Summary of the risk management plan for Zynquista (sotagliflozin)

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

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

This summary of the RMP for Zynquista 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 Zynquista's RMP.

I. The medicine and what it is used for

Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus (T1DM) with a body mass index (BMI) ≥27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy (see SmPC for the full indication). It contains sotagliflozin which is the active substance in ZYNQUISTA and it is given by oral route.

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Zynquista, together with measures to minimize such risks and the proposed studies for learning more about Zynquista's risks, are outlined in the next sections.

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 the case of Zynquista, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

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 Zynquista is not yet available, it is listed under 'missing information' outlined in the next section.

II. A List of important risks and missing information

Important risks of Zynquista 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 Zynquista. 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).

List of important risks and missing information

Important identified risk	Diabetic ketoacidosis (DKA)
Important potential risks	Lower limb amputation Malignancies Pancreatitis Bone fractures
Missing information	Use of sotagliflozin in pregnant and lactating women Use of sotagliflozin in patients ≥75 years Long-term cardiovascular safety

DKA: Diabetic Ketoacidosis.

II.B Summary of important risks

Important identified risk: Diabetic ketoacidosis (DKA)

Important identified risk: Diabetic ketoacidosis (DKA)	
Evidence for linking the risk to the medicine	o Diabetic ketoacidosis presents a significant and potentially severe risk complication of T1DM, resulting from the insulin deficiency. o The incidence of positively adjudicated DKA increased with increased dose of sotagliflozin (0.5%, 2.7%, and 3.2% in the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups, respectively. A similar trend was observed in EAIR per 1000 PY, 7.55, 30.72, and 52.95, respectively. o Assessment report of the Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data in SGLT2 inhibitors o Food and Drug Administration database for SGLT2 inhibitors. The FDA issued a drug safety communication regarding events of DKA.
Risk factors and risk groups	Use of sotagliflozin was associated with an increased risk of DKA and ketosis-related events. Diabetic ketoacidosis occurred more frequently in patients using CSII that were often due to pump-related issues. Reductions in total insulin dose of approximately 20% or more were associated with BHB elevation. Having a history of DKA or ketosis, higher baseline A1C, and higher BHB (at Baseline and during treatment) are also associated with increased risk of DKA. In addition, common precipitating factors for DKA include infections, intercurrent illnesses, psychological stress, alcohol consumption and noncompliance with insulin therapy.
Risk minimization measures	<u>Routine risk minimization measures:</u> SmPC: Sections 4.1, 4.2, 4.4 and 4.8 PL: Sections 2 and 4 Prescription only medicine Legal status: Therapy with Zynquista should be under the supervision of a physician experienced in the management of T1DM <u>Additional risk minimization measures:</u> o HCP Guide (including prescriber checklist) o Patient alert card o Patient/carer's guide
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> DKA PASS to evaluate the incidence of DKA with sotagliflozin treated patients in real life as compared to non SGLTi treated patients in the post approval setting.

CSII: Continuous Subcutaneous Insulin Infusion; DKA: Diabetic Ketoacidosis; BMI: Body Mass Index; EC: European Commission; HCP: Healthcare Professional; PASS: Post-Authorization Safety Study; PL: Patient Leaflet; SmPC: Summary of Product Characteristics; BHB: Beta-Hydroxybutyrate; CI: Confidence Interval; EAIR: Exposure-Adjusted Incidence Rate; FDA: Food and Drug Administration; PY: Patient-Years; SGLT2: Sodium-Glucose Co-Transporter 2; SGLTi: Sodium-Glucose Co-Transporter inhibitor; T1DM: Type 1 Diabetes Mellitus.

Important potential risk: Lower limb amputation

Important potential risk: Lower limb amputation	
Evidence for linking the risk to the medicine	European Medicines Agency review prompted by an increase in amputations (mostly affecting the toes) in patients taking canagliflozin in two clinical trials, CANVAS and CANVAS-R. Initially, this review that was carried out by PRAC for canagliflozin was extended to include the other medicines in the same class, dapagliflozin and empagliflozin, on 07-Jul-2016. On 24-Feb-2017, the CHMP confirmed PRAC's recommendation to add a warning on potential risk of toe amputation in the label of canagliflozin, but also of empagliflozin and dapagliflozin. Food and Drug Administration Drug Safety Communication issued in May-2016 and updated in May-2017: Food and Drug Administration confirmed increased risk of leg and foot amputations with canagliflozin (based on the results from the CANVAS and CANVAS-R trials) and required the addition of a boxed warning for increased risk of leg and foot amputations to the label for canagliflozin. Two cases of amputation, one in 200 mg and one 400 mg sotagliflozin arm were reported.
Risk factors and risk groups	People with diabetes mellitus are at an increased risk for having amputation. Numbness in the feet due to diabetic neuropathy can make people less aware of injuries and foot ulcers. These ulcers may fail to heal, which can in turn lead to serious infections.
Risk minimization measures	<u>Routine risk minimization measures:</u> SmPC: Section 4.4 PL: Section 2 Prescription only medicine Legal status: Therapy with Zynquista should be under the supervision of a physician experienced in the management of T1DM <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> SCORED Study

CHMP: Committee for Medicinal Products for Human Use; PRAC: Pharmacovigilance Risk Assessment Committee; PL: Patient Leaflet; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus.

Important potential risk: Malignancies

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	United States label for dapagliflozin warning for bladder cancer, One thyroid (papillary) and 2 bladder cancers (one reported as bladder transitional cell carcinoma; and one as bladder cancer) were reported in the sotagliflozin program. Those were considered as unrelated due to lack of temporal relationship. The overall incidence of malignancies in the development program showed no imbalance with placebo, however, due to limitation (duration or studies) this has to be interpreted with caution.

Important potential risk: Malignancies	
Risk factors and risk groups	National Cancer Institute's Division of Cancer Epidemiology and Genetics and the Epidemiology and Genomics Research Program in National Cancer Institute's Division of Cancer Control and Populations Sciences conduct and fund research to identify and evaluate a range of exposures and risk factors that may be associated with cancer, including: o Genetics o Substances in the environment and workplace, such as air pollutants, water pollutants, and chemicals o Infectious agents, such as viruses and bacteria o Radiation, including ionizing radiation and non-ionizing radiation o Pharmaceutical agents and exogenous and endogenous hormones o Behavioral and lifestyle factors, such as diet and nutrition, tobacco use, alcohol use, energy balance, physical activity, and obesity o Immune system status and inflammation
Risk minimization measures	Routine risk minimization measures: SmPC: Section 5.3 PL: None Prescription only medicine Legal status: Therapy with Zynquista should be under the supervision of a physician experienced in the management of T1DM Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: SCORED Study Malignancy PASS to examine if there is an association between sotagliflozin use and the risk of bladder, renal, breast, Leydig cell, pancreatic, thyroid, and prostate cancers

PASS: Post Authorization Safety Study; PL: Patient Leaflet; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus.

Important potential risk: Pancreatitis

Important potential risk: Pancreatitis	
Evidence for linking the risk to the medicine	At the PRAC meeting 24 to 27-Oct-2016, as part of the conclusion of canagliflozin PSUSA/00010077/201603, the PRAC considered that pancreatitis should be closely monitored and included in the RMP for all SGLT2 inhibitors.
Risk factors and risk groups	Gallstones are the most common cause for acute pancreatitis, accounting for 35%–40% of cases worldwide, and together with alcohol, and metabolic disorders such as hyperlipidemia and hypercalcemia make up around 90% of all cases. Medications are infrequently associated with pancreatitis with a reported incidence of only 0.1%–2% although several drugs have been implicated including diuretics, didanosine, tetracycline, sulfonamides, and steroids, among others.
Risk minimization measures	Routine risk minimization measures: SmPC: None PL: None

Important potential risk: Pancreatitis	
	Prescription only medicine Legal status: Therapy with Zynquista should be under the supervision of a physician experienced in the management of T1DM Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: SCORED Study

PL: Patient Leaflet; PRAC: Pharmacovigilance Risk Assessment Committee; PSUSA: Periodic Safety Update Report Single Assessment; SGLT2: Sodium Glucose Co Transporter 2; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus.

Important potential risk: Bone fractures

Important potential risk: Bone fractures	
Evidence for linking the risk to the medicine	An increased risk of fracture was observed in the canagliflozin Cardiovascular Assessment Study. It should be noted that this study included patients with T2DM who were older, had preexisting microvascular diseases, had impaired baseline renal function, and were at higher baseline risk of fall.
Risk factors and risk groups	Fragility fractures are recognized as a potential comorbidity of T1DM.
Risk minimization measures	Routine risk minimization measures: SmPC: None PL: None Prescription only medicine Legal status: Therapy with Zynquista should be under the supervision of a physician experienced in the management of T1DM Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: o SCORED Study o SOTA-BONE Study

PL: Patient Leaflet; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus.

Missing information: Use of sotagliflozin in pregnant and lactating women

Missing information: Use of sotagliflozin in pregnant and lactating women	
Risk minimization measures	Routine risk minimization measures: SmPC: Section 4.6 PL: Section 2 Prescription only medicine Legal status: Therapy with Zynquista should be under the supervision of

Missing information: Use of sotagliflozin in pregnant and lactating women	
	a physician experienced in the management of T1DM Additional risk minimization measures: None

PL: Patient Leaflet; SmPC: Summary of Product Characteristics.

Missing information: Use of sotagliflozin in patients ≥75 years

Missing information: Use of sotagliflozin in patients ≥75 years	
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.2, 4.4 and 5.2 PL: None Prescription only medicine Legal status: Therapy with Zynquista should be under the supervision of a physician experienced in the management of T1DM Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: SCORED Study

PL: Patient Leaflet; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus.

Missing information: Long-term cardiovascular safety

Missing information: Long-term cardiovascular safety	
Risk minimization measures	Routine risk minimization measures: SmPC: None PL: None Prescription only medicine Legal status: Therapy with Zynquista should be under the supervision of a physician experienced in the management of T1DM Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: SCORED Study

PL: Patient Leaflet; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation:

Risk of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus Treated with Sotagliflozin as an Adjunct to Insulin Versus Insulin Alone
Purpose of the study: DKA is an important identified risk for sotagliflozin. The objective is to evaluate the incidence of DKA with sotagliflozin treated patients in real life as compared to non SGLTi treated patients in the post approval setting.

DKA: Diabetic Ketoacidosis; SGLTi: Sodium-Glucose Co-Transporter inhibitor.

II.C.2 Other studies in post-authorisation development plan

A randomized double-blind, placebo-controlled, parallel-group, multicenter study to demonstrate the effects of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes, cardiovascular risk factors and moderately impaired renal function
Purpose of the study: Primary objectives: To demonstrate that, when compared to placebo in patients with type 2 diabetes, cardiovascular risk factors, and moderately impaired renal function, sotagliflozin: • Is non-inferior to placebo on the composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke (3-point MACE) • Reduces the composite endpoint of cardiovascular death or hospitalization for heart failure Secondary objectives: • The secondary objectives of this study are to demonstrate that, when compared to placebo in patients with type 2 diabetes, cardiovascular risk factors, and moderately impaired renal function, sotagliflozin: - Reduces the composite endpoint of cardiovascular death, non-fatal MI or non-fatal stroke (3-point MACE) - In patients with baseline eGFR ≥30 mL/min/1.73 m^2, reduces the composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) - In patients with Baseline eGFR ≥30 mL/min/1.73 m^2 and baseline UACR ≥300 mg/g (34 mg/mmol), reduces the composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) - Reduces the composite endpoint of cardiovascular death, hospitalization for heart failure, or urgent heart failure visit - Reduces cardiovascular death - Reduces all-cause mortality • To assess the safety and tolerability of sotagliflozin in patients with type 2 diabetes, cardiovascular risk factors, and moderately impaired renal function

A 26-week randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 study with a 78-week extension period to evaluate the efficacy and safety of sotagliflozin in patients 55 years and older with type 2 diabetes mellitus and inadequate glycemic control

Purpose of the study:

The safety database of this study will provide information on bone safety.

Use of Sotagliflozin and Risk of Malignancies in Adult Patients with Type 1 Diabetes Mellitus

Purpose of the study:

The objective is to examine if there is an association between sotagliflozin use and the risk of bladder, renal, breast, Leydig cell, pancreatic, thyroid, and prostate cancers.

HCP: Healthcare Professional; T1DM: Type 1 Diabetes Mellitus; eGFR: Estimated Glomerular Filtration Rate; MACE: Major Adverse Cardiac Event; MI: Myocardial Infarction; UACR: Urinary Albumin-to-Creatinine Ratio.