ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zynquista 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg sotagliflozin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Oval, blue, film-coated tablet printed with “2456” on one side in black ink (tablet length: 14.2 mm, tablet width: 8.7 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) $\geq$ 27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.

4.2 Posology and method of administration

Therapy with Zynquista should be initiated and supervised by a physician experienced in the management of type 1 diabetes mellitus.

Posology

The recommended dose is 200 mg sotagliflozin once daily before the first meal of the day. After at least three months, if additional glycaemic control is needed, in patients tolerating sotagliflozin 200 mg, the dose may be increased to 400 mg once daily.

Before initiating treatment with sotagliflozin 200 mg and before increasing dose to sotagliflozin 400 mg:

- Risk factors for diabetic ketoacidosis (DKA) should be assessed and ketone levels should be evaluated as normal. If ketones are elevated (blood beta-hydroxybutyrate (BHB) reading is greater than 0.6 mmol/L or urine ketones one plus (+)) treatment with sotagliflozin should not be initiated nor the dose should be increased to sotagliflozin 400 mg until the ketone levels are normal (see sections 4.4).
- It is recommended that patients obtain several baseline blood or urine ketone levels over one to two weeks prior to initiation of sotagliflozin therapy, and, patients should become familiar with how their behaviours and circumstances affect their ketone levels.

- Patients must be able to perform self-management of the day-to-day aspects of their disease including self-monitoring of glucose and ketones.
- Patients should be informed, in a dedicated education session, on the risk of DKA, how to recognize DKA risk factors, signs or symptoms, how and when to monitor ketone levels and what actions to take when ketone levels are elevated (see section 4.4).
- Correction of volume depletion prior to initiation of sotagliflozin is recommended in patients with this condition (see section 4.4).

Sotagliflozin must only be administered as an adjunct to insulin. In order to avoid hypoglycaemia with the first dose of sotagliflozin a 20% reduction in the first mealtime bolus insulin may be considered. Subsequent bolus doses should be adjusted individually based on blood glucose results. No reduction in basal insulin is recommended when initiating sotagliflozin. Subsequently, basal insulin should be adjusted based on blood glucose results. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.

Ketone monitoring during treatment:
During the initial one to two weeks of treatment with sotagliflozin, ketones should be monitored on a regular basis. After starting therapy, the frequency of ketone level testing (either blood or urine) should be individualized, according to the patient's lifestyle and/or risk factors (see section 4.4). Patients should be informed about what actions to take if ketone levels are elevated. The recommended actions are listed in Table 1. Measurement of blood ketone levels is preferred over urine.

Table 1: Actions to take in case of elevated ketone levels

Clinical stage	**Blood Ketone (beta-hydroxybutyrate)**	**Urine Ketone**	**Actions**
Ketonaemia or Ketonuria	0.6-1.5 mmol/L	Trace or Small +	The patient may need to take extra rapid-acting insulin and drink water. Extra carbohydrates should be taken if the glucose levels are normal or low. Ketone levels should be measured again after two hours. Check glucose levels frequently to avoid hyperglycaemia or hypoglycaemia. The patient should immediately seek medical advice and stop taking sotagliflozin if levels persist and symptoms present.
Impending DKA	> 1.5-3.0 mmol/L	Moderate ++	The patient should immediately seek medical advice and stop taking sotagliflozin. The patient may need to take extra rapid acting insulin and drink water. Extra carbohydrates should be taken if the glucose levels are normal or low. Ketone levels should be measured again after two hours. Check glucose levels frequently

			to avoid hyperglycaemia or hypoglycaemia.
Probable DKA	> 3.0 mmol/L	Large to very large +++ / ++++	The patient should go to emergency department without delay and stop taking sotagliflozin. The patient may need to take extra rapid-acting insulin and drink water. Extra carbohydrates should be taken if the glucose levels are normal or low.

Missed dose
If a dose is missed, it should be taken as soon as the patient remembers the missed dose. A double dose should not be taken on the same day.

Special populations

Elderly
No dosage adjustment is recommended based on age.
In patients 65 years and older, renal function and an increased risk for volume depletion should be taken into account (see sections 4.4 and 4.8). Due to the limited therapeutic experience in patients aged 75 years and older, initiation of sotagliflozin therapy is not recommended.

Renal impairment
Assessment of renal function is recommended prior to initiation of sotagliflozin and periodically thereafter (see section 4.4).

Initiation of sotagliflozin is not recommended when eGFR is less than 60 ml/min/1.73 m^2 and should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2 (see sections 4.4 and 4.8).

Sotagliflozin should not be used in patients with severe renal impairment, end stage renal disease (ESRD) or in patients on dialysis as it has not been studied in these patients (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is recommended in patients with mild hepatic impairment. Sotagliflozin is not recommended in patients with moderate and severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of sotagliflozin in children and adolescents has not yet been established. No data are available.

Method of administration

Oral use.
Sotagliflozin should be taken once daily before the first meal of the day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Diabetic ketoacidosis

Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased risk of DKA. In the clinical trials (pool of two 52-week placebo-controlled trials) of sotagliflozin, the incidence of diabetic ketoacidosis (DKA) was higher in the sotagliflozin treatment group compared with the placebo group (see section 4.8).

Before initiating sotagliflozin
Before starting treatment, patients should be evaluated with respect to DKA risk.
Sotagliflozin should not be initiated when patients are at a higher risk of DKA, such as:
- Patients with low insulin needs.
- Patient not on optimal insulin dose or who have recent issues with noncompliance or recurrent errors with insulin dosing and who are unlikely to maintain adequate insulin dosing.
- Patients with recent or recurrent history of DKA (e.g.1 episode in the past 3 months or more than 1 episode in the past 6 months).
- Patients with increased insulin requirements due to acute medical illness or surgery.
- Patients with elevated ketones levels (BHB reading is greater than 0.6 mmol/L or urine ketones one plus (+)). If ketones are elevated (BHB reading is greater than 0.6 mmol/L), treatment with sotagliflozin should not be started until the ketone levels are normal (see section 4.2).
- Patients unable or unwilling to monitor ketones.
- Patients who insist on maintaining caloric restriction, carbohydrate restriction or ketogenic diet or who chronically under-dose insulin (e.g. in order to remain in a lipolytic state).
- Patients with excessive alcohol consumption or who use illicit drugs.

Patients using an insulin infusion pump have a higher risk of DKA and should be experienced with pump use, common trouble-shooting strategies when interruptions of insulin delivery via pump occur (issues with insertion site, clogged tubing, empty reservoir, etc.) and use of supplemental insulin injections with pen or syringe as needed in case of pump failure. Patients should consider monitoring ketones levels three to four hours after changing pump materials. Patients using a pump should also check their ketone levels with any suspected insulin interruption, regardless of blood glucose levels. Insulin injections should be given within 2 hours of an unexplained high blood glucose value and sotagliflozin treatment should be interrupted. If ketones are high follow instructions given above in Table 1 (see section 4.2).

Sotagliflozin should only be given to patients:
- with access to ketone testing materials and immediate access to a clinician if blood or urine ketones are elevated.
- who are able to monitor ketone levels and are educated in when it is most appropriate to do so.

During a dedicated counselling session with the patient at the time of first prescription of sotagliflozin the Patient/Carer Guide and Patient Alert card, also available via the QRcode or website, should be presented. The Patient Alert Card is also provided in the product packaging.

The patient should be informed:
- how to recognize the risk factors which can predispose to ketosis and DKA (including, but not limited to, recent or recurrent history of DKA, missed or reduced insulin doses, decreased caloric intake or severe dehydration, vigorous exercise, intercurrent illness, surgery, alcohol abuse, and in patients using an insulin infusion pump, insulin infusion interruption),
- how to recognize DKA signs or symptoms, emphasizing that DKA could occur even when blood glucose levels are below 14 mmol/L (250 mg/dL),
- when to discontinue sotagliflozin therapy (see section 4.2),
- what actions to take when ketosis/DKA is suspected.

It is recommended that patients obtain several baseline blood or urine ketone levels over one to two weeks period prior to initiation of sotagliflozin therapy, and patients should become familiar with the behaviours/circumstances associated with elevated ketone levels and how to address them.

Management of DKA risk
The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. It is possible that adverse effects occurring with sotagliflozin may be similar to presenting symptoms of DKA. Patients should be assessed for ketoacidosis immediately if these symptoms occur, by measuring the urine or blood ketones, regardless of blood glucose level. DKA episodes during sotagliflozin use can be atypical, with patients not having blood sugar levels as high as expected. This atypical presentation of DKA (i.e. normal or slightly elevated blood glucose levels) can delay diagnosis and treatment.

During treatment with sotagliflozin
- The patient should remain on optimal insulin dosing.
- When needed to prevent hypoglycaemia, insulin dose reduction should be done cautiously to avoid ketosis and DKA (see section 4.2).
- Consider discontinuing sotagliflozin if adequate insulinisation cannot be achieved on treatment.

Treatment with sotagliflozin should be stopped in patients who are hospitalized for major surgical procedures or acute serious medical illnesses.

Ketone monitoring during treatment
After initiating sotagliflozin ketones should be monitored on a regular basis during the initial one to two weeks, then the frequency of ketone level testing should be individualised, according to the patient's lifestyle and/or risk factors. For all patients, it is recommended that ketones should be measured with changes to the normal routine, including reduced carbohydrate intake, intercurrent illness, reductions in total daily insulin dosing, physical activity and stress. Ketones should be measured repetitively when any signs or symptoms consistent with DKA or euglycaemic DKA are present. Measurement of blood ketone levels is preferred over urine.

Patients must be informed about what actions to take if ketone levels are elevated. The recommended actions are listed in Table 1 (see section 4.2).

Management of DKA
In patients where DKA is suspected or diagnosed, treatment with sotagliflozin should be discontinued immediately.

With sotagliflozin DKA may be present with low, normal or high blood glucose levels. DKA should be treated as per standard of care. Supplemental carbohydrate may be required based on glucose levels in addition to hydration and additional rapid acting insulin (see Table 1 in section 4.2).

Restarting sotagliflozin is not recommended, unless a cause for the ketoacidosis is identified and resolved (e.g., pump malfunction, acute intercurrent illness, excessive reduction of insulin).

<u>Renal impairment</u>

Renal function abnormalities (increased serum creatinine and decreased eGFR) can occur after initiating sotagliflozin (see section 4.8). Patients with hypovolemia may be more susceptible to these changes.

Sotagliflozin should not be initiated in patients with an eGFR < 60 mL/min and should be discontinued at eGFR persistently below 45 mL/min (see section 4.2 and 4.8).

Sotagliflozin should not be used in patients with severe renal impairment, end stage renal disease (ESRD) or in patients on dialysis as it has not been studied in these patients (see section 4.2).

Monitoring of renal function is recommended as follows:
- Prior to initiation of sotagliflozin and monitored periodically, at least yearly, thereafter (see section 4.2).
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.
- More frequent, at least 2 to 4 times per year, renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hepatic impairment

There is limited experience in clinical trials in patients with moderate and severe hepatic impairment. Sotagliflozin is not recommended in patients with moderate and severe hepatic impairment, as sotagliflozin exposure is increased in these patients (see sections 4.2 and 5.2).

Hypotension/ volume depletion

Based on the mode of action of sodium glucose co-transporter 2 (SGLT-2) inhibitors, by increasing urinary glucose excretion (UGE), sotagliflozin induces an osmotic diuresis which may reduce intravascular volume and decrease blood pressure (see sections 4.8 and 5.1). Sotagliflozin may cause intravascular volume contraction (see section 4.8). Symptomatic hypotension may occur after initiating sotagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating sotagliflozin, volume contraction should be assessed and volume status should be corrected if indicated. Patients should be monitored for signs and symptoms of hypotension after initiating therapy.

In case of conditions that may lead to fluid loss (e.g., gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving sotagliflozin. Temporary interruption of treatment with sotagliflozin should be considered until the fluid loss is corrected.

Genital mycotic infections

Consistent with the mechanism of SGLT2 inhibition with increased UGE, sotagliflozin increases the risk for genital mycotic infections as reported in clinical trials (see section 4.8).
Patients with a history of chronic or recurrent genital mycotic infections are more likely to develop genital mycotic infections. Patients should be monitored and treated as appropriate.

Urinary tract infections
Temporary interruption of sotagliflozin should be considered when treating pyelonephritis and urosepsis.

Elderly patients

Elderly may be at an increased risk of volume depletion (see section 4.2).

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking other SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotizing fasciitis. If Fournier's gangrene is suspected, sotagliflozin should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urine laboratory assessments

Due to its mechanism of action, patients taking sotagliflozin will test positive for glucose in their urine.

Drug/Laboratory test interference

Interference with 1,5-anhydroglucitol (1,5-AG) Assay
Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking medicinal products that inhibit SGLT2. Alternative methods should be used to monitor glycaemic control.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sotagliflozin
The coadministration of a multiple dosing regimen of rifampicin, an inducer of various UGT and CYP metabolizing enzymes, with a single dose of 400 mg sotagliflozin resulted in a decrease in the $AUC_{0\text{-}inf}$ (60%) and C_{max} (40%) of sotagliflozin. This decrease in exposure to sotagliflozin may decrease efficacy. If an enzyme inducer (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) must be co-administered with sotagliflozin, consider frequent monitoring of glucose level.

Interaction studies in healthy volunteers showed that metformin, metoprolol, midazolam, rosuvastatin and oral contraceptives had no clinically relevant effect on the pharmacokinetics of sotagliflozin.

Effects of sotagliflozin on other medicinal products
There is an increase in $AUC_{0\text{-}inf}$ and C_{max} of digoxin (27% and 52% respectively) when co-administered with sotagliflozin 400mg, due to inhibition of P-gp by sotagliflozin. Patients taking sotagliflozin with concomitant digoxin should be monitored appropriately.

An increase in total exposure and C_{max} of rosuvastatin of ca 1.2- and 1.4-fold, respectively, was demonstrated when co-administered with sotagliflozin and is not deemed clinically relevant. However, the mechanism behind the limited increase in exposure is not completely elucidated as sotagliflozin and M19 (sotagliflozin 3-O-glucuronide) are characterized as BCRP inhibitors in vitro and M19 also as an inhibitor OATP1B3 and OAT3. Rosuvastatin is a known OATP, BCRP and OAT3 substrate. It cannot be ruled out that sotagliflozin may interact with other sensitive OAT3, OATP- and/or BCRP-substrates (e.g.: fexofenadine, paclitaxel, bosentan, methotrexate, furosemide, benzylpenicillin) resulting in potentially larger increases of exposure than seen for rosuvastatin. It should be evaluated if additional safety monitoring is needed when using these substrates.

Based on in-vitro data, induction of CYP2C9, CYP2B6 and CYP1A2 cannot be ruled out. Substrates of these enzymes should be monitored for decreases in efficacy.

Interaction studies conducted in healthy volunteers show that sotagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, metoprolol, midazolam and oral contraceptives.

Insulin
Insulin may increase the risk of hypoglycaemia. A lower dose of insulin may be required to minimise the risk of hypoglycaemia when used in combination with sotagliflozin (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of sotagliflozin in pregnant women.
Animal studies have shown that sotagliflozin crosses the placenta.
Animal studies do not indicate direct or indirect harmful effects with respect to fertility and pregnancy (see section 5.3). Pharmacologically-related reversible renal changes were observed in a rat postnatal study, corresponding to the second and third trimesters of human pregnancy (see section 5.3).
Therefore, sotagliflozin is not recommended during the second and third trimesters of pregnancy.
As a precautionary measure, when pregnancy is detected, treatment with sotagliflozin should be discontinued.

Breast-feeding

No data in humans are available on excretion of sotagliflozin into milk.
Available toxicological data in animals have shown excretion of sotagliflozin into milk.
A risk to the newborns/infants cannot be excluded.
Sotagliflozin should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted for sotagliflozin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Sotagliflozin has no or negligible influence on the ability to drive and use machines.
However, patients should be alerted to the risk of hypoglycaemia as sotagliflozin is used in combination with insulin.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were genital mycotic infections, diabetic ketoacidosis and diarrhoea.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the pool of two 52-week placebo-controlled clinical trials described above. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 2: Tabulated list of adverse reactions

System Organ class	Frequency of occurrence		
	Very common	**Common**	**Uncommon**
Infections and infestations	Female genital mycotic infections*,a, †	Male genital mycotic infections*,b, † urinary tract infections*, †	
Metabolism and nutrition disorders		Diabetic ketoacidosis*, †	
Vascular disorders		Volume depletion*, c, †	
Gastrointestinal disorders		Diarrhoea, flatulence	
Renal and urinary disorders		Increased urination[d], blood creatinine increased/ glomerular filtration decreased†	
Investigations		Blood ketone body increased, serum lipids increased[e], haematocrit increased[f]	

* See section 4.4
† See subsections below for additional information.
[a] Adverse event grouping, including, but not limited to, vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, vulvovaginitis, urogenital infection fungal.
[b] Adverse event grouping, including, but not limited to, balanoposthitis, genital infections fungal, balanitis candida, epididymitis.
[c] Adverse events grouping, including dehydration, hypovolaemia, postural dizziness, orthostatic hypotension, hypotension, syncope and presyncope when reported in context of volume depletion.
[d]Adverse events grouping, including urine output increased, polydipsia, micturition urgency, nocturia, pollakiuria and polyuria
[e]Mean percent changes from baseline for sotagliflozin 200 mg and 400 mg versus placebo, respectively, were HDL-C 3.3% and 4.2% versus 0.5%; LDL-C 5.0% and 6.1% versus 3.3%; triglycerides 5.7% and 5.4% versus 2.7%.
[f]The proportion of subjects that met the criteria haematocrit >50% was higher in the sotagliflozin 200 mg and 400 mg groups (6.7% and 8.2%) compared to the placebo group (2.7%)

Description of selected adverse reactions

Diabetic ketoacidosis
In placebo-controlled clinical trials of sotagliflozin, patients were advised to monitor urine or blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was > 0.6 mmol/l. In the pooled 52-week data, the incidence of DKA was increased in a dose-dependent manner for sotagliflozin (2.9% and 3.8% for sotagliflozin 200 mg and 400 mg, respectively) compared to placebo (0.2%). The exposure-adjusted incidence rate was 3.12, 4.19 and 0.21 subjects per 100 patient-years for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo. Fifteen of the 35 cases (43%) experienced DKA with glucose values in the glycaemic range 8 to 14 mmol/L. In the broader pool, including all type 1 diabetes mellitus patients in phase 2 and 3 studies, the exposure-adjusted incidence rate was 3.07, 5.29 and 0.76 subjects per 100 patient-years for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo (see section 4.4).

Volume depletion
Sotagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. Adverse reactions related to volume depletion (e.g., hypovolemia, blood pressure decreased, blood pressure systolic decreased, dehydration, hypotension, orthostatic hypotension, and syncope) were reported by 2.7%, 1.1% and 1.0% of patients treated with sotagliflozin 200mg, sotagliflozin 400 mg and placebo. Sotagliflozin may increase the risk of hypotension in patients at risk for volume contraction (see section 4.4).

Genital mycotic infections
The incidence of female genital infections (e.g. vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis and vulvitis) was increased in the sotagliflozin 200 mg and 400 mg group (15% and 17%, respectively) as compared to placebo (4.7%). Most of the events were mild or moderate and no serious case was reported. Discontinuation due to genital mycotic infections occurred in 1.2%, 1.1% and 0.8% of patients treated with sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively.

The incidence of male genital infections (e.g. balanoposthitis, genital infection fungal) was increased for sotagliflozin 200 mg (3.0%), sotagliflozin 400 mg (6.3%) compared to placebo (1.1%). All events were mild or moderate in intensity and no serious cases. Discontinuation due to genital mycotic infections occurred in 0%, 0.4% and 0.4% of patients treated with sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively.

Urinary tract infections
The overall frequency of urinary tract infections reported were 7.1% and 5.5% for sotagliflozin 200 mg and sotagliflozin 400 mg compared to 6.1% for placebo. The incidence of UTI in female subjects was 12%, 7.0% and 11% and the incidence of UTI in male subjects was 2.3%, 4.0% and 1.8% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively. All UTI events were mild or moderate in intensity except for one severe case (male subject in the sotagliflozin 400 mg group). Two cases (2 cases of cystitis) were serious; both occurred in male subjects in the sotagliflozin 400 mg group.

Blood creatinine increased/Glomerular filtration decreased and renal-related events
Sotagliflozin was associated with decreases in mean eGFR at week 4 (-4.0% and -4.3% for sotagliflozin 200 mg and 400 mg) versus placebo (-1.3%) that were generally reversible during continuous treatment. Mean increases in serum creatinine from baseline to week 4 was 4.0%, 4.3% and 1.4% for sotagliflozin 200mg, sotagliflozin 400 mg and placebo, respectively. At week 24 and 52 the change from baseline in creatinine was equal to or less than 0.02 mg/dL for both sotagliflozin 200 and sotagliflozin 400 mg.

The incidence of renal-related events was low and similar across the groups (1.5%, 1.5% and 1.3% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo).

Table 3: Changes from baseline in serum creatinine and eGFR in the pool of two 52-week placebo-controlled studies

		Placebo (N=526)	**Sotagliflozin 200mg** (N=524)	**Sotagliflozin 400 mg** (N=525)
Mean baseline values	N	526	524	525
	Creatinine (mg/dL)	0.85	0.85	0.85
	eGFR (mL/min/1.73 m^2)	90.2	89.3	89.1
Mean change from baseline at week 4	N	511	502	505
	Creatinine (mg/dL)	0.01	0.03	0.04
	eGFR (mL/min/1.73 m^2)	-1.15	-3.57	-3.81
Mean change from baseline at week 24	N	481	479	477
	Creatinine (mg/dL)	0.01	0.02	0.02
	eGFR (mL/min/1.73 m^2)	-1.06	-1.79	-1.66
Mean change from baseline at week 52	N	374	392	380
	Creatinine (mg/dL)	0.01	0.02	0.01
	eGFR (mL/min/1.73 m^2)	-0.70	-2.14	-0.57

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Multiple doses of 800 mg once daily were administrated in healthy volunteers and these doses were well tolerated.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.
The removal of sotagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK06

Mechanism of action

Sotagliflozin is a dual inhibitor of sodium glucose cotransporter type 1 (SGLT1) and SGLT2. Local intestinal inhibition of SGLT1, the major transporter for glucose absorption, delays and reduces glucose absorption in the proximal intestine, resulting in a blunting and delay of postprandial hyperglycaemia. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, sotagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Pharmacodynamic effects

Urinary glucose excretion
In a 12-week dose ranging study, consistent with SGLT2 inhibition, 24-h placebo corrected change from baseline Urinary Glucose Excretion (UGE) increased by 57.7 grams ($p<0.001$) and 70.5 grams ($p<0.001$) in patients with type 1 diabetes taking 200 mg and 400 mg sotagliflozin respectively, which is consistent with SGLT2 inhibition.

Post prandial glucose reduction
In a 12 week dose ranging study, consistent with SGLT1 inhibition, placebo corrected change from baseline 2-hour post prandial glucose (PPG), measured after a standardised mixed meal, was reduced by 1.52 mmol/L ($p=0.15$) and 2.73 mmol/L ($p=0.006$) in patients taking 200 mg and 400 mg sotagliflozin respectively, which is consistent with SGLT1 inhibition.

Clinical efficacy and safety

The efficacy and safety of sotagliflozin in patients with type 1 diabetes not adequately controlled on their current insulin therapy was evaluated in three double-blind, placebo-controlled studies. In InTandem1 (study 1) and in InTandem2 (study 2) sotagliflozin was used as add on to optimised insulin and in InTandem3 (Study 3) sotagliflozin was used as add on to any existing insulin regimen in patients not on HbA1c goal.

Study 1 and study 2
On a background of optimised insulin, the efficacy and safety of sotagliflozin 200 mg or 400 mg once daily versus insulin alone were evaluated in two double-blind, placebo controlled studies (study 1 and 2) performed in 1575 patients with type 1 diabetes on insulin pump or multiple daily injection therapy. Each study was of 52 weeks duration, with primary and key secondary endpoints at 24 weeks. Beginning 6 weeks prior to randomization, insulin dose was adjusted (optimised) to achieve the following glycaemic goals fasting/preprandial, self-monitored blood glucose (SMBG) 4.4-7.2 mmol/L and 2-hour/peak postprandial SMBG glucose <10 mmol/L.
Patients were then maintained on optimised insulin and randomized to sotagliflozin 200 mg, sotagliflozin 400 mg or insulin alone. For the first meal on Day 1, patients were instructed to decrease their calculated (or usual) mealtime carbohydrate bolus insulin by 30%. Insulin optimisation was continued throughout the study.

In study 1, a total of 793 patients entered the study. The mean age of patients was 46 years, 8.1% were 65 years or older. Mean duration of diabetes was 24.4 years, 60% of patients were using insulin pump and 40% were using multiple daily injections. In the study 48% were male and 92% were White and 84% of randomised patients completed the study. The mean eGFR was 87 mL/min/1.73 m^2 and 5.7% of patients had eGFR between 45 and 60 mL/min/1.73 m^2. The mean BMI was 30 kg/m^2 and 23% of patients had SBP $\geq$ 130 mmHg. At screening the HbA1c was 8.21%, 8.26% and 8.20% for insulin, insulin+sotagliflozin 200 mg and insulin+sotagliflozin 400 mg.

In study 2, a total of 782 patients entered the study. The mean age of patients was 41 years, 4.2% were 65 years or older. Mean duration of diabetes was 18 years, 26% of patients were using insulin pump and 74% were using multiple daily injections. In the study 52% were male and 96.2% were White and 87% of randomised patients completed the study. The mean eGFR was 92 mL/min/1.73 m^2 and 3.3% had eGFR between 45 and 60 mL/min/1.73 m^2. The mean BMI was 28 kg/m^2 and 32% of patients had SBP $\geq$ 130 mmHg. At screening the HbA1c was 8.42%, 8.35% and 8.38% for insulin, insulin+sotagliflozin 200 mg and insulin+sotagliflozin 400 mg.

At week 24, treatment with 200 mg or 400 mg sotagliflozin provided statistically significant reductions in HbA1c (p-value <0.001) compared to insulin alone. Treatment with sotagliflozin also resulted in reduction in body weight and FPG compared with insulin alone (see Table 4).

Main results for insulin dose and Diabetes Treatment Satisfaction Questionnaire and Diabetes Distress Screening Scale are presented in Table 4.

Table 4: Results at 24-week trial with sotagliflozin in patients with type 1 diabetes mellitus inadequately controlled on insulin (Study 1 – Study 2)

	Study 1			Study 2		
	Insulin	**Insulin + sotagliflozin 200 mg**	**Insulin + sotagliflozin 400 mg**	**Insulin**	**Insulin + sotagliflozin 200 mg**	**Insulin + sotagliflozin 400 mg**
N	268	263	262	258	261	263
HbA1c (%)						
Baseline (after 6-week insulin optimisation), mean	7.54	7.61	7.56	7.79	7.74	7.71
At Week 24, mean	7.50	7.17	7.08	7.79	7.36	7.35
Change from baseline, LS mean	-0.07	-0.43	-0.48	-0.02	-0.39	-0.37
Difference from insulin alone, LS mean [95%CI]	N/A	-0.36 * [-0.45, -0.27]	-0.41 * [-0.50, -0.32]	N/A	-0.37* [-0.48, -0.25]	-0.35* [-0.47, -0.24]
HbA1c < 7.0% at week 24, n (%)	61 (22.8)	97 (36.9)	123(46.9)	39 (15.1)	87 (33.3)	89 (33.8)
Body Weight (kg)						
Baseline, mean	87.30	86.96	86.50	81.08	81.93	81.97
Change from baseline, LS mean	0.78	-1.57	-2.67	0.11	-1.88	-2.47
Difference from insulin alone, LS mean [95%CI]	N/A	-2.35 * [-2.85, -1.85]	-3.45 * [-3.95, -2.94]	N/A	-1.98 * [-2.53, -1.44]	-2.58 * [-3.12, -2.04]
Bolus insulin dose (units/day)						
Baseline, mean	31.72	30.27	30.75	32.08	31.12	31.89
% Change from baseline, LS mean	3.89	-1.80	-8.78	5.90	-7.04	-10.47
% Difference from insulin alone, adjusted mean [95%CI]	N/A	-5.70† [-12.82, 1.42]	-12.67 * [-19.79, -5.55]	N/A	-12.95* [-20.50, -5.38]	-16.37* [-23.90, -8.83]
Diabetes Treatment Satisfaction Questionnaire						
Baseline, mean	28.9	28.4	29.2	28.2	28.3	28.4
Difference from placebo, LS mean [95%CI]	N/A	2.5 [1.7, 3.3]	2.5 [1.8, 3.3]	N/A	2.0 [1.3, 2.7]	1.7 [1.0, 2.4]
Diabetes Distress Screening Scale						
Baseline score, mean	5.0	5.1	4.9	5.3	5.6	5.5
Difference	N/A	-0.7*	-0.8*	N/A	-0.3	-0.4

	Study 1			Study 2		
	Insulin	**Insulin + sotagliflozin 200 mg**	**Insulin + sotagliflozin 400 mg**	**Insulin**	**Insulin + sotagliflozin 200 mg**	**Insulin + sotagliflozin 400 mg**
from placebo, LS mean [95%CI]		[-0.9, -0.4]	[-1.0, -0.5]		[-0.6, -0.0]	[-0.7, -0.2]
Basal insulin dose (units/day)						
Baseline, mean	35.06	34.84	33.39	29.76	29.18	29.50
% Change from baseline, LS mean	3.77	-1.73	-5.35	1.66	-4.16	-3.01
% Difference from insulin alone, LS mean [95% CI]	N/A	-5.51* [-8.71, -2.30]	-9.12* [-12.32, -5.91]	N/A	-5.82 [-10.04, -1.59]	-4.67 [-8.88, -0.47]
N: all randomised and treated patients Post-Baseline LS means, LS mean differences, 95% CLs, and p-values for each individual study were obtained from accounting for missing data *p <0.001 † p 0.12 ‡ p=0.034						

No differences in HbA1c decrease could be detected across subgroups including age, gender, race, geographic region, baseline BMI, age at diagnosis, baseline HbA1c, eGFR, duration of disease and insulin delivery method.

In studies 1 and 2 combined, patient 24-week completion rates were 89.5% among insulin alone patients, and 91.4% and 90.7% among patients receiving 200 mg and 400 mg of sotagliflozin, respectively. The 52-week completion rates were 84.2%, 86.6%, and 85.3% respectively.

Efficacy over a 52-week period
At the end of 24 weeks the reduction in HbA1c was -0.36% and -0.38% and at 52 weeks it was -0.23% and -0.32% with sotagliflozin 200mg and 400 mg, respectively. The proportion of patients with A1C <7.0% at 24 weeks was 19.0% for placebo, 35.1% for sotagliflozin 200mg, 40.4% for sotagliflozin 400mg and at 52 weeks was 18.3%, 28.6% and 31.6% for placebo, sotagliflozin 200 mg and 400 mg respectively.
At the end of 52 weeks the reduction in body weight, mean daily bolus insulin dose, FPG were sustained compared to insulin alone.

CGM substudy: 2-hr PPG and time in range
From study 1 and study 2, 278 subjects participated in a blinded continuous glucose monitoring (CGM) sub-study (see Table 5).

Table 5: Results of CGM sub study at week 24 (Pooled data, study 1 and study 2)

Characteristic	Insulin	Insulin + sotagliflozin 200 mg	Insulin + sotagliflozin 400 mg
N	93	89	96
Percent Time in range 3.9-10.0 mmol/L			
Baseline (after 6-week insulin optimisation) , LS mean	52.30	52.19	50.66
Change from baseline, LS mean	-1.26	4.09	10.45
Difference from insulin alone, LS mean % (p-value)	N/A	5.35 (0.026)*	11.71 (<0.001) †
2-hour postprandial glucose following a standardized mixed meal, mmol/L			
Baseline (after 6-week insulin optimisation), mean	12.76	11.75	11.64
Change from baseline, LS mean	-0.44	-2.37	-2.71
Difference from insulin alone, LS mean (p-value)	N/A	-1.93 (0.004)	-2.27 (<0.001)

* 5.35% more time in range, correspond to 1.3 hours

† 11.71% more time in range, correspond to 2.8 hours

Study 3

InTandem 3 (study 3) was a 24-week duration study performed on a background of existing insulin regimen in type 1 diabetes patients with screening HbA1c ≥7.0% to ≤11.0%, to evaluate efficacy and safety of sotagliflozin 400 mg once daily versus insulin alone.

For the first meal on Day 1, patients were instructed to decrease their calculated (or usual) mealtime carbohydrate bolus insulin by 30%.

The mean age of patients was 43 years, 7.2% were 65 years or older. Mean duration of diabetes was 20 years, 39% of patients were using insulin pump and 61 % were using non-pump insulin therapy. In the study 50% were male and 88 % were White and 87% of randomised patients completed the study. The mean eGFR was 92 mL/min/1.73 m^2 and 5 % had eGFR between 45 and 60 mL/min/1.73 m^2. The mean BMI was 28 kg/m^2 and 29% had SBP ≥ 130 mmHg.

At week 24, treatment with 400 mg sotagliflozin before the first meal of the day resulted in statistically significant more patients achieving the net benefit primary endpoint (proportion of patients with HbA1c <7.0% at week 24 and no episode of severe hypoglycaemia, and no episode of DKA from randomisation to Week 24) compared with insulin alone (28.6% versus 15.2%) (p-value<0.001) and provided statistically significant mean reductions in HbA1c (p-value <0.001).

Treatment with sotagliflozin also resulted in reduction in body weight and bolus insulin dose compared with insulin alone (see Table 6). Treatment with sotagliflozin also resulted in reduction in body weight and systolic blood pressure (in patients with baselines SBP ≥130 mmHg) compared with insulin alone (see Table 6). Main results regarding insulin dose are presented in Table 6.

Table 6: Efficacy results of a 24 week placebo-controlled study of sotagliflozin as add-on to insulin therapy in patients not at HbA1c goal (Study 3):

Characteristic	Insulin	Insulin + sotagliflozin 400 mg
N	**703**	**699**
HbA1c (%)		
Baseline, LS mean	8.21	8.26
Change from baseline, mean	-0.33	-0.79
Difference from insulin alone, LS mean [95% CI]	N/A	- 0.46† [-0.54, -0.38]
HbA1c < 7.0% at week 24, n (%)	111 (15.8)	207 (29.6)
Body Weight (kg)		
Baseline, mean	81.55	82.40
Change from baseline, LS mean	0.77	-2.21
Difference from insulin alone, LS mean [95% CI]	N/A	- 2.98† [-3.31, -2.66]
Bolus insulin		
Baseline, mean in units	28.72	27.34
% change from baseline, LS mean	6.62	-5.71
% difference from insulin alone, LS mean	N/A	-12.32†
Basal insulin		
Baseline, mean in units/day	29.63	29.54
% change from baseline, LS mean	6.76	-3.11
% difference from insulin alone, LS mean	N/A	-9.88†
Systolic Blood Pressure in those with baseline SBP ≥ 130 mmHg*		
N	203	203
Baseline, mean in mmHg	139.9	140.5
Change from baseline, LS mean	-5.7	-9.2
Difference from insulin alone, adjusted mean [95% CI]	N/A	-3,5‡ [-5.7, -1.3]

*Systolic blood pressure was assessed at week 16
† p <0.001
‡ p=0.002

Hypoglycaemia
The incidence of severe hypoglycaemia and rates of documented hypoglycaemia (overall and nocturnal) were lower on sotagliflozin compared to insulin alone in the 52-week studies, as shown in Table 7.

Table 7: Incidence of severe hypoglycaemia and rates of documented, (overall and nocturnal) hypoglycaemic events in the pool of two 52-week placebo-controlled clinical studies

	Insulin (N=526)	**Insulin + sotagliflozin 200 mg (N=524)**	**Insulin + sotagliflozin 400 mg (N=525)**
Incidence of severe hypoglycaemia (%)*	7.4	5.7	4.4
Reduction in risk of severe hypoglycaemia compared to insulin alone (%)	-	24[a]	41[b]
Rate of documented hypoglycaemia† (events per patient year) at thresholds of ≤3.1 or ≤3.9 mmol/L	≤3.1 mmol/L: 19.0 ≤3.9 mmol/L: 95.6	≤3.1 mmol/L: 14.9 ≤3.9 mmol/L: 81.3	≤3.1 mmol/L: 15.0 ≤3.9 mmol/L: 83.7
Reduction in risk of documented hypoglycaemia, compared to insulin alone at threshold of ≤3.1 mmol/L (%)	-	21[c]	18[c]
Rate of nocturnal‡ documented hypoglycaemia† (events per patient year) at thresholds of ≤3.1 or ≤3.9 mmol/L	≤3.1 mmol/L: 2.7 ≤3.9 mmol/L: 12.2	≤3.1 mmol/L: 2.3 ≤3.9 mmol/L: 11.0	≤3.1 mmol/L: 2.3 ≤3.9 mmol/L: 11.1

* Defined as an event consistent with hypoglycaemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). All severe hypoglycaemia presented were positively adjudicated.
† Defined as a documented SMBG or laboratory blood glucose value below or equal to threshold of 3.1 or 3.9 mmol/L.
‡ Defined as event that occurred between 00:00 and 05:59 hours.
[a] p=0.28
[b] p=0.04
[c] p<0.01

In study 3 at 24 weeks incidences of severe hypoglycaemia were 2.4% and 3.0% on placebo and sotagliflozin 400 mg, respectively and the reduction in the rate of hypoglycaemic events at 24 weeks (blood glucose ≤3.1 mmol/L) for sotagliflozin 400 mg was 22% (p<0.001) compared to insulin alone.

Patients with renal impairment
In the 3 Phase 3 randomized clinical studies in patients with type 1 diabetes, patients with eGFR < 45 mL/min/1.73 m^2 were excluded, 79 patients exposed to sotagliflozin had an eGFR < 60 mL/min/1.73 m^2 and 841 patients had an eGFR ≥ 60 to ≤ 90 mL/min/1.73 m^2. The HbA1c reduction observed in patients with eGFR ≥60 to <90 mL/min/1.73 m^2 was comparable to the HbA1c reduction observed in patients with eGFR ≥90 mL/min/1.73 m^2. In patients with eGFR <60 mL/min/1.73 m^2 a numerical HbA1c reduction was observed. No overall differences in safety were observed with sotagliflozin treatment as compared to insulin alone in subjects with eGFR between 45 and 60 mL/min/1.73 m^2.

Fasting plasma glucose
In a pre-specified pooled analysis of study 1 and study 2, treatment with sotagliflozin as adjunct to insulin resulted in LS mean changes from baseline in FPG of -0.56 mmol/l for sotagliflozin 200 mg and -0.87 mmol/l for sotagliflozin 400 mg compared to insulin alone (0.32 mmol/l) at week 24.
In study 3 there was a significant reduction in FPG of 0.79 mmol/L (p<0.001) with sotagliflozin 400 mg at 24 weeks compared to insulin alone.

Blood pressure
In a pre-specified pooled analysis of study 1 and study 2, treatment with sotagliflozin as adjunct to insulin resulted in a reduction of SBP (-0.6 mmHg for placebo, -2.6 mmHg for sotagliflozin 200 mg and -4.1 mmHg for sotagliflozin 400 mg) at week 12. Pooled analysis of change in SBP in patients with baseline SBP ≥130 mmHg showed greater reduction in SBP at week 12 (-5.4 mmHg for placebo, -9.0 mmHg for sotagliflozin 200 mg and -10.7 mmHg for sotagliflozin 400 mg).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Zynquista in one or more subsets of the paediatric population in type 1 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of sotagliflozin has been characterized in healthy subjects and in diabetic patients. No clinically relevant differences were noted between the two populations.

Absorption

The median T_{max} ranged from 1.25 to 3 hours, over a single-dose range of 400 to 2000 mg. Following administration of multiple doses (400 and 800 mg dose), the median T_{max} values ranged from 2.5 to 4 hours.
The fraction of drug absorbed following administration of a single dose of [^{14}C]-sotagliflozin was estimated to be at least 71%, based on the detected percentage of dose of radioactivity in the urine and for the metabolites of sotagliflozin in the faeces.
When sotagliflozin tablets were administered with a high-caloric breakfast, plasma exposure to sotagliflozin as measured by C_{max} and $AUC_{0\ inf}$ was about 2.5- and 1.5-fold higher, respectively, compared to fasted condition.

Distribution

Both sotagliflozin and its major human metabolite 3-O-glucuronide (M19), exhibited high binding to human plasma proteins in vitro (fraction unbound approx. 2%) which was not dependent on the concentration of sotagliflozin and M19. In clinical studies the high protein binding was confirmed and was not influenced by reduced renal or hepatic function.
The apparent volume of distribution of sotagliflozin following administration of a single 400 mg oral dose of [^{14}C]-sotagliflozin was found to be very high with a mean value of 9392 L.

Biotransformation

In healthy subjects following the administration of a single dose of 400 mg [^{14}C]-sotagliflozin indicated that sotagliflozin was extensively metabolized predominantly to M19 which represented 94% of the radioactivity in plasma.
The primary route of metabolism of sotagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases primarly by UGT1A9, and to a much lesser extent by UGT1A1 and UGT2B7 as well as oxidation, by CYP3A4.
When sotagliflozin is incubated with UGT1A9, M19 was the main conjugate observed. No acyl glucuronides of sotagliflozin were identified.

In in vitro studies, sotagliflozin did not inhibit CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6, or 3A4.
Sotagliflozin and M19 have no significant potential to inhibit OCT1, OCT2, OAT1, OAT3, OATP1B1 and OATP1B3.
M19 is an inducer and inhibitor of CYP3A4 and an inhibitor of CYP2D6.
In vitro sotagliflozin was shown to have inhibitory effects on P-gp and breast cancer resistance protein (BCRP). M19 demonstrated inhibitory effects against OATP1B1/B3 and MRP2 in-vitro.

Elimination/excretion

Following the administration of a single dose of 400 mg [^{14}C]-sotagliflozin, showed 57% and 37% of the radioactivity were excreted in the urine and faeces, respectively. These results indicate that the main route of elimination of drug related material was renal.
The predominant metabolite detected in urine was M19, representing a mean of 33% of the administered radioactive dose. Unchanged [^{14}C]-sotagliflozin was the predominant radioactive peak detected in faecal extracts representing a mean of 23% of the total administered radioactive dose. In healthy volunteers, mean apparent total body clearance (CL/F) of sotagliflozin ranged from 261 to 374 L/hr. The CL/F estimated using a population PK, which mostly evaluated T1DM patients, was 239 L/hr. Mean terminal $T_{1/2}$ ranged from 21 to 35 hours for sotagliflozin and from 19 to 26 hours for M19.

Linearity/non-linearity

The PK of sotagliflozin appeared to be dose proportional in the therapeutic dose range of 200 mg to 400 mg QD.

Special populations

Renal impairment
Exposure of sotagliflozin was evaluated in a dedicated study of subjects with mild (creatinine clearance [CL_{cr}]: 60 to less than 90 mL/min) and moderate (CL_{cr}: 30 to less than 60 mL/min) renal impairment and with normal renal function. In subjects with renal impairment, exposure to sotagliflozin following a single dose of 400 mg was approximately 1.7 fold higher in subjects with mild and up to 2.7 fold higher in subjects with moderate renal impairment compared to subjects with normal renal function.
The apparent clearance of sotagliflozin decreases with decreasing renal function. A population PK model integrating data from renally impaired patients and healthy subjects estimated for subjects with CKD Stage II (eGFR ≥60 and <90 mL/min/1.73 m^2) and CKD Stage IIIa (eGFR ≥45 and <60 mL/min/1.73 m^2) that sotagliflozin exposures were 1.5 fold higher compared to subjects with normal renal function. For subjects with CKD Stage IIIb (eGFR ≥30 and <45 mL/min/1.73 m^2) and CKD Stage IV (eGFR ≥15 and <30 mL/min/1.73 m^2) sotagliflozin exposures were 1.95 and 2.25 fold higher compared to subjects with normal renal function.

Hepatic impairment
In a study with subjects with reduced hepatic function, AUC of sotagliflozin was not increased in mild (Child Pugh A) hepatic impaired subjects, but was increased by ~3 fold in moderate (Child Pugh B) and ~ 6 fold in severe (Child Pugh C) hepatic impaired subjects.
No dose adjustment is needed in patients with mild hepatic impairment.

Elderly
Based on a population PK analysis, age had no clinically meaningful effect on the pharmacokinetics of sotagliflozin.

Body weight
Based on a population PK analysis, sotagliflozin exposure was found to decrease with increased body weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful and therefore no dose adjustment is required based on weight.

Gender and race
Based on a population PK analysis gender and race had no clinically meaningful effect on the PK of sotagliflozin.

Paediatric patients
No data are available.

5.3 Preclinical safety data

In a rat carcinogenicity study, a statistically significant increase in thyroid follicular cell carcinoma was observed in males at 75 mg/kg/day, approx. 14 times the MRHD, the highest dose evaluated. In a repeat-dose study evaluating potential mechanisms responsible for the increase incidence of thyroid carcinoma observed in the rat carcinogenicity study, it was concluded that the increase was associated with a sotagliflozin-related increase in thyroid stimulating hormone (TSH). In the rat, TSH was considered the primary carcinogen with sotagliflozin functioning as a secondary carcinogen. These changes were not considered relevant for humans as TSH is not carcinogenic in humans.

Sotagliflozin was not mutagenic or clastogenic.

In a fertility study in rats, sotagliflozin had no effect on reproductive performance, fertility, and embryo/fetal viability.

In a juvenile toxicology study in rats, renal changes were observed when sotagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Exposure was approximately 5 times (males) and 11 times (females) the clinical exposure at the Maximum Recommended Human Dose (MRHD) and caused reversible renal tubular dilation.
In embryo-fetal development studies in rats and rabbits, sotagliflozin was orally administered at doses up to 350 mg/kg in rats and 200 mg/kg in rabbits. In the rat study, embryo-lethality, effects on fetal growth along with cardiovascular and skeletal abnormalities were observed at an exposure multiple of 158-times the human exposure at 400 mg/day. The adverse effects on embryo-fetal development at 350 mg/kg/day were associated with maternal toxicity (body weight loss/decreased body weight gain and decreased food consumption during gestation day (GD) 6 to 8). Exposure at the rat no-observed-effect level was 40-times the exposure at the MRHD. No developmental toxicity was observed at doses up to 200 mg/kg/day in the rabbit, which was up to 9-times the human exposure at the MRHD.

In a pre-/post-natal development study, no sotagliflozin-related adverse effects in pregnant and lactating females and offspring development were observed in rats
In a study evaluating the potential effects of sotagliflozin on the development of juvenile rats, no sotagliflozin-related toxicity was observed following the administration of oral doses up to approximately 18 and 31 fold that of the MRHD (400 mg/day) for males and females, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460i)
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate
Talc

Film-coating

Poly(vinyl alcohol)
Macrogol
Titanium dioxide (E171)

Talc
Indigo carmine aluminium lake (E132).

Printing ink

Shellac
Iron oxide black (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium opaque blisters.
Pack sizes of 10, 20, 30, 60, 90, 100, 180 film-coated tablets, and a multipack of 200 film-coated tablets (2 packs of 100 film-coated tablets).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F - 75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

Zynquista 200 mg film coated tablets:
EU/1/19/1363/001 10 film coated tablets
EU/1/19/1363/002 20 film coated tablets
EU/1/19/1363/003 30 film coated tablets
EU/1/19/1363/004 60 film coated tablets
EU/1/19/1363/005 90 film coated tablets
EU/1/19/1363/006 100 film coated tablets
EU/1/19/1363/007 180 film coated tablets
EU/1/19/1363/008 200 (2x100) film coated tablets (multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD Month YYYY}

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Sanofi Winthrop Industrie
1 rue de la Vierge
Ambares et Lagrave
33565 Carbon Blanc Cedex
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Zynquista (sotagliflozin), as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) $\geq$ 27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy, in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of educational materials for sotagliflozin, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.
The educational materials are aimed at providing guidance on how to manage risk of diabetic ketoacidosis (DKA) in patients with type 1 diabetes.

The MAH shall ensure that in each Member State where sotagliflozin is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use the product have access to:

- Guide for Health Care Professionals including a prescriber's checklist
- Patient's/Carer's Guide
- Patient Alert Card

The guide for healthcare professionals including the prescriber's checklist should contain the following key elements:

- Sotagliflozin is not a substitute for insulin (and does not alter insulin-sensitivity).
- The risk of DKA is increased with sotagliflozin treatment.
- If treated with sotagliflozin, glucose levels will not adequately reflect insulin needs, and DKA may occur in patients treated with sotagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl). Therefore, glucose monitoring must be supplemented by ketone monitoring.
- Patients with euglycaemic DKA may need glucose in addition to standard of care for DKA and sotagliflozin should be discontinued if DKA occurs.
- Guidance to the physician for assessing whether the patient is eligible for sotagliflozin prescription, e.g. patient selection criteria including adherence to insulin treatment and insulin thresholds, patient's beta-hydroxybutyrate (BHB) < 0.6 mmol/L or urine ketones < 1+, BMI ≥ 27 kg/m^2, absence of DKA risk factors.
- Guidance to the physician for assessing whether the patient is prepared and engaged to perform self-ketone testing before and during therapy.
- Summary of the recommendations for patients, particularly regarding blood ketone measurement and managing sick days.
- For pump users: restrict sotagliflozin prescription to patients experienced in pump use, common trouble-shooting strategies when interruptions of insulin delivery via pump occur in case of pump failure.
- Counsel the patient and evaluate their adherence to ketone monitoring while establishing their baseline ketone level 1 to 2 weeks before treatment initiation and ensure the patient
  - Has received education/training in ketone testing and interpreting/acting upon test results.
  - Is willing/able to perform ketone testing as prescribed.
  - Is adequately informed about managing sick days.
- Ensure the patient is on optimal insulin therapy prior to initiation of sotagliflozin treatment.
- Sotagliflozin treatment should be temporarily stopped before surgical procedures or in case of hospitalisation for acute serious illness.
- If addition of sotagliflozin leads to marked reduction of insulin need, discontinuation of sotagliflozin should be considered to avoid high risk of DKA.

The patient's/carer's guide should contain the following key elements:

- Sotagliflozin is not a substitute for insulin.
- DKA may occur in patients treated with sotagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl), i.e. an explanation of the concept of euglycaemic DKA.
- Signs/symptoms of DKA - if not adequately managed DKA can be severe and fatal.
- How to measure ketones, how to interpret the results and what to do in case of hyperketonaemia/DKA (contact HCP immediately if BHB > 0.6 mmol/L with symptoms or if BHB > 1.5 mmol/L with or without symptoms).
- Insulin dose reduction during treatment should only be done when needed to prevent hypoglycaemia and should be done cautiously to avoid ketosis and DKA.
- Do not start caloric restriction or carbohydrate restriction while treated with sotagliflozin.

The patient alert card should contain the following key elements:

- The patient alert card should be presented to any HCP consulted.

- DKA may occur in patients treated with sotagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl).
- Signs/symptoms of DKA.
- Patients with euglycaemic DKA should receive glucose, insulin and fluids for DKA, sotagliflozin should be discontinued.
- Sotagliflozin should be temporarily stopped before surgical procedures or hospitalisation for acute serious illness.
- Contact details of the sotagliflozin 'prescriber' and 'Name of patient'.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional PASS: In order to estimate the incidence of DKA in T1DM sotagliflozin treated patients to assess the effectiveness of the risk minimisation measures implemented in Europe, the MAH should conduct and submit the results from an observational cohort study using existing data sources in European countries where sotagliflozin will be launched for T1DM.	31/12/2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON with blue box

1. NAME OF THE MEDICINAL PRODUCT

Zynquista 200 mg film-coated tablets
sotagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg sotagliflozin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
10 film-coated tablets
20 film-coated tablets
30 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[‘QR code to be included’ + <www.qr-zynquista.sanofi.eu>*]*

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F - 75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1363/001 (200 mg – 10 film coated tablets)
EU/1/19/1363/002 (200 mg – 20 film coated tablets)
EU/1/19/1363/003 (200 mg – 30 film coated tablets)
EU/1/19/1363/004 (200 mg – 60 film coated tablets)
EU/1/19/1363/005 (200 mg – 90 film coated tablets)
EU/1/19/1363/006 (200 mg – 100 film coated tablets)
EU/1/19/1363/007 (200 mg – 180 film coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zynquista

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON multipack (with Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Zynquista 200 mg film-coated tablets
sotagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg sotagliflozin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
Multipack: 200 (2 packs of 100) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[‘QR code to be included’ + <www.qr-zynquista.sanofi.eu>*]*

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1363/008 200 film-coated tablets (2 packs of 100)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zynquista

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON without Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Zynquista 200 mg film-coated tablets
sotagliflozin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg sotagliflozin.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 film-coated tablets
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

['QR code to be included' + <www.qr-zynquista.sanofi.eu>*]*

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F - 75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1363/008 (200 mg – 2 packs of 100 film coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zynquista

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zynquista 200 mg tablets
sotagliflozin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Patient Alert Card

Patient Alert Card
This card contains important safety information about diabetic ketoacidosis (DKA)
▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get: [To be adjusted per Country (include phone number…)]

Information for the patient:
Please carry this card with you at all times and show it to any healthcare professional (HCP) consulted in order to inform them about your current treatment with ZYNQUISTA.

Please consult the Patient/Carer's Guide for more information discussed with your doctor about taking Zynquista and the risk of DKA. Read the Zynquista package leaflet for full information and instructions for use.

Information for healthcare professionals:
This patient is using ZYNQUISTA for the treatment of Type 1 Diabetes Mellitus (T1DM). This treatment is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with T1DM with a BMI ≥27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.

- ZYNQUISTA increases the risk of DKA. DKA may occur in patients treated with Zynquista even if blood glucose levels are below 14 mmol/l (250 mg/dl). This atypical presentation of DKA can delay diagnosis and treatment.
- For patients taking ZYNQUISTA, glucose is not a reliable marker for DKA and must be supplemented with ketone monitoring
- Signs and symptoms of DKA include:
  - nausea, vomiting, or abdominal pain
  - anorexia
  - excessive thirst
  - unusual fatigue or sleepiness
  - difficulty breathing
  - confusion
- Hold Zynquista immediately if patient's BHB level is > 0.6 mmol/L (1+ urine ketone) with symptoms or if BHB > 1.5 mmol/L (2+ urine ketone) with or without symptoms.
- Patients with euglycaemic DKA should receive glucose, insulin and fluids for DKA management, sotagliflozin should be discontinued.
- ZYNQUISTA should be temporarily stopped before surgical procedures or hospitalisation for acute serious illness.

Patient name:----------
Date ZYNQUISTA first prescribed:----------
Center name:----------
Treating HCP name:----------
Treating HCP contact number:----------

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zynquista 200 mg film-coated tablets
sotagliflozin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zynquista is and what it is used for

Zynquista contains the active substance sotagliflozin, a medicine which lowers blood glucose (blood sugar) levels. Sotagliflozin works by slowing and reducing the absorption of glucose from food, and by increasing the amount of glucose that is passed out in urine. Together these actions help to lower the increased amount of glucose in the blood that occurs in patients with diabetes.

Zynquista is used as an addition to insulin treatment in adults with type 1 diabetes with a body mass index (BMI) greater than or equal to 27. BMI is a measure of your weight in relation to your height.Type 1 diabetes is a disease where your body's immune system destroys the insulin-producing cells in the pancreas and the body produces little to no insulin, the hormone that normally controls the level of your blood sugar.

It is important that you also continue with your diet and exercise plan and insulin treatment as agreed with your doctor, pharmacist or nurse.

2. What you need to know before you take Zynquista

Do not take Zynquista:
- if you are allergic to sotagliflozin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Diabetic ketoacidosis (DKA) is a potentially life-threatening problem you can get with diabetes because of increased levels of "ketone bodies" in your urine or blood, seen in tests. If you develop symptoms contact your doctor or go to the nearest hospital right away.

The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, drug abuse, dehydration, sudden reductions in insulin dose, or a higher need for insulin due to major surgery, serious illness or infection. See also section 4.
In addition to this leaflet, a patient alert card is included in the packaging which contains important safety information that you need before and during treatment with Zynquista. Your doctor will schedule a dedicated education session, to discuss the risk of DKA, how to recognize DKA risk factors, signs or symptoms, how and when to monitor ketone levels and what actions to take when ketone levels are elevated.

Talk to your doctor, pharmacist or nurse before taking Zynquista, and during treatment:
- if you have the following symptoms, which may be a sign of a serious condition, diabetic ketoacidosis **(see also section 4)**:
  - nausea, vomiting, or abdominal pain
  - excessive thirst
  - constantly feeling tired
  - high levels of ketones in urine tests or beta-hydroxybutyrate (BHB) in blood tests
  - difficulty breathing/rapid, deep breathing
  - breath with fruity odour
  - difficulty paying attention, or confusion
  - rapid weight loss
- if you have an acute medical illness or surgery
- if you have no access to ketone testing materials or no immediate access to a doctor if blood or urine ketones are elevated
- if you are using a low dose of insulin
- if you are on caloric restriction, carbohydrate restriction or ketogenic diet
- if you had a recent or recurrent history of diabetic ketoacidosis (e.g. 1 episode in the past 3 months or more than 1 episode in the past 6 months)
- if you have kidney problems
- if you have liver problems
- if you have an infection of the kidney or the urinary tract. Your doctor may ask you to stop taking Zynquista until you have recovered
- if you have a history of chronic or recurrent yeast infections of the genitals (thrush)
- if you might be at risk of dehydration (for example, if you are taking medicines that increase urine production [diuretics] or lower blood pressure or if you are over 65 years old). Ask about ways to prevent dehydration.
- if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotizing fasciitis of the perineum or Fournier's gangrene which destroys the tissue under the skin. Fournier´s gangrene has to be treated immediately.

Foot care
For all patients with diabetes it is important to check your feet regularly and follow any other advice on foot care from your doctor or nurse.

Urine glucose
Because of how Zynquista works, your urine will test positive for sugar while you are on this medicine.

Children and adolescents
Zynquista is not recommended for children and adolescents under 18 years of age, because it has not been studied in these patients.

Other medicines and Zynquista
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking any of the following medicines:
- digoxin or digitoxin (medicines used for heart problems). The level of digoxin or digitoxin in your blood may need to be checked if you take these medicines with Zynquista.
- phenytoin or phenobarbital (epilepsy medicines used to control fits)
- ritonavir (a medicine used to treat HIV infection)
- rifampicin (an antibiotic used to treat tuberculosis and some other infections).

As sotagliflozin is taken together with insulin, hypoglycaemia may occur during treatment.
Your doctor may reduce the dose of insulin.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Talk to your doctor about the best way to control your blood sugar while you are pregnant. Zynquista should not be used during the last six months of pregnancy.

Talk to your doctor before taking this medicine if you would like to breast-feed or if you are breast-feeding. It is not known if this medicine passes into breast milk. You should not take this medicine if you are breast-feeding.

Driving and using machines
Zynquista is not likely to affect your ability to drive and use machines. However, Zynquista is taken with insulin, which can cause your blood sugar levels to fall too low (hypoglycaemia) resulting in symptoms such as shaking, sweating and change in vision, and this may affect your ability to drive and use machines. Do not drive or use any tools or machines, if you feel dizzy during diabetes treatment.

3. How to take Zynquista

Always take this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
The recommended dose of Zynquista is one 200-mg tablet once a day before the first meal of the day.
Your doctor will decide whether to increase your dose to 400 mg once a day.
Your doctor will prescribe the dose that is right for you. Do not change your dose unless your doctor has told you to.

Taking this medicine
- Zynquista should be taken once daily by mouth.
- The tablet should be taken before the first meal of the day
- Follow your doctor’s instructions about insulin dose while taking Zynquista.

Your doctor will prescribe Zynquista together with insulin treatment to lower the amount of sugar in your blood. Follow your doctor’s instructions on taking these other medicine(s) to achieve the best results for your health.

If you take more Zynquista than you should
If you take more Zynquista tablets than you should, talk to a doctor or go to a hospital immediately. Take the medicine pack with you.

If you forget to take Zynquista
If a dose is missed, it should be taken as soon as you remember the missed dose.
Do not take a double dose of Zynquista o make up the forgotten dose.

If you stop taking Zynquista

Do not stop taking Zynquista without first checking with your doctor. Your blood sugar levels may increase when you stop taking Zynquista.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:

Diabetic ketoacidosis (DKA), seen commonly (may affect up to 1 in 100 people)
These are the signs and symptoms of diabetic ketoacidosis (see also section 2 under '**Warnings and precautions**'):
- nausea, vomiting, or abdominal pain
- excessive thirst
- constantly feeling tired
- high levels of ketones in urine tests or beta-hydroxybutyrate (BHB) in blood tests
- difficulty breathing/rapid, deep breathing
- breath with fruity odour
- difficulty paying attention, or confusion
- rapid weight loss.

While treated with Zynquista the risk of DKA is increased and may occur with low, normal or high blood glucose level. Check your ketones regularly during the first two weeks after starting Zynquista. If you have any of these symptoms, or if you are in a situation that could increase your risk for DKA, you must check your ketones, either in the blood or in the urine. If you are using an insulin pump, monitor your ketones levels three to four hours after changing pump materials.
In case of a potential DKA or elevated ketone levels are elevated contact your doctor immediately or go to the nearest hospital right away. The doctor may decide to temporarily stop the treatment with Zynquista.
During a dedicated session your doctor may schedule, discuss how to manage elevated ketone levels to prevent DKA (see section 2).

Make sure you carry the Patient Alert Card, that was given to you by your physician and that is also enclosed in the product packaging, with you at all times. Share it with all of your doctors, nurses or pharmacists when you need any treatment. You can also get the Patient Alert Card by scanning the QR code or by visiting the website below:

['*QR code to be included*' www.qr-zynquista.sanofi.eu*]*

Other side effects:
Very common (may affect more than 1 in 10 people)
- yeast infection (thrush) of the vagina (signs may include irritation, itching, unusual discharge or odour)

Common (may affect more than 1 in 100 people)
- diarrhoea
- raised ketone levels in your blood
- yeast infection (thrush) of the penis (signs may include irritation, itching, unusual discharge or odour)
- passing more urine than usual or needing to pass it more often
- urinary tract infection, signs include burning sensation when passing urine, urine that appears cloudy, pain in the pelvis, or mid back pain (when kidneys are infected)
- dehydration (losing too much water from your body, symptoms include dry mouth, feeling dizzy, light-headed, or weak, especially when you stand up, fainting)

- flatulence
- blood tests may show increase in the amount of bad cholesterol (called LDL - a type of fat in your blood)
- blood tests may show increase in the amount of red blood cells in your blood (called haematocrit)
- blood tests may show increase related to kidney function (such as 'creatinine').

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zynquista

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after "EXP".
The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the packaging is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer used. These measures will help protect the environment.

6. Contents of the pack and other information

What Zynquista contains
- The active substance is sotagliflozin.

Each tablet contains 200 mg sotagliflozin.
- The other ingredients are:
  - tablet core: microcrystalline cellulose (E460i), croscarmellose sodium, colloidal anhydrous silica; magnesium stearate; talc.
  - film-coating: poly(vinyl alcohol); macrogol; titanium dioxide (E 171); talc; indigo carmine aluminium lake (E132).
  - Printing ink: shellac; iron oxide black (E172); propylene glycol.

What Zynquista looks like and contents of the pack

Zynquista 200 mg film-coated tablets (tablets) are oval, blue, with "2456" on one side printed in black ink (tablet length: 14.2 mm, tablet width: 8.7 mm)..
Zynquista is available in PVC/PCTFE/Aluminium opaque blisters.
Pack sizes of 10, 20, 30, 60, 90, 100, 180 film-coated tablets, and a multipack of 200 film-coated tablets (2 packs of 100 film-coated tablets).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
sanofi-aventis groupe
54, rue La Boétie
F - 75008 Paris
France

Manufacturer :

Sanofi Winthrop Industrie
1, rue de la Vierge
Ambarès et Lagrave
F – 33565 Carbon Blanc
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
UAB "SANOFI-AVENTIS LIETUVA"
Tel: +370 5 2755224

България
SANOFI BULGARIA EOOD
Тел.: +359 (0)2 970 53 00

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi Denmark A/S
Tlf: +45 45 16 70 00

Malta
Sanofi Malta Ltd.
Tel: +356 21493022

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel.: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
sanofi-aventis Netherlands B.V.
Tel: +31 (0)20 245 4000

Eesti
sanofi-aventis Estonia OÜ
Tel: +372 627 34 88

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger : +33 1 57 63 23 23

Portugal
Sanofi - Produtos Farmacêuticos, Lda
Tel: +351 21 35 89 400

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: 800 536389

Κύπρος
sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0) 845 372 7101

This leaflet was last revised in.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/