis.	Individuals who experience the characteristic symptoms of acute pancreatitis (persistent, severe abdominal pain) should call their doctor. Resolution of pancreatitis has been observed after discontinuation of sitagliptin, one of the medicines in ertugliflozin/sitagliptin. If pancreatitis is suspected, ertugliflozin/sitagliptin and other potentially suspect medicinal products should be discontinued.
Bullous pemphigoid (blistering, immune skin condition)	Bullous pemphigoid is a rare skin condition that causes fluid-filled blisters. The occurrence of bullous pemphigoid increases significantly with age and is observed most commonly among elderly people. Bullous pemphigoid occurs when the body's immune system attacks the skin. The reason is unknown, but possibly could be drug induced in some cases. There have been reports of patients taking sitagliptin and developing bullous pemphigoid.	Preventability is unknown. Patients who are suspected to have bullous pemphigoid should discontinue ertugliflozin/sitagliptin.

Important Potential Risks

Table 5 Summary of Important Potential Risks

Risks	What is Known
Impaired Renal Function, Including Acute Renal Failure (Sometimes Requiring Dialysis) (kidney problems)	Patients with diabetes are at increased risk of kidney problems. Clinical trial data did not show an increased occurrence of events of kidney problems in most patients, but there may be an increased risk in patients who already have kidney problems.
Lower limb amputations	Another drug that works by the same mechanism as ertugliflozin has an increased risk for lower limb amputations. It has not yet been determined whether ertugliflozin/sitagliptin increases the risk of amputations.
Bone fracture	Ertugliflozin/sitagliptin did not increase the risk of bone fracture in clinical trials but some other drugs that work by the same mechanism as ertugliflozin have resulted in an increased risk.
Malignancy	Patients with diabetes are at increased risk of malignancies or tumors of unspecified malignant potential. In clinical trials, there was a low occurrence of malignancy, but there was a slight imbalance with the use of ertugliflozin, a component of ertugliflozin/sitagliptin, versus comparator. There was no increased risk of any specific tumor type. There has been no reported plausible mechanism of action to support a causal relationship between SGLT2 inhibition and tumor promotion. No risk groups or factors have been identified for ertugliflozin.
Infections	Sitagliptin, one of the medicines in ertugliflozin/sitagliptin, is an inhibitor of the DPP-4 enzyme which may potentially affect the function of the body's defense system (immune system). In clinical trials, nose and throat infections (such as colds) and upper respiratory tract infections were seen more frequently in patients taking sitagliptin, compared to patients not treated with sitagliptin. Compared to patients receiving sitagliptin alone, ertugliflozin/sitagliptin does not increase the risk of infections.

Neurotoxicity (nerve and brain-related problems)	Observations of neurotoxicity are based on physical signs (balance problems and shaking) in dogs receiving high doses of sitagliptin, one of the medicines in ertugliflozin/sitagliptin, that are not used in people. To date, review of data in humans does not show a safety concern for neurotoxicity in patients. Compared to patients receiving sitagliptin alone, ertugliflozin/sitagliptin does not increase the risk of neurotoxicity events.
Skin reactions: contact dermatitis (an allergic skin reaction)	Contact dermatitis was rare with sitagliptin, one of the medicines in ertugliflozin/sitagliptin, in clinical trials. Compared to patients receiving sitagliptin alone, ertugliflozin/sitagliptin does not increase the risk of contact dermatitis.
Cancer of the pancreas	Patients with diabetes are at increased risk of cancer of the pancreas. Review of clinical trial data showed no increase in occurrence of cancer of the pancreas in patients taking sitagliptin, one of the medicines in ertugliflozin/sitagliptin, compared to patients not treated with sitagliptin. Compared to patients receiving sitagliptin alone, ertugliflozin/sitagliptin does not increase the risk of cancer of the pancreas.

Missing Information

Table 6 Summary of Missing Information

Missing Information	What is Known
Use in elderly patients (≥75 years)	Ertugliflozin/sitagliptin has been studied in a limited number of patients 75 years of age and older. There was an increased risk for volume depletion (water loss) in elderly patients, but otherwise there have been no unexpected differences in safety in elderly patients compared to younger patients.
Use in pregnancy and breastfeeding	There are no studies on the use of ertugliflozin/sitagliptin in pregnant and breastfeeding women. Studies in animals have shown some problems in the developing fetus with ertugliflozin. Ertugliflozin/sitagliptin is not recommended during pregnancy. There is no information regarding the presence of ertugliflozin/ sitagliptin in human milk. Ertugliflozin and sitagliptin were detected in the milk of nursing rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, ertugliflozin/sitagliptin is not recommended during breast-feeding.
Use in patients with CHF Class II-IV (heart failure)	There is limited safety data in patients with moderate heart failure and no safety data in patients with severe heart failure.
Long-term CV Safety (long term heart and blood vessel safety)	The effects of ertugliflozin/sitagliptin on long-term cardiovascular (heart and blood vessel) safety have not been fully characterized.

2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Product Circular which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

The current information for professionals and patients for Steglujan® can be found on www.swissmedicinfo.ch.

This medicine has no additional risk minimisation measures.

2.6 Planned Post-Authorisation Development Plan

2.6.1 List of Studies in Post-Authorisation Development Plan

Table 7 List of Studies in Post-Authorisation Development Plan

Study/Activity (Including Study Number)	Objectives	Safety Concerns/Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and) Final Results
Study 8835-004/B1521021 / Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study To Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK-8835/PF-04971729) in Subjects with T2DM and Established Vascular Disease / Category 3	To continue monitoring and gain further information on 1) the characteristics of ertugliflozin use in patients with CHF Class II-III 2) the long-term CV safety profile in patients treated with ertugliflozin 3) the frequency and characteristics of volume depletion events in patients treated with ertugliflozin 4) the frequency and characteristics of events of DKA in patients treated with ertugliflozin 5) the frequency and characteristics of events of renal impairment in patients treated with ertugliflozin 6) the frequency and characteristics of events of lower limb amputation in patients treated with ertugliflozin 7) the frequency and characteristics of events of bone fracture in patients treated with ertugliflozin 8) the frequency and characteristics of events of malignancy in patients treated with ertugliflozin and 9) the characteristics of ertugliflozin use in elderly patients (≥75 years)	Use in patients with CHF Class II-IV, long-term CV safety, volume depletion, DKA with atypical presentation, renal impairment, bone fracture, lower limb amputations, malignancy and use in elderly patients (≥75 years)	Started	2020

2.6.2 Studies which are a Condition of the Marketing Authorisation

None of the above studies are conditions of the marketing authorization

2.7 Summary of Changes to the Risk Management Plan Over Time

Major changes to the Risk Management Plan over time are shown in Table 8.

Table 8 Major Changes to the Risk Management Plan

RMP Version	Date	Safety Concerns	Comment
1.0	Jan 2017	**Identified Risks** • Genital mycotic infections • Volume depletion • Hypoglycemia in combination with insulin and/or an insulin secretagogue • Diabetic ketoacidosis with atypical presentation • Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson syndrome • Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis) • Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (eg, arthralgia, myalgia, myopathy) • Acute pancreatitis • Bullous pemphigoid **Potential Risks** • Hypoglycemia in the absence of insulin and/or an insulin secretagogue • Urinary tract infections • Infections: URTI, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis) • Impaired renal function, including acute renal failure (sometimes requiring dialysis) • Bone fracture • Neurotoxicity: tremor, ataxia, and balance disorders • Skin reactions: contact dermatitis • Pancreatic cancer	This is the first RMP which has been submitted for ertugliflozin/sitagliptin

		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 • Theoretic carcinogenic potential	
2.0	Sep 2017	**Identified Risks** • Volume depletion • DKA with atypical presentation • Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson syndrome • Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis) • Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (eg, arthralgia, myalgia, myopathy) • Acute pancreatitis • Bullous pemphigoid **Potential Risks** • Impaired renal function, including acute renal failure (sometimes requiring dialysis) • Lower limb amputations • Bone fracture • Infections: URTI, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis) • Neurotoxicity: tremor, ataxia, and balance disorders • Skin reactions: contact dermatitis • Pancreatic cancer **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 • Theoretic carcinogenic potential	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 • Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson syndrome • Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea,	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.

		abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis) • Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (eg, arthralgia, myalgia, myopathy) • Acute pancreatitis • Bullous pemphigoid **Potential Risks** • Impaired renal function, including acute renal failure (sometimes requiring dialysis) • Lower limb amputations • Bone fracture • Infections: URTI, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis) • Neurotoxicity: tremor, ataxia, and balance disorders • Skin reactions: contact dermatitis • Pancreatic cancer **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 • Theoretic carcinogenic potential	
3.0	Dec 2017	**Identified Risks** • Volume depletion • DKA with atypical presentation • Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson syndrome • Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis) • Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (eg, arthralgia, myalgia, myopathy) • Acute pancreatitis • Bullous pemphigoid **Potential Risks** • Impaired renal function, including acute renal failure (sometimes requiring dialysis) • Lower limb amputations • Bone fracture • Infections: URTI, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis,	Missing information was removed based on the updated (Mar 2017) EMA Guideline on good pharmacovigilance practices (GVP) Module V (Rev 2) and review of sitagliptin clinical trial data in TECOS.

		and rhinitis) • Neurotoxicity: tremor, ataxia, and balance disorders • Skin reactions: contact dermatitis • Pancreatic cancer **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	

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

Table 9 Major Changes to the Swiss Annex

Version	Date	Safety Concerns	Comment
1.0 (according to current RMP Version 3.0)	Dec 2017	**Potential Risks** Malignancy	This is the first Swiss Annex which has been submitted for ertugliflozin/sitagliptin.