AUSTRALIAN PRODUCT INFORMATION

XIGDUO® XR

(dapagliflozin propanediol monohydrate/metformin hydrochloride) Tablets

1 NAME OF THE MEDICINE

XIGDUO XR (dapagliflozin propanediol monohydrate/metformin hydrochloride) modified release tablets contain two oral antihyperglycaemic drugs used in the management of type 2 diabetes: dapagliflozin propanediol monohydrate and metformin hydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dapagliflozin

Dapagliflozin drug substance is a white to off-white powder, is non-hygroscopic, crystalline. Dapagliflozin is non-ionisable; thus, its aqueous solubility and partition coefficient are not affected by changes in pH. Dapagliflozin is a Biopharmaceutical Classification System (BCS) Class III drug.

Metformin hydrochloride

Metformin hydrochloride is a white to off-white crystalline compound. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

XIGDUO XR

XIGDUO XR is available for oral administration as tablets containing the following active ingredients:

- XIGDUO XR 10/500: 10 mg dapagliflozin (as dapagliflozin propanediol monohydrate) and 500 mg metformin hydrochloride.
- XIGDUO XR 10/1000: 10 mg dapagliflozin (as dapagliflozin propanediol monohydrate) and 1000 mg metformin hydrochloride.
- XIGDUO XR 5/1000: 5 mg dapagliflozin (as dapagliflozin propanediol monohydrate) and 1000 mg metformin hydrochloride.

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

- XIGDUO XR 10/500 (dapagliflozin 10 mg /metformin HCl extended release 500 mg) tablets are pink biconvex, capsule-shaped, film-coated tablet with "1072" and "10/500" debossed on one side and plain on the reverse side.

- XIGDUO XR 10/1000 (dapagliflozin10 mg /metformin HCl extended-release 1000 mg) tablets are yellow to dark yellow, biconvex, oval-shaped, film-coated tablet with "1073" and "10/1000" debossed on one side and plain on the reverse side.
- XIGDUO XR 5/1000 (dapagliflozin 5 mg /metformin HCl extended-release 1000 mg) tablets are pink to dark pink, biconvex, oval-shaped, film-coated tablet with "1071" and "5/1000" debossed on one side and plain on the reverse side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Glycaemic control

XIGDUO XR is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control when treatment with both dapagliflozin and metformin is appropriate

Prevention of hospitalisation for heart failure

XIGDUO XR is indicated in adults with type 2 diabetes mellitus and established cardiovascular disease or risk factors for cardiovascular disease to reduce the risk of hospitalization for heart failure

(see section 5.1 Pharmacodynamic properties – Clinical trials and 4.4 Special warnings and precautions for use for available data on the combination therapy).

4.2 DOSE AND METHOD OF ADMINISTRATION

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment, other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per day.

The dosage of antihyperglycaemic therapy with XIGDUO XR should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of dapagliflozin 10 mg and metformin extended-release 2000 mg.

XIGDUO XR should generally be administered once daily with the evening meal. The following tablet strengths are available:

XIGDUO XR 10/500 (dapagliflozin 10 mg/metformin HCl extended-release 500 mg)

XIGDUO XR 10/1000 (dapagliflozin 10 mg/metformin HCl extended-release 1000 mg)

XIGDUO XR 5/1000 (dapagliflozin 5 mg/metformin HCl extended-release 1000 mg)

Initial therapy

If therapy with a combination tablet containing dapagliflozin and metformin is considered appropriate, the recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin extended-release is 500 mg once daily, which can be titrated to

2000 mg once daily. The maximum dose of XIGDUO XR is dapagliflozin 10 mg/metformin extended-release 2000 mg taken as two 5 mg/1000 mg tablets once daily.

Add on combination therapy

In patients treated with metformin, the dose of XIGDUO XR should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose. Following a switch from metformin immediate-release to metformin extended-release, glycaemic control should be monitored closely and dosage adjustments made accordingly.

When dapagliflozin is used as an add-on therapy with insulin or an insulin secretagogue, a lower dose of insulin or an insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

No studies have been performed specifically examining the safety and efficacy of XIGDUO XR in patients previously treated with other antihyperglycaemic agents and switched to XIGDUO XR. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycaemic control can occur.

If no adequate strength of XIGDUO XR is available, individual mono-components should be used instead of the fixed dose combination.

Patients should be informed that XIGDUO XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of XIGDUO XR will be eliminated in the faeces as a soft, hydrated mass that may resemble the original tablet.

Renal Impairment

Assess renal function prior to initiation of XIGDUO XR and periodically thereafter (see sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Factors that may increase the risk of lactic acidosis (see section 4.4 Special Warnings and precautions for use) should be reviewed before considering initiation of metformin in patients with eGFR < 60 mL/min/1.73 m^2.

Mild renal impairment

No dose adjustment of XIGDUO XR is required for patients with mild renal impairment (estimated glomerular filtration [eGFR] 60-89 mL/min/1.73 m^2 by Modified Diet in Renal Disease [MDRD] eGFR equation).

Moderate renal impairment

No dose adjustment is required for patients with eGFR ≥ 45 mL/min/1.73 m^2 .XIGDUO XR is contraindicated in patients with eGFR persistently below 45 mL/min/1.73 m^2). (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).).

Severe renal impairment

XIGDUO XR is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see section 4.3 Contraindications).

Table 1 Dosage in patients with renal impairment

eGFR mL/min/ 1.73 m^2 *	Metformin XR	Dapagliflozin
60-89	Maximum daily dose is 2000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum total daily dose is 10mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum total daily dose is 10mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Dapagliflozin is contraindicated when eGFR is persistently below 45.
<30	Metformin is contraindicated	Dapagliflozin is contraindicated.

*GFR was originally used to establish these dosing categories based on renal function, all values were normalized to an average surface area (size) of 1.73m^2. As eGFR is considered a reasonable estimate of GFR and is more widely used in clinical practice, treatment recommendations in this prescribing information are based on eGFR.

Hepatic Impairment

Since impaired hepatic function has been associated with some cases of lactic acidosis in patients taking metformin, XIGDUO XR should not be used in patients with clinical or laboratory evidence of hepatic impairment. (See section 4.4 Special warnings and precautions for use - Use in hepatic impairment).

Paediatric and Adolescent

Safety and effectiveness of XIGDUO XR in paediatric and adolescent patients have not been established.

Use in the Elderly

Because metformin is eliminated by the kidney, and because elderly patients are more likely to have decreased renal function, XIGDUO XR should be used with caution as age increases.

4.3 CONTRAINDICATIONS

XIGDUO XR is contraindicated in patients with:

- Patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients.
- Metabolic acidosis: Acute or chronic metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- diabetic pre-coma

- eGFR persistently < 45 mL/min/1.73m^2 (See section 4.4 Special warnings and precautions for use)
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, or intravascular administration of iodinated contrast agents (See section 4.4 Special warnings and precautions for use)
- acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, pulmonary embolism, recent myocardial infarction, shock, acute significant blood loss, sepsis, gangrene, pancreatitis
- during or immediately following surgery where insulin is essential, elective major surgery
- hepatic impairment
- acute alcohol intoxication, alcoholism
- lactation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

XIGDUO XR should not be used in patients with type 1 diabetes mellitus (see section 4.1 Therapeutic Indications) or for the treatment of diabetic ketoacidosis (see section 4.4 Special Warnings and Precautions for Use – Ketoacidosis).

Lactic acidosis

Metformin hydrochloride

Lactic acidosis is a very rare, but serious and potentially fatal in the absence of prompt treatment, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in patients with diabetes with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, dehydration, any acute conditions associated with hypoxia or impacting renal function, (see section 4.4 special warning and precautions for use).

Medicinal products that can acutely impair renal function, such as antihypertensives, diuretics and nonsteroidal anti-inflammatory drug (NSAIDs), should be initiated with caution in metformin-treated patients.

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterized by symptoms such as acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. Lactic acidosis is a medical emergency that must be treated in a hospital setting. If lactic acidosis is suspected, treatment with XIGDUO XR should be discontinued and the patient hospitalized immediately.

Patients with known or suspected mitochondrial diseases

Metformin hydrochloride

In patients with known mitochondrial diseases such as Mitochondrial Encephalomyopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternally Inherited Diabetes and Deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Use in renal impairment

Dapagliflozin increases serum creatinine and decreases eGFR (see 4.8 Adverse effects (Undesirable effects)). Renal function abnormalities can occur after initiating dapagliflozin. Patients with hypovolaemia may be more susceptible to these changes.

There have been postmarketing reports of acute kidney injury, some requiring hospitalisation and dialysis, in patients receiving SGLT2 inhibitors, including dapagliflozin; some reports involved patients younger than 65 years of age.

XIGDUO XR should not be used for the treatment of diabetes in patients with eGFR persistently below 45 mL/min/1.73 m^2 as the glycaemic efficacy of dapagliflozin is dependent on renal function (see section 4.2 Dosage and method of administration).

Dapagliflozin has not been studied in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2 by MDRD) or end stage renal disease (ESRD). Based on the mechanism of action, dapagliflozin was not anticipated to be effective in these populations.

Metformin is excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function,

Monitoring of renal function is recommended as follows:

- prior to initiation of XIGDUO XR and at least yearly thereafter;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter;
- for renal function approachingeGFR 45 mL/min/1.73 m^2 and in elderly patients, at least 2 to 4 times per year. If renal function falls persistently eGFR < 45mL/min/1.73 m^2, treatment with XIGDUO XR should be discontinued

Change in clinical status of patients with previously controlled type 2 diabetes

A patient with type 2 diabetes previously well controlled on XIGDUO XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH,

lactate, pyruvate, and metformin levels. If acidosis of either form occurs, XIGDUO XR must be stopped immediately and other appropriate corrective measures initiated.

Use in hepatic impairment

Dapagliflozin

There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment. Dapagliflozin should not be used in patients with severe hepatic impairment (see section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties).

Metformin hydrochloride

Since impaired hepatic function has been associated with some cases of metformin associated lactic acidosis, XIGDUO XR should be avoided in patients with clinical or laboratory evidence of hepatic disease.

Radiologic studies with intravascular iodinated contrast materials

Metformin hydrochloride

Intravascular administration of iodinated contrast agents in radiological studies can lead to an acute decrease in renal function and has been associated with lactic acidosis in patients receiving metformin. Therefore, XIGDUO XR should temporarily be discontinued prior to, or at the time of the procedure and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be stable (see section 4.3 Contraindications).

Acute conditions associated with hypoxia or impacting renal function

Metformin hydrochloride

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction, and other conditions characterised by hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. Acute conditions such as dehydration, severe infections, and hypoperfusion, have potential to alter renal function. In these situations, metformin must be discontinued.

Surgery

Treatment with XIGDUO XR should be ceased at least 48 hours prior to major surgery or procedures associated with prolonged fasting (see also Special Warnings and Precautions for Lactic acidosis and Diabetic ketoacidosis). An increase in other glucose lowering agents may be required during this time.

Patients scheduled for non-urgent surgery who have not ceased treatment with XIGDUO XR should be assessed and consideration should be given to postponing the procedure.

Treatment with XIGDUO XR may be restarted not earlier than 48 hours following the surgery once the patient's condition has stabilised, oral intake is normal and only after renal function has been evaluated and found to be normal.

Use in Patients at Risk for Volume Depletion and or Hypotension

Dapagliflozin

The diuretic effect of dapagliflozin is a potential concern for volume depleted patients. Due to its mechanism of action, dapagliflozin induces osmotic diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1 Pharmacodynamic properties – Clinical trials)

When considering initiating dapagliflozin, there may be patients for whom the additional diuretic effect of dapagliflozin is a potential concern either due to acute illness (such as gastrointestinal illness) or a history of hypotension or dehydration with diuretic therapy for patients who may become volume depleted. Initiation of therapy with dapagliflozin is therefore not recommended in these patients.

In case of intercurrent conditions that may lead to volume depletion, such as gastrointestinal illness, heat stress or severe infections, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including electrolytes) is recommended. Temporary interruption of XIGDUO XR is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8 Adverse effects (Undesirable effects)).

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on antihypertensive therapy with a history of hypotension or elderly patients.

Urinary Tract Infections

Dapagliflozin

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including dapagliflozin. Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to control in a placebo-pooled analysis up to 24 weeks (4.7% vs. 3.5%, respectively). Urinary glucose excretion may be associated with an increased risk of urinary tract infection. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (see section 4.8 Adverse effects (Undesirable effects)). Temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis. Discontinuation of dapagliflozin may be considered in cases of recurrent urinary tract infections; see section 4.8 Adverse effects (Undesirable effects).

Necrotising fasciitis of the perineum (Fournier's gangrene)

Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and potentially life-threatening necrotising infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including dapagliflozin (see section 4.8 (Adverse effects (Undesirable effects). Serious outcomes have included hospitalisation, multiple surgeries, and death.

Patients treated with XIGDUO XR who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotising fasciitis. If suspected, XIGDUO XR should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Lower limb amputations

Dapagliflozin

In one long-term clinical study with another SGLT2 inhibitor, an increase in cases of lower limb amputation (primarily of the toe) has been observed. The medicine in that study is not dapagliflozin. However, it is unknown whether this constitutes a class effect. It is important to regularly examine the feet and counsel all patients with diabetes on routine preventative footcare.

Vitamin B12 decrease/deficiency

Metformin hydrochloride

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines (see section 4.8 Adverse effects (Undesirable effects).

Excessive alcohol intake

Metformin hydrochloride

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake, while receiving XIGDUO XR.

Ketoacidosis

XIGDUO XR should not be used for the treatment of diabetic ketoacidosis (DKA).

There have been reports of ketoacidosis, including DKA, a serious life-threatening condition requiring urgent hospitalisation in patients taking dapagliflozin and other SGLT2 inhibitors. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin.

Patients treated with XIGDUO XR who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, XIGDUO XR should be suspended, the patient should be evaluated and prompt treatment initiated. Treatment of ketoacidosis generally requires insulin, fluid, potassium and carbohydrate replacement.

Ketoacidosis and glucosuria may be prolonged after discontinuation of XIGDUO XR in some patients, i.e. it may last longer than expected based on the plasma half-lives of dapagliflozin (see Section 5.2 Pharmacokinetic Properties). Consider monitoring for ketoacidosis and glucosuria in patients on dapagliflozin, even if drug treatment has been interrupted or discontinued.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.

Before initiating XIGDUO XR, consider factors in the patient history that may predispose to ketoacidosis.

Factors that predispose patients to ketoacidosis include insulin deficiency from any cause (including insulin pump failure, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, low carbohydrate diet, acute illness, surgery, a previous ketoacidosis, dehydration and alcohol abuse. XIGDUO XR should be used with caution in these patients. Consider monitoring patients for ketoacidosis and temporarily discontinuing XIGDUO XR in clinical situations known to predispose to ketoacidosis.

Loss of Control of Blood Glucose

Metformin hydrochloride

When a patient stabilised on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold XIGDUO XR and temporarily administer insulin. XIGDUO XR may be reinstituted after the acute episode is resolved.

Use with Medications Known to Cause Hypoglycaemia

Dapagliflozin

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with XIGDUO XR (see section 4.8 Adverse effects (Undesirable effects)).

Metformin hydrochloride

Hypoglycaemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication, are particularly susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognise in the elderly and in people who are taking beta-adrenergic blocking drugs.

Paediatric use

Safety and effectiveness of XIGDUO XR in paediatric patients have not been established.

Use in the elderly

Because metformin is eliminated by the kidney, and because elderly patients are more likely to have decreased renal function, XIGDUO XR should be used with caution as age increases. The renal function recommendations provided for all patients also apply to elderly patients (see section 4.4 Special Warnings and Precautions for Use).

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and the risk of serious adverse reactions to the drug is greater in patients with impaired renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. (See sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties – Special Populations).

Cardiac failure

Dapagliflozin

There is no experience in clinical studies with dapagliflozin in NYHA class -IV.

Effects on laboratory tests

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 SGLT2 inhibitors. Use alternative methods to monitor glycaemic control.

Haematocrit

In the pool of 13 short-term placebo-controlled studies (see section 4.8 Adverse effects (Undesirable effects)), increases from baseline in mean haematocrit values were observed in dapagliflozin-treated patients starting at Week 1. At Week 24, the mean changes from baseline in haematocrit were −0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By Week 24, haematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg–treated patients.

In the pool of 9 placebo-controlled studies with short-term and long-term data, at week 102, the mean changes in haematocrit values were 2.68% vs. -0.46%, respectively. Results for haematocrit values >55% during the short-term plus long-term phase (the majority of patients were exposed to treatment for more than one year), were similar to week 24.

Most patients with marked abnormalities of elevated haematocrit or haemoglobin had elevations measured a single time that resolved at subsequent visits.

Increased Haematocrit

Increased haematocrit has been observed with dapagliflozin treatment (see section 4.8 Adverse effects (Undesirable effects)). Patients with pronounced elevations in haematocrit should be monitored and investigated for underlying haematological disease.

Serum Inorganic Phosphorus

In the pool of 13 short-term placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin-treated patients compared with placebo-treated patients (mean increase of 0.042 mmol/L versus −0.0013 mmol/L, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphataemia (≥1.81 mmol/L for age 17-65 years or ≥1.65 mmol/L for age ≥66 years) were reported on dapagliflozin at Week 24 (0.9% versus 1.7% for placebo and dapagliflozin 10 mg, respectively).

In the pool of 9 placebo-controlled studies with short-term and long-term data, at week 102, reported increases in mean serum phosphorus were similar to week 24 results. During the short-term plus long-term phase laboratory abnormalities of hyperphosphataemia were reported in a higher proportion of patients in the dapagliflozin group compared to placebo (3.0% vs. 1.6%, respectively). The clinical relevance of these findings is unknown.

Lipids

In the 13-study short-term placebo-controlled pool (see 4.8 Adverse effects (Undesirable effects)), small changes from baseline in mean lipid values were reported at week 24 in dapagliflozin 10 mg treated patients compared with placebo. Mean percent change from baseline at week 24 for dapagliflozin 10 mg vs. placebo, respectively was as follows: total cholesterol 2.5% vs. 0.0%; HDL cholesterol 6.0% vs. 2.7%; LDL cholesterol 2.9% vs. -1.0%; triglycerides -2.7% vs. -0.7%. The ratio between LDL cholesterol and HDL cholesterol decreased for both treatment groups at week 24.

In the pool of 9 placebo-controlled studies with short-term and long-term data, the mean percent change from baseline at week 102 for dapagliflozin 10 mg vs. placebo, respectively was as follows: total cholesterol 2.1% vs. -1.5%; HDL cholesterol 6.6% vs. 2.1%; LDL cholesterol 2.9% vs. -2.2%; triglycerides -1.8% vs. -1.8%.

In the cardiovascular outcomes study, no clinical important differences in total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides were seen.

Liver Function Tests

In the 21-study active and placebo-controlled pool (see section 4.8 Adverse effects (Undesirable effects)), there was no imbalance across treatment groups in the incidence of elevations of ALT or AST. ALT >3 x ULN was reported in 1.2% of patients treated with dapagliflozin 10 mg and 1.6% treated with comparator. ALT or AST >3 x ULN and bilirubin

>2 x ULN was reported in 0.1% of patients on any dose of dapagliflozin, 0.2% of patients on dapagliflozin 10 mg, and 0.1% of patients on comparator.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In in-vitro studies, dapagliflozin neither inhibited CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered drugs that are metabolised by these enzymes and drugs which inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of dapagliflozin were not altered by metformin (an hOCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate, and P-glycoprotein substrate), glimepiride(a CYP2C9 substrate), voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). Therefore, meaningful interaction of dapagliflozin with other substrates of hOCT-1, hOCT-2, hOAT-3, P-gp, CYP2C8, CYP2C9, CYP3A4, and other α-glucosidase inhibitors would not be expected.

Concomitant use of dapagliflozin and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

Dapagliflozin also did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin (a P-gp substrate), or warfarin (S-warfarin is a CYP2C substrate). Therefore, dapagliflozin is not a clinical meaningful inhibitor of hOCT-1, hOCT-2, hOAT-3, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mediated metabolism.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) or mefenamic acid (an inhibitor of UGT1A9), a 22% decrease and a 51% increase, respectively, in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion in either case. No dose adjustment of dapagliflozin is recommended when dapagliflozin is coadministered with either rifampicin or mefenamic acid.

Metformin hydrochloride

Cationic drugs

Cationic drugs (eg, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Glibenclamide

In a single-dose interaction study in patients with type 2 diabetes, coadministration of metformin and glibenclamide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glibenclamide AUC and maximum concentration (C_{max}) were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glibenclamide blood levels and pharmacodynamic effects makes the clinical significance of this interaction uncertain.

Frusemide

A single-dose, metformin-frusemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Frusemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of frusemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in frusemide renal clearance. No information is available about the interaction of metformin and frusemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Use with Other Drugs

Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid

products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycaemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Other interactions

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of XIGDUO XR have not been specifically studied.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Dapagliflozin

In a study of fertility in rats, no effects on mating, fertility, or early embryonic development were seen when males received oral doses up to 210 mg/kg/day or when females received oral doses up to 75 mg/kg/day (yielding plasma AUC values at least 1000 times the clinical exposure at the maximum recommended human dose [MRHD] of 10 mg/day). However, at 210 mg/kg/day, a dose associated with profound toxicity (including mortality), seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were increased numbers of morphologically abnormal sperm. No adverse effects on sperm or male reproductive organs were seen at 75 mg/kg/day (700 times the clinical exposure at the MRHD).

Use in pregnancy – Category D

There are no adequate and well-controlled studies of XIGDUO XR or its individual components in pregnant women. When pregnancy is detected, treatment with XIGDUO XR should be discontinued.

Dapagliflozin

Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 4.4 Special warnings and precautions for use). Therefore, dapagliflozin must not be used during the second and third trimesters of pregnancy.

In conventional studies of embryofoetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the period of organogenesis in humans. An increased incidence of embryofoetal lethality, decreased foetal weight and an increased

incidence of foetal visceral and skeletal anomalies were seen in rats at maternotoxic doses (oral doses greater than or equal to 150 mg/kg/day). The no observed effect level for embryofoetal effects in rats was an oral dose of 75 mg/kg/day (1530 times the exposure in patients at the maximum recommended human dose [MRHD]). No developmental toxicities were observed in rabbits at oral doses up to 180 mg/kg/day (1265 times the exposure in patients at the MRHD).

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of foetal concentrations demonstrated a partial placental barrier to metformin.

Use in lactation

XIGDUO XR must not be used by breastfeeding women.

No studies in lactating animals have been conducted with the combined components of XIGDUO XR. In studies performed with the individual components, both dapagliflozin and metformin are excreted in the milk of lactating rats.

Studies in rats have shown excretion of dapagliflozin in milk. Direct and indirect exposure of dapagliflozin to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. The long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body weight gain associated with lactational exposure in weanling juvenile rats suggest that dapagliflozin must be avoided during the first 2 years of life.

It is not known whether dapagliflozin or metformin are secreted in human milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed with XIGDUO XR or dapagliflozin. It should be taken into account that dizziness has been reported in studies with dapagliflozin.

Patients should be alerted to the risk of hypoglycaemia when XIGDUO XR is used with a sulphonylurea or insulin.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Significant adverse events are also described in the 4.4 Special warnings and precautions for use section.

Clinical Experience – Dapagliflozin

Two major pools of patients were used to evaluate adverse effects with dapagliflozin 10 mg versus control; a pool of 13 placebo-controlled studies and a larger pool comprised of 21 active- and placebo-controlled studies.

In the dedicated cardiovascular outcomes study in patients with type 2 diabetes mellitus, 8574 patients received dapagliflozin 10 mg and 8569 received placebo for a median exposure time of 48 months. In total, there were 30623 patient-years of exposure to dapagliflozin.

Placebo-controlled studies

The first pool is a pre-specified pool of patients from 13 short-term, placebo-controlled studies including the monotherapy studies, add-on studies, and the initial combination with metformin study. In the pool, 2360 patients were treated with dapagliflozin 10 mg and 2295 were treated with placebo with a mean duration of exposure of 22 weeks.

The overall incidence of adverse events in patients treated with dapagliflozin 10 mg was 60.0% compared to 55.7% for the placebo group. The incidence of discontinuation of therapy due to adverse events in patients who received dapagliflozin 10 mg was 4.3% compared to 3.6% for the placebo group. The most commonly reported events leading to discontinuation in patients and reported in at least 3 dapagliflozin 10 mg treated patients were renal impairment (0.8%), decrease in creatinine clearance (0.6%), increased blood creatinine (0.3%), urinary tract infections (0.2%), and vulvovaginal mycotic infection (0.1%).

Active- and Placebo- Controlled Studies

The second pool is a pool of patients from 21 active- and placebo-controlled studies used to evaluate and present data for malignancies and liver tests. In this pool, 5936 patients were treated with dapagliflozin and 3403 were treated with control (either as monotherapy or in combination with other antidiabetic therapies). These 21 studies provide a mean duration of exposure to dapagliflozin 10 mg of 55 weeks (6247 patient-years).

The adverse events in the 13-study placebo-controlled pool reported (regardless of investigator assessment of causality) in ≥2% of patients treated with dapagliflozin 10 mg and ≥1% more and at least 3 patients more than treated with placebo are shown in Table 2.

Table 2. Adverse reactions (Regardless of Investigator Assessment of Causality) in the 13-Placebo-Controlled Study Pool Reported in ≥2% of Patients Treated with Dapagliflozin 10 mg and ≥1% More Frequently than in Patients Treated with Placebo

	% of patients	
	Dapagliflozin 10mg N=2360	**Placebo N=2295**
Infections and infestations		
Genital Infection[§]	5.5	0.6
Urinary tract infection[*]	4.7	3.5

Musculoskeletal and Connective Tissue Disorders		
Back pain	3.5	2.4
Renal and Urinary disorders		
Polyuria¶	3.3	1.2
Metabolism and nutrition disorders		
Hypoglycaemia‡	13.5	10.1

§ Genital infection includes the preferred terms, listed in order of frequency reported: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, and vulval abscess.
*Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.
¶Polyuria includes the preferred terms, listed in order of frequency reported: pollakiuria, polyuria, urine output increased.
‡ see Hypoglycaemia below.

Additional adverse reactions in ≥5% of patients treated with dapagliflozin 10 mg, ≥1% more than patients in placebo/comparator, and reported in at least three more patients treated with dapagliflozin 10 mg and regardless of relationship to dapagliflozin reported by investigator, are described below by treatment regimen.

In the add-on to metformin studies: headache (5.3% dapagliflozin 10mg and 3.1% placebo).

Diabetic ketoacidosis was identified with a frequency of rare (≥ 1/10,000 to < 1/1000), based on annual rate, in a large cardiovascular outcomes study with dapagliflozin in patients with type 2 diabetes.

Description of selected adverse events

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in each study. Studies with add-on sulfonylurea and add-on insulin therapies had higher rates of hypoglycaemia with dapagliflozin treatment than with placebo treatment (see section 4.4 Special warnings and precautions for use).

In studies of dapagliflozin in initial combination therapy with metformin, add-on to metformin alone up to 102 weeks there were no major episodes of hypoglycaemia reported. In a study of dapagliflozin added on to sitagliptin (with or without metformin) for up to 48 weeks, one major episode of hypoglycaemia was reported in a patient treated with dapagliflozin 10 mg plus sitagliptin (without metformin). In these studies, the frequency of minor episodes of hypoglycaemia was similar (<5%) between treatment groups, including placebo.

In a study with dapagliflozin 10 mg added on to glimepiride for up to 48 weeks, that also included other doses of dapagliflozin, one episode of major hypoglycaemia in a patient in the

dapagliflozin 2.5 mg plus glimepiride group was reported. Minor episodes of hypoglycaemia were reported in 7.9% patients in the dapagliflozin 10 mg plus glimepiride group and 2.1% patients in the placebo plus glimepiride group.

In an add-on to metformin study that compared dapagliflozin to glipizide up to 104 weeks, there were 3 episodes of major hypoglycaemia in the glipizide plus metformin group and none in the dapagliflozin plus metformin group. Minor episodes of hypoglycaemia were reported in 2.5% of patients in the dapagliflozin plus metformin group and 42.4% of patients in the glipizide plus metformin group.

In an add-on to metformin and a sulfonylurea study, up to 52 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 15.6% of subjects who received dapagliflozin 10 mg plus metformin and a sulfonylurea and in 4.6% of subjects who received placebo plus metformin and a sulfonylurea.

In the analysis of pooled safety data of 1169 patients from trials evaluating saxagliptin in combination with dapagliflozin at 24 weeks, the overall incidence of hypoglycaemia for the pooled safety data of was low (≤1.8% in any treatment group); there was no increase in hypoglycaemia in saxagliptin plus dapagliflozin plus metformin treatment group compared to the saxagliptin plus metformin or dapagliflozin plus metformin treatment groups. The combined use of saxagliptin plus dapagliflozin plus metformin was not associated with an increase in the risk of hypoglycaemia when compared to the individual agents as monotherapy. This was consistent with prior clinical trial experience regardless of whether the combination was added to metformin concurrently or sequentially.

In a study of dapagliflozin 10 mg initiated concomitantly with extended release exenatide (on a background of metformin), there were no episodes of major or minor hypoglycaemia reported.

In an add-on to insulin study up to 24 weeks, episodes of major hypoglycaemia were reported in 1 (0.5%) and 1 (0.5%) patient in dapagliflozin 10 mg plus insulin and placebo plus insulin groups, respectively. Up to 104 weeks, 2 (1.0%) and 1 (0.5%) of patients in dapagliflozin 10 mg plus insulin and placebo plus insulin groups reported major episodes. Up to 24 weeks, minor episodes were reported in 79 (40.3%) patients in the dapagliflozin 10 mg plus insulin group and in 67 (34%) patients in placebo plus insulin group. Up to 104 weeks, minor episodes were reported in patients were 53.1% for dapagliflozin 10 mg plus insulin and 41.6% for placebo. Patients in this study could also be treated with a maximum of two oral anti-diabetes medications (OADs) including metformin.

In the dapagliflozin cardiovascular outcomes study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 patients (0.7%) treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

Volume depletion

In the pooled analysis of 13 short-term, placebo-controlled studies, events suggestive of volume depletion (including reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of patients who received dapagliflozin 10 mg and placebo, respectively. Across the pool of 21 active and placebo-controlled studies, serious events occurred in ≤0.2% of patients and were balanced between dapagliflozin 10 mg and comparator (see section 4.4 Special warnings and precautions for use).

Adverse events of volume depletion were more commonly seen in patients with moderate renal impairment.

In the cardiovascular outcomes study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use. In patients with eGFR < 60 mL/min/1.73 m^2 at baseline, there were 19 events of serious adverse events suggestive of volume depletion in 604 patients in the dapagliflozin group and 13 events in 658 patients in the placebo group.

Genital Infections

In the pooled analysis of 13 short-term, placebo-controlled studies, events of genital infections were reported in 5.5% and 0.6% of patients who received dapagliflozin 10 mg and placebo, respectively. The events of genital infections reported in patients treated with dapagliflozin 10 mg were all mild to moderate. Most events of genital infection responded to an initial course of standard treatment and rarely resulted in discontinuation from the study (0.2% dapagliflozin 10 mg vs. 0% placebo). Subjects with a history of recurrent genital infection were more likely to experience an infection. Infections were more frequently reported in females (8.4% dapagliflozin 10 mg vs. 1.2% placebo) than in males (3.4% dapagliflozin 10 mg vs. 0.2% placebo). The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.

In 9 of the 13 studies in the placebo-controlled pool, long-term data was available. In this short-term plus long-term placebo-pooled analysis (mean duration of treatment was 439.5 days for dapagliflozin 10 mg and 419.0 days for placebo); the proportions of patients with events of genital infections were 7.7% (156/2026) in the dapagliflozin 10 mg group and 1.0% (19/1956) in the placebo group. Of the patients treated with dapagliflozin 10 mg who experienced an infection, 67.9% had only one and 10.9% had 3 or more. Of the patients treated with placebo who experienced an infection, 89.5% had only one and none had 3 or more.

In the cardiovascular outcomes study, the number of patients with serious adverse events of genital infections were few and balanced: 2 (<0.1%) patients in each of the dapagliflozin and placebo groups. There were 74 and 7 patients with non-serious adverse events of genital

infections leading to study drug discontinuation in the dapagliflozin group and placebo group, respectively.

Cases of phimosis/acquired phimosis have been reported with dapagliflozin concurrent with genital infections and in some cases, circumcision was required.

Necrotising fasciitis of the perineum (Fournier's gangrene)

In the dapagliflozin cardiovascular outcomes study with 17,160 patients with type 2 diabetes mellitus and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported on treatment, one in the dapagliflozin-treated group and 5 in the placebo group.

Urinary Tract Infections

In the pooled analysis of 13 short-term, placebo-controlled studies, events of urinary tract infections were reported in 4.7% and 3.5% of patients who received dapagliflozin 10 mg and placebo, respectively. Most events of urinary tract infections reported in patients treated with dapagliflozin 10 mg were mild to moderate. Most patients responded to an initial course of standard treatment, and urinary tract infections rarely caused discontinuation from the study (0.2% dapagliflozin 10 mg vs. 0.1% placebo). Subjects with a history of recurrent urinary tract infection were more likely to experience an infection. Infections were more frequently reported in females (8.5% dapagliflozin 10 mg vs. 6.7% placebo) than in males (1.8% dapagliflozin 10 mg vs. 1.3% placebo) (see section 4.4 Special warnings and precautions for use).

In the short-term plus long-term placebo-pooled analysis of 9 short-term studies with long term data available, the proportions of patients with events of urinary tract infections were 8.6% in the dapagliflozin 10 mg group and 6.2% in the placebo group. Of the 59 patients treated with dapagliflozin 10 mg who experienced an infection, 77.6% had only one and 6.3% had 3 or more. Of the patients treated with placebo who experienced an infection, 77.7% had only one and 9.9% had 3 or more.

In the cardiovascular outcomes study there were fewer patients with serious adverse events of urinary tract infections in the dapagliflozin group compared with the placebo group: 79 (0.9%) and 109 (1.3%), respectively.

Diabetic ketoacidosis (DKA)

In a large cardiovascular outcomes study with dapagliflozin in patients with type 2 diabetes, where 8574 patients received dapagliflozin 10 mg and 8569 patients received placebo, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see Section 4.4 Special warnings and precautions for use).

Events related to decreased renal function

Use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR. These changes were observed to reverse after treatment discontinuation, suggesting acute haemodynamic changes play a role in the renal function abnormalities observed with dapagliflozin.

Renal-related adverse reactions (e.g. acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with dapagliflozin.

In the 13-study, short-term, placebo-controlled pool, mean serum creatinine levels increased a small amount at Week 1 (mean change from baseline: 0.041 mg/dL dapagliflozin 10 mg versus 0.008 mg/dL placebo) and decreased toward baseline by Week 24 (mean change from baseline: 0.019 mg/dL dapagliflozin 10 mg versus 0.008 mg/dL placebo). There were no further changes through Week 102.

In the cardiovascular outcomes study, there were fewer patients with marked laboratory abnormalities of creatinine, creatinine clearance, eGFR, and urine albumin to creatinine ration (UACR) in the dapagliflozin group compared with the placebo group. Fewer renal events (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine, and decreased glomerular filtration rate) were reported in the dapagliflozin group compared with the placebo group: 422 (4.9%) and 526 (6.1%), respectively. There were fewer patients with events reported as acute kidney injury in the dapagliflozin group compared with the placebo group: 125 (1.5%) and 175 (2.0%), respectively. There were fewer patients with SAEs of renal events in the dapagliflozin group compared with the placebo group: 80 (0.9%) and 136 (1.6%), respectively. eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

Metformin hydrochloride

Metformin adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from the Product Information for metformin available in Australia.

Gastrointestinal

Very common: Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite) are the most frequent reactions to metformin (>1/10), especially during the initial treatment period. These symptoms are generally transient and resolve spontaneously during continued treatment.

Occurrence of gastrointestinal symptoms, once a patient is stabilised on any dose of metformin, could be due to lactic acidosis or other serious disease.

Systemic/metabolic

Very rare: Lactic acidosis (see section 4.4 Special warnings and precautions for use) is a very rare (< 1/10,000) but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin.

The onset of lactic acidosis is often subtle and accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in hospital. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted.

Nervous System Disorders

Common: Taste disturbance (3%) is common.

Dermatological

Very rare: Skin reactions such as erythema, pruritus and urticaria have been reported, but the incidence is very rare (< 1/10,000).

Haematological

Common: A decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long term with metformin (>1/100, <1/10). Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia. Therefore, serum B12 levels should be appropriately monitored or periodic parenteral B12 supplementation considered (see section 4.4 Special warnings and precautions for use).

Hepatobiliary Disorders

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, have been reported.

In clinical trials in children and adolescents with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

Postmarketing experience

The following post-marketing case reports have been reported during post-approval use of XIGDUO XR. Because these cases are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

Metabolism and nutrition disorders – Ketoacidosis, vitamin B12 decrease/deficiency

Infections and infestations – Pyelonephritis, urosepsis, necrotising fasciitis of the perineum (Fournier's gangrene)

Skin and subcutaneous tissue disorders – Rash, angioedema

Investigations – Increased haematocrit (frequency: common)

Renal and Urinary disorders – Tubulointerstitial nephritis (frequency: very rare)

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Dapagliflozin
Orally-administered dapagliflozin has been shown to be safe and well-tolerated in healthy subjects at single doses up to 500 mg (50 times the MRHD). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension, or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) were administered for 2 weeks in healthy subjects and patients with type 2 diabetes, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters including serum electrolytes and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

Metformin hydrochloride
High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital. The most effective method to remove lactate and metformin is haemodialysis. Events of hypoglycaemia have been reported with overdoses of metformin, although a causal association has not been established.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

XIGDUO XR combines two anti-hyperglycaemic agents with complementary mechanisms of action to improve both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with type 2 diabetes: dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin

Dapagliflozin is a reversible competitive inhibitor of sodium glucose co-transporter 2 (SGLT2) with nanomolar potency that improves glycaemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary glucose excretion (glucuresis).

SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in healthy subjects with normal glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is approximately 1000-3000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Metformin hydrochloride

Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal

subjects (except in special circumstances, see section 4.4 Special warnings and precautions for use) and does not cause hyperinsulinaemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

In humans, independently of its action on glycaemia metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Pharmacodynamics

General

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 18.3 to 48.3 μmol/L.

Cardiac Electrophysiology

Dapagliflozin

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended dose) dapagliflozin in healthy subjects.

Clinical trials

There have been no clinical efficacy studies conducted with XIGDUO XR; however, bioequivalence of XIGDUO XR with coadministered dapagliflozin and metformin hydrochloride extended release tablets was demonstrated.

Addition of Dapagliflozin to Metformin

The coadministration of dapagliflozin and metformin has been studied in patients with type 2 diabetes inadequately controlled on metformin alone or in combination with a sulfonylurea, dipeptidyl peptidase 4 (DPP4) inhibitor or insulin, in treatment-naive patients inadequately controlled on diet and exercise alone, and compared with a sulfonylurea in combination with metformin in patients with inadequate glycaemic control on metformin alone. Additionally, dapagliflozin 10 mg or placebo were studied in patients with type 2 diabetes with cardiovascular disease (approximately 37% of patients across 2 studies received dapagliflozin 10 mg or placebo plus metformin alone [with or without insulin]) and patients with type 2 diabetes with hypertension (approximately 90% of patients across 2 studies received dapagliflozin 10 mg or placebo plus metformin).

Initial Combination Therapy with Metformin

641 patients were randomised to one of three treatment arms following a 1-week lead-in period: dapagliflozin 10 mg plus metformin XR (up to 2000 mg per day), dapagliflozin 10 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin dose was up-titrated weekly in 500 mg increments, as tolerated, with the maximum and median dose achieved being 2000 mg. The patients were treatment-naïve, defined as either never having received diabetes medication or having had such for less than 24 weeks since the diagnosis of diabetes, not for more than 14 days during the 12 weeks prior to enrolment, and not at all during the 4 weeks prior to enrolment.

The combination treatment of dapagliflozin 10 mg plus metformin provided significant improvements in haemoglobin A1c (HbA1c) and FPG, compared with either of the monotherapy treatments and significant improvements in body weight compared with metformin alone (Table 3). Dapagliflozin 10 mg as monotherapy also provided significant improvements in FPG and body weight compared with metformin alone and was non-inferior to metformin monotherapy in lowering HbA1c. The proportion of patients who were rescued or discontinued for lack of glycaemic control during the 24 week double-blind treatment period (adjusted for baseline HbA1c) was higher on treatment with metformin plus placebo (13.5%) than on dapagliflozin 10 mg plus placebo and dapagliflozin 10 mg plus metformin (7.8%, and 1.4%).

Table 3. Results at Week 24 (LOCF[*]) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter	**Dapagliflozin 10 mg + Metformin XR N=211[†]**	**Dapagliflozin 10 mg N=219[†]**	**Metformin XR N=208[†]**
HbA1c (%)			
Baseline (mean)	9.10	9.03	9.03
Change from baseline (adjusted mean[‡])	−1.98	−1.45	−1.44
Difference from dapagliflozin (adjusted mean[‡]) (95% CI)	−0.53[§] (−0.74, −0.32)		

Table 3. Results at Week 24 (LOCF*) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter	Dapagliflozin 10 mg + Metformin XR	Dapagliflozin 10 mg	Metformin XR
Difference from metformin (adjusted mean‡) (95% CI)	−0.54§ (−0.75, −0.33)	−0.01¶ (−0.22, 0.20)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6%#	31.7%	35.2%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−2.59#	−2.14	−2.05
Body Weight (kg)			
Baseline (mean)	88.56	88.53	87.24
Change from baseline (adjusted mean‡)	−3.33	−2.73	−1.36
Difference from metformin (adjusted mean‡) (95% CI)	−1.97§ (−2.64, −1.30)	−1.37§ (−2.03, −0.71)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.
† All randomised patients who took at least one dose of double-blind study medication during the short-term double-blind period.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001.
¶ Non-inferior versus metformin.
# p-value <0.05.

Add-on to Metformin

As add-on treatment to metformin, dapagliflozin 10 mg provided significant improvements in HbA1c at week 24 (Table 4).

Table 4. Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin

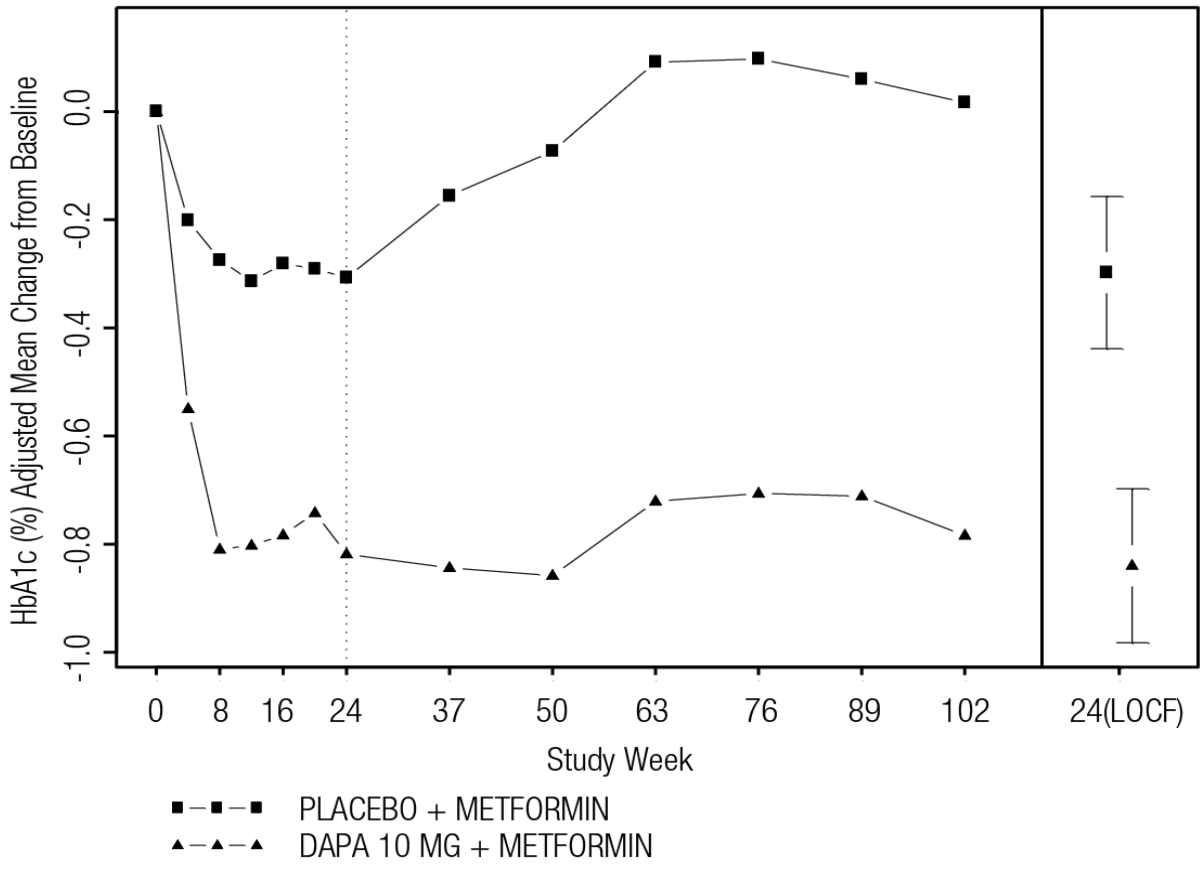
Efficacy Parameter	Dapagliflozin 10 mg + Metformin N=135†	Placebo + Metformin N=137†
HbA1c (%)		
Baseline mean	7.92	8.11
Change from baseline (adjusted mean‡)	−0.84	−0.30
Difference from placebo (adjusted mean‡) (95% CI)	−0.54§ (−0.74, −0.34)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%¶	25.9%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−1.32¶ (N= 18)	−0.53 (N= 22)

Table 4. Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin

Efficacy Parameter	Dapagliflozin 10 mg + Metformin N=135†	Placebo + Metformin N=137†
Body Weight (kg)		
Baseline mean	86.28	87.74
Change from baseline (adjusted mean‡)	−2.86	−0.89
Difference from placebo (adjusted mean‡)	−1.97§	
(95% CI)	(−2.63, −1.31)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.
† All randomised patients who took at least one dose of double-blind study medication during the short-term double-blind period.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.00001 vs placebo + metformin.
¶ p-value <0.05 vs placebo + metformin.

Figure 1: Adjusted Mean Change from Baseline Over Time in HbA1c in a 102-Week Placebo-Controlled Study of Dapagliflozin in Combination with Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)



LOCF: Last observation (prior to rescue for rescued subjects) carried forward.
Values for 24 (LOCF) represent adjusted mean and 95% confidence intervals based on an ANCOVA model.
Values for other weeks represent adjusted means based on a longitudinal repeated measures model.

Active Glipizide Controlled Study Add-on to Metformin

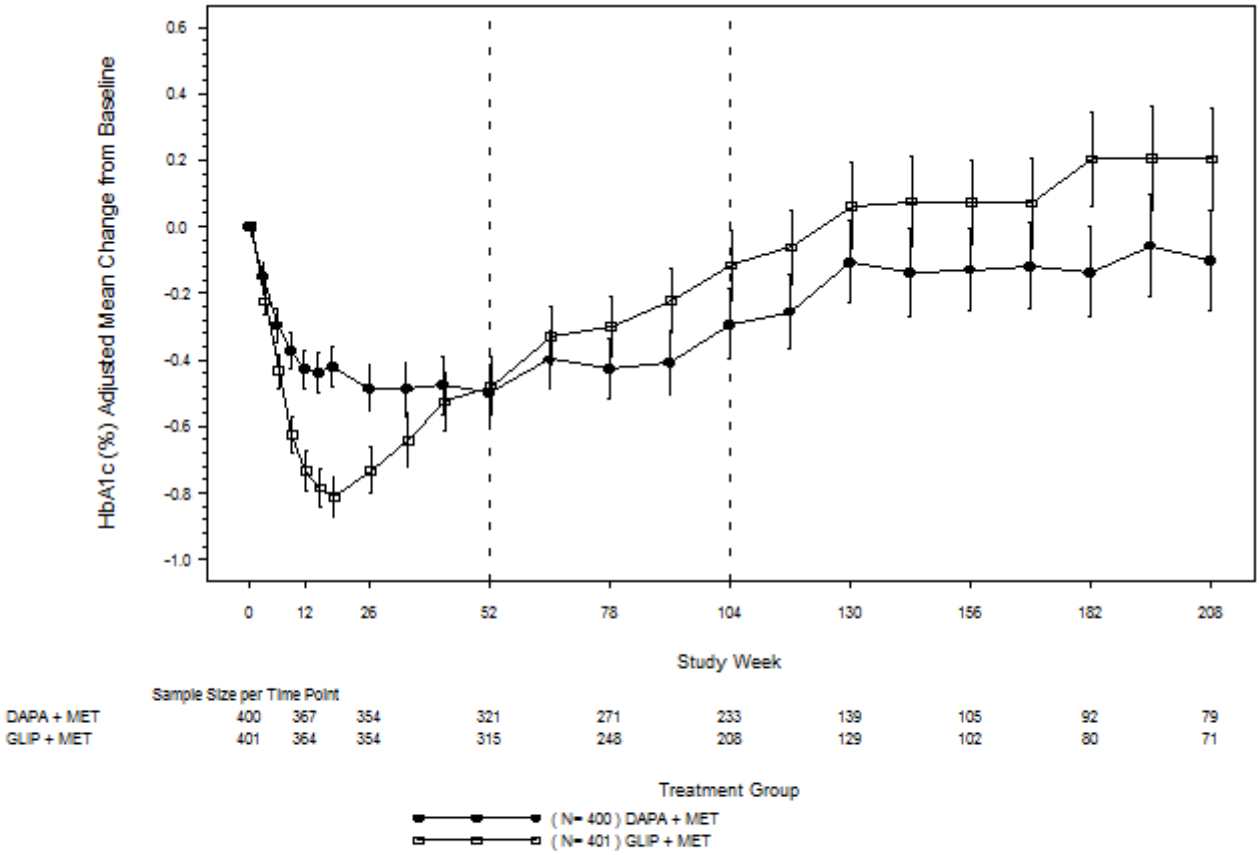
In a 52 week, active-controlled non-inferiority study (with 52 week and 104 week extension periods), dapagliflozin was evaluated as add on therapy to metformin compared with a sulfonylurea (glipizide) as add on therapy to metformin in subjects with inadequate glycaemic control (HbA1c > 6.5% and ≤ 10%). The results showed a similar mean reduction in HbA1c from baseline to Week 52, compared to glipizide, thus demonstrating non-inferiority (Table 5). At Week 104, adjusted mean change from baseline in HbA1c was -0.32% for dapagliflozin and -0.14% for glipizide. At Week 208, the secondary endpoint of adjusted mean change from baseline in HbA1c was 0.10% for FORXIGA and 0.20% for glipizide (see Fig 2). At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with dapagliflozin (3.5%, 4.3% and 5.0%, respectively) experienced at least one event of hypoglycaemia compared to the group treated with glipizide (40.8%, 47.0% and 50.0%, respectively). The proportions of subjects remaining in the study at Week 104 and Week 208 were 56.2% and 39% respectively for the group treated with dapagliflozin and 50.0% and 34.6% respectively for the group treated with glipizide.

Table 5. Results at Week 52 (LOCF[*]) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-on to Metformin

Efficacy Parameter	**Dapagliflozin +Metformin N=400[†]**	**Glipizide +Metformin N=401[†]**
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline (adjusted mean[‡])	−0.52	−0.52
Difference from Glipizide+Metformin (adjusted mean[‡])	0.00[¶]	
(95% CI)	(−0.11, 0.11)	
Body Weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline (adjusted mean[‡])	−3.22	1.44
Difference from Glipizide+Metformin (adjusted mean[‡])	−4.65[§]	2.5%
(95% CI)	(−5.14, −4.17)	

*LOCF: last observation carried forward.
† Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001.
¶ non-inferior to glipizide + metformin

Figure 2: **Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 208-Week Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)**



Subjects in the full analysis set.
Mean value based on repeated measures analysis model:
post-baseline = baseline treatment week week*treatment week*baseline.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping.

Combination therapy with Other Anti-hyperglycaemic Agents

Dapagliflozin as an add-on with either sitagliptin (with or without metformin), metformin with saxagliptin, metformin with a sulfonylurea, or insulin, resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo ($p<0.0001$; Tables 6, 7, 8 and 9).

Table 6. Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Sitagliptin (Stratum with Metformin)

Efficacy Parameter	Dapagliflozin 10 mg + Sitagliptin[a] +Metformin[b] N=113[†]	Placebo + Sitagliptin[a] +Metformin[b] N=113[†]
HbA1c (%)		
Baseline (mean)	7.80	7.87
Change from baseline (adjusted mean[‡])	-0.43	-0.02
Difference from placebo (adjusted mean[‡])	-0.40[§]	
(95% CI)	(-0.58; -0.23)	
Body Weight (kg)		
Baseline (mean)	93.95	94.17
Change from baseline (adjusted mean[‡])	-2.35	-0.47
Difference from placebo (adjusted mean[‡])	-1.87[§]	
(95% CI)	(-2.61; -1.13)	

[a] sitagliptin 100 mg/day
[b] Metformin ≥1500 mg/day
* LOCF: last observation (prior to rescue for rescued patients) carried forward.
† Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001 versus placebo.

Table 7. Results of 24-week placebo-controlled studies of dapagliflozin in add-on combination saxagliptin with metformin

	Dapagliflozin 10 mg + Saxagliptin[3] + metformin[1]	Placebo + Saxagliptin + Metformin
N [a]	160	160
HbA1c (%)[#]		
Baseline (mean)	8.24	8.16
Change from baseline[c]	−0.82	−0.10
Difference from placebo[c]	−0.72[*]	
(95% CI)	(-0.91, -0.53)	
Subjects (%) achieving HbA1c < 7%		
Adjusted for baseline	38.0[*]	12.4
Body weight (kg)		
Baseline (mean)	85.83	88.24
Change from baseline[b]	-1.91	-0.41
Difference from placebo[b]	-1.50[*]	
(95% CI)	(-2.12, -0.89)	

[1]Metformin ≥1500 mg/day; [3]saxagliptin 5 mg
[#] LRM = Longitudinal repeated measures (using values prior to rescue).
[a] Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement
[c]Least squares mean adjusted for baseline value
[*]p-value <0.0001 versus placebo + oral glucose-lowering medicinal product

Table 8. Results of a 24-Week Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin and a Sulfonylurea

Efficacy Parameter	Dapagliflozin 10 mg + Metformin[a] + Sulfonylurea N=108[†]	Placebo +Metformin[a] + Sulfonylurea N=108[†]
HbA1c (%)[^]		
Baseline (mean)	8.08	8.24
Change from baseline (adjusted mean[‡])	-0.86	-0.17
Difference from placebo (adjusted mean[‡])	-0.69[§]	
(95% CI)	(-0.89; -0.49)	
Subjects (%) achieving HbA1c < 7% (LOCF)[*]		
Adjusted for baseline	31.8[§]	11.1
Body Weight (kg) LOCF[*]		
Baseline (mean)	88.57	90.07
Change from baseline (adjusted mean[‡])	-2.65	-0.58
Difference from placebo (adjusted mean[‡])	-2.07[§]	
(95% CI)	(-2.79; -1.35)	

[a] Metformin (immediate- or extended-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulfonylurea for at least 8 weeks prior to enrollment.
[^] HbA1c analysed using Longitudinal Repeated Measures (LRM) analysis
* LOCF: last observation (prior to rescue for rescued patients) carried forward.
† Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001 versus placebo.

Table 9. Results of 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Combination with Insulin (alone or with oral glucose-lowering medicinal products)

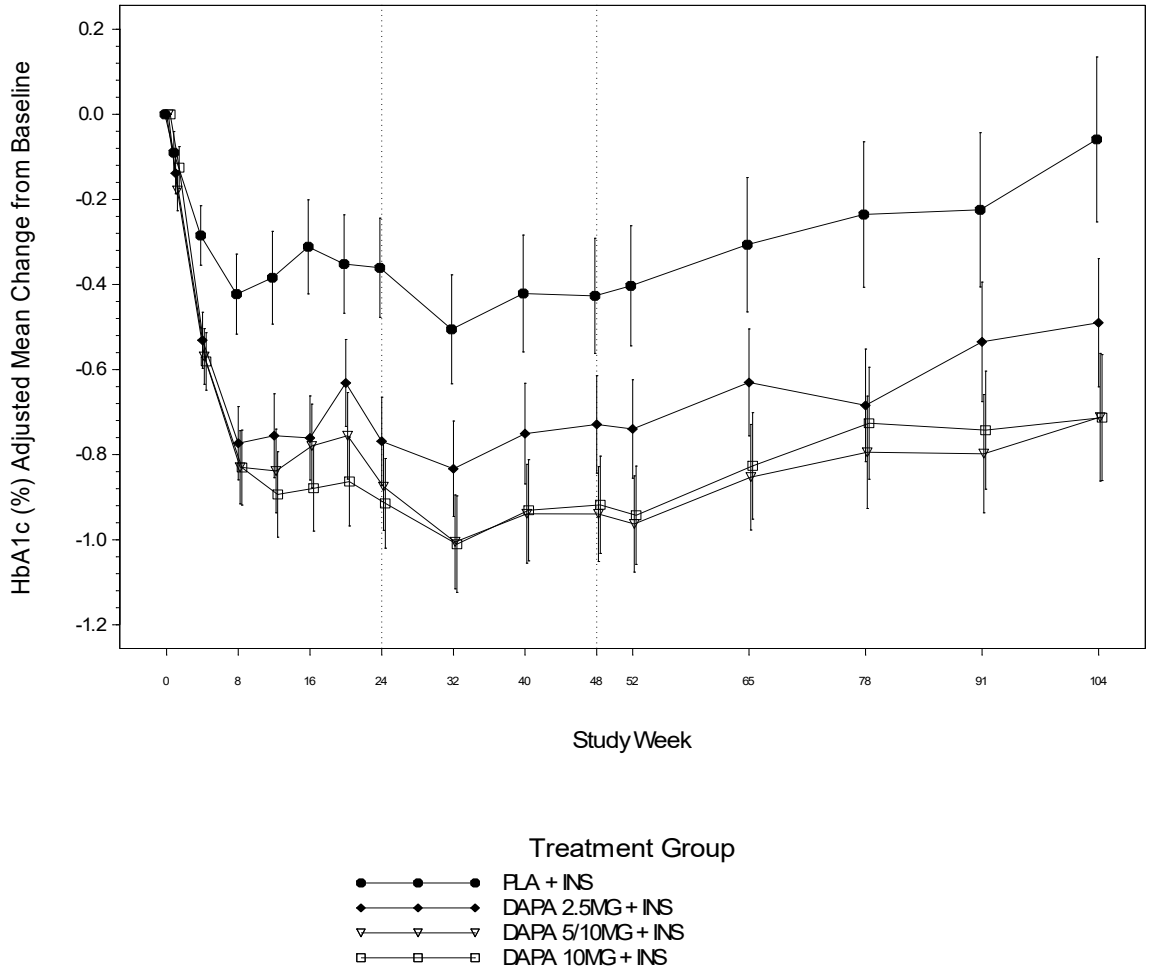
Efficacy Parameter	Dapagliflozin 10 mg + insulin ± oral glucose-lowering medicinal products^	Placebo + insulin ± oral glucose-lowering medicinal products^
Intent-to-Treat Population	**N=194†**	**N=193†**
HbA1c (%)		
Baseline (mean)	8.58	8.46
Change from baseline (adjusted mean‡)	−0.90	−0.30
Difference from placebo (adjusted mean‡)	−0.60§	
(95% CI)	(−0.74, −0.45)	
Mean Daily Insulin Dose (IU)††		
Baseline (mean)	77.96	73.96
Change from baseline (adjusted mean‡)	−1.16	5.08
Difference from placebo‡	−6.23§	
(95% CI)	(−8.84, −3.63)	
Percent of patients with mean daily insulin dose reduction of at least 10% adjusted for baseline	19.7%**	11.0%
Body Weight (kg)		
Baseline (mean)	94.63	94.21
Change from baseline (adjusted mean‡)	−1.67	0.02
Difference from placebo (adjusted mean‡)	−1.68§	
(95% CI)	(−2.19, −1.18)	

* LOCF: last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward.
† All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double blind period.
‡ Least squares mean adjusted for baseline value and presence of oral glucose lowering-medicinal product.
§ p-value <0.0001 versus placebo+ insulin ± oral glucose-lowering medicinal product.
** p-value <0.05 versus placebo+ insulin ± oral glucose-lowering medicinal product.
^ Fifty percent of subjects were on insulin therapy monotherapy at baseline: 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group 80% were on metformin alone, 12 % were on metformin plus sulfonylurea therapy and the rest were on other oral glucose-lowering medicinal products
†† Up-titration of insulin regimens (including short acting, intermediate and basal insulin) was only allowed if subjects met pre-defined FPG criteria.

The reductions in HbA1c observed at Week 24 were sustained in add on combination studies and up to 104 week data (insulin, see Fig 3). At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.30% and 0.38%, respectively. For the add on to metformin study, HbA1c reductions were sustained through Week 102 (-0.78% and 0.02% adjusted mean change from baseline for 10 mg and placebo, respectively, see also Fig 3). At Week 104 for insulin (with or without additional oral glucose lowering medicinal products), the HbA1c reductions were -0.71% and -0.06% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively. At Weeks 48 and 104, the insulin dose remained stable compared to baseline in subjects treated with dapagliflozin 10 mg at an average dose of 76 IU/day (see Fig. 4). In the

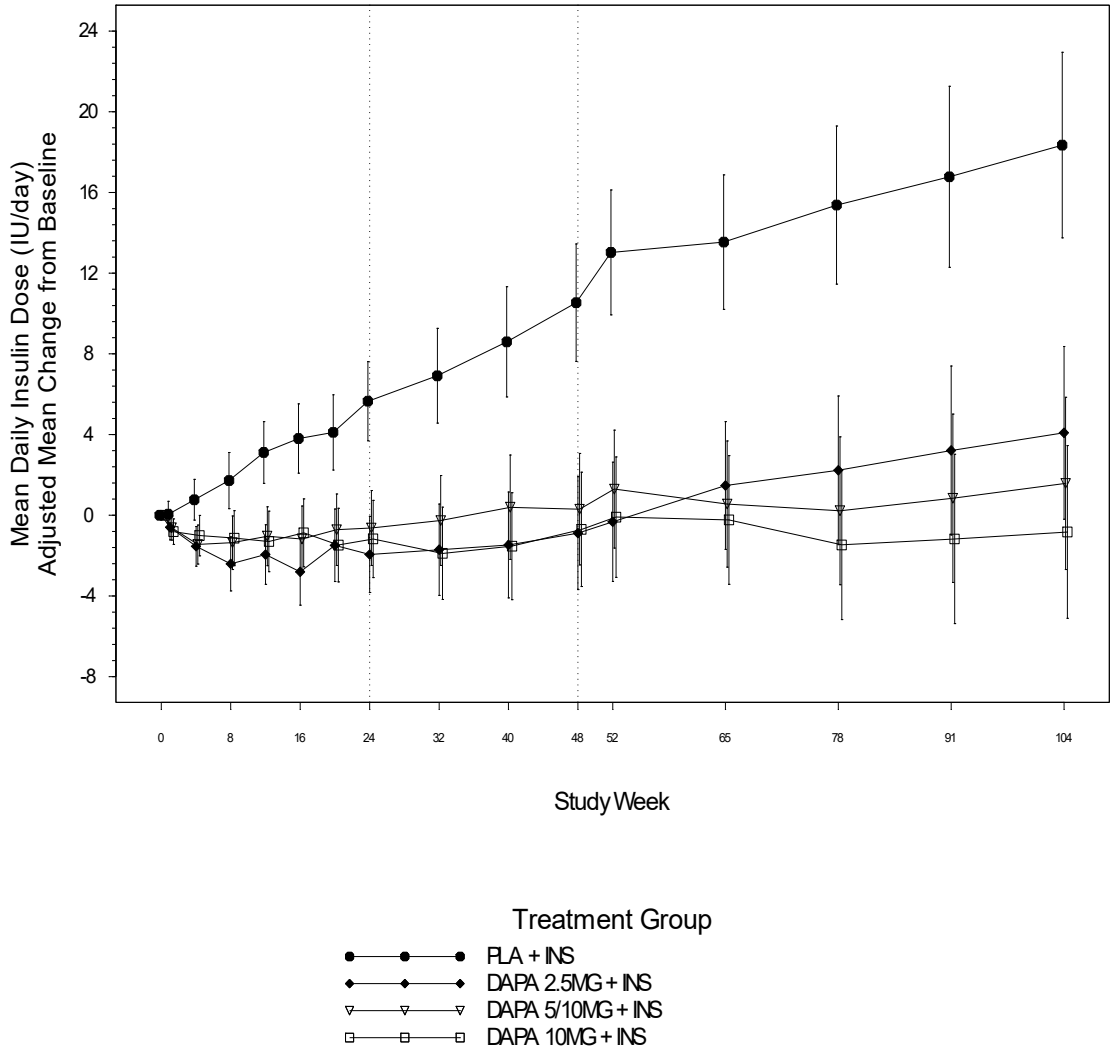
placebo group there was a mean increase of 10.5 IU/day and 18.3 IU/day from baseline at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4% for the group treated with dapagliflozin 10 mg and 54.8% for the placebo group.

Figure 3: HbA1c (%) Adjusted Mean Change from Baseline Over Time Short-term and Long-term Treatment Period in a Placebo-controlled Study of Dapagliflozin in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Excluding Data After Insulin Up-titration.



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 4: **Mean Daily Insulin Dose (IU/day) Adjusted Mean Change from Baseline Over Time in a Placebo-controlled Study of Dapagliflozin in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Short-term and Long-term Treatment Period Including Data After Insulin Up-titration**



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Fasting plasma glucose

Treatment with dapagliflozin 10 mg as an add on to either metformin, metformin and a sulfonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in fasting plasma glucose (-1.90 to -1.20 mmol/L) compared to placebo (-0.33 to 0.21 mmol/L) at 24 weeks. This effect was observed at Week 1 of treatment and maintained in studies extended through Week 104.

Concomitant Initiation therapy with saxagliptin and dapagliflozin in patients inadequately controlled on metformin

In a 24-week randomised, double-blind, active comparator-controlled superiority study comparing the combination of saxagliptin and dapagliflozin added concomitantly to metformin, versus saxagliptin (DPP4-Inhibitor) or dapagliflozin (SGLT2 inhibitor) added to metformin in patients with type 2 diabetes mellitus with inadequate glycaemic control on metformin alone (HbA1c ≥8% and ≤12%).The saxagliptin and dapagliflozin group achieved significantly greater reductions in HbA1c versus either the saxagliptin group or dapagliflozin group at 24 weeks (see Table 10).

Table 10. HbA1c at Week 24 in Active-Controlled Study Comparing the Combination of Saxagliptin and Dapagliflozin Added Concurrently to Metformin with either Saxagliptin or Dapagliflozin Added to Metformin

Efficacy Parameter	**Saxagliptin 5 mg + Dapagliflozin 10 mg + Metformin XR[#] N=179[b]**	**Saxagliptin 5 mg + Metformin XR N=176[b]**	**Dapagliflozin 10 mg + Metformin XR N=179[b]**
HbA1c (%) at week 24[a]			
Baseline (mean)	8.9	9.0	8.9
Change from baseline (adjusted mean)	−1.5	−0.9	−1.2
(95% CI)	(−1.6, −1.3)	(−1.0, −0.7)	(−1.4, −1.0)
Difference from saxagliptin+metformin (adjusted mean[c])	-	−0.6[d]	-
(95% CI)		(−0.8, −0.4)	
Difference from dapagliflozin+metformin (adjusted mean[c])	-	-	−0.3[e]
(95% CI)			(−0.5, −0.0)
Subjects (%) achieving HbA1C <7% (LOCF[f])			
Adjusted for baseline	41.4	18.3	22.2
Body weight (kg)			
Baseline (mean)	87.13	87.98	86.25
Change from Baseline[c]	-2.05	0.00	-2.39
Difference from placebo +saxa+met[c]		-2.05	
(95% CI)		(-2.73, -1.37)	
Difference from placebo +dapa+met[c]			-1.50
(95% CI)			(-2.12, -0.89)

[#] XR = extended release
[a] LRM = Longitudinal repeated measures (using values prior to rescue).
[b] Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
[c] Least squares mean adjusted for baseline value.
[d] p-value < 0.0001.

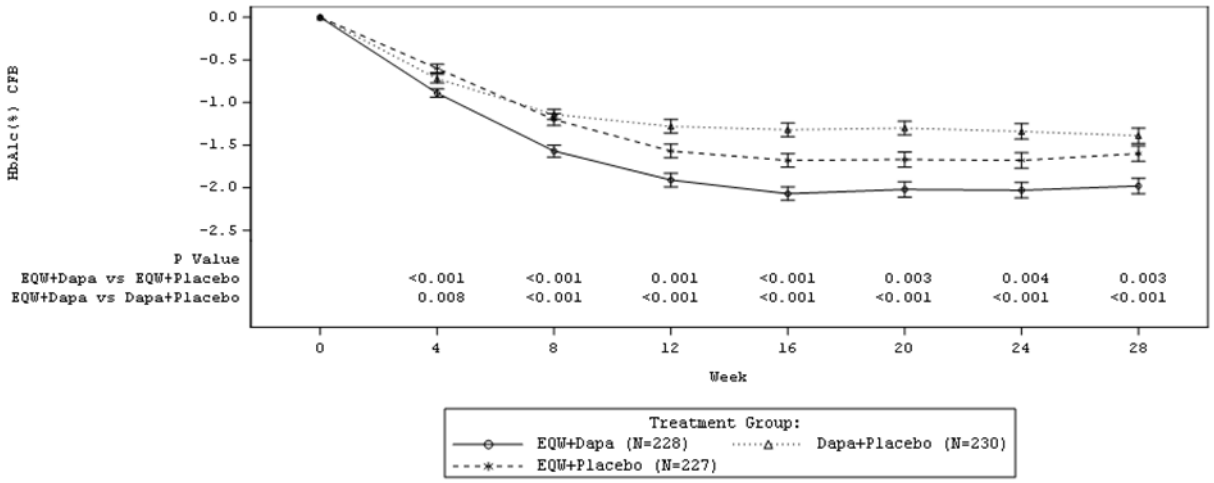
[e] p-value=0.0166
[f] LOCF = Last Observation Carried Forward

Concomitant Initiation of Dapagliflozin and Extended Release Exenatide in patients Inadequately Controlled on Metformin

A total of 694 adult patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥8.0 and ≤12.0%) on metformin alone (≥1,500 mg/day) participated in this 28-week randomised, double-blind, active-controlled trial to compare the concomitant initiation of dapagliflozin 10 mg once daily and extended release exenatide 2 mg once weekly on a background of metformin versus extended release exenatide 2 mg once weekly (GLP-1 receptor agonist) alone and dapagliflozin 10 mg once daily alone when added to metformin. Following a 1-week placebo lead-in period, patients were randomised equally to one of three double-blind treatment groups to receive either dapagliflozin 10 mg and extended release exenatide, dapagliflozin 10 mg and placebo or extended release exenatide and placebo. During the treatment period, patients continued on the same type and dose of metformin as when they entered the study. At baseline, patients had a mean age of 54.2 years and a BMI of 32.73 kg/m2. Randomisation was stratified by HbA1c at baseline (<9.0% or ≥9.0%) and patients were regularly monitored every 4 weeks in this study.

The primary endpoint was the change in HbA1c from baseline to Week 28 (Fig 5). Compared to dapagliflozin 10 mg alone and extended release exenatide alone, concomitant initiation of dapagliflozin 10 mg and extended release exenatide resulted in statistically significant reductions in HbA1c from baseline at Week 28 (Table 11).

Figure 5: Change in HbA1c over Time, LS Mean (SE) – 28-Week Treatment Period (Intent-to-Treat Analysis Set)



CFB=change from baseline; EQW=exenatide 2 mg once weekly; Dapa=dapagliflozin 10 mg once daily.
Baseline is defined as Week 0.

Table 11. Results of a 28-Week Active-Controlled Trial of Dapagliflozin 10 mg and extended Release Exenatide 2 mg Concomitant Add-On to Metformin

	Dapagliflozin 10 mg QD + Extended release exenatide 2 mg QW	Dapagliflozin 10 mg QD + Placebo QW	Extended release exenatide 2 mg QW + Placebo QD
Intent-to-Treat population (N) [c]	**228**	**230**	**227**
HbA1c (%)			
Baseline (mean)[a]	9.29	9.25	9.26
Change from baseline	-1.98	-1.39	-1.60
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-0.59* (-0.84 -0.34)		
Mean difference in change from baseline vs. Extended release exenatide QW (95% CI)	-0.38** (-0.63 -0.13)		
Percent of patients achieving HbA1c <7.0%[b]	44.7%	19.1%	26.9%
Body weight (kg)			
Baseline (mean)[a]	92.13	90.87	89.12
Change from baseline	-3.55	-2.22	-1.56
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-1.33 ** (-2.12 -0.55)		
Mean difference in change from baseline vs. Extended release exenatide (95% CI)	-2.00* (-2.79 -1.20)		
FPG (mmol/L)			
Baseline (mean)[a]	10.9	10.5	10.5
Change from baseline	-3.7	-2.7	-2.5
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-0.92* (-1.36 -0.49)		
Mean difference in change from baseline vs. Extended release exenatide (95% CI)	-1.12* (-1.55 -0.68)		
2-hour PPG (mg/dL)			
Standard meal test population (n)	198	199	188
Baseline (mean)[a]	14.9	14.5	14.8

Table 11. Results of a 28-Week Active-Controlled Trial of Dapagliflozin 10 mg and extended Release Exenatide 2 mg Concomitant Add-On to Metformin

Change from baseline	-4.9	-3.4	-3.3
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-1.49* (-2.04 -0.93)		
Mean difference in change from baseline vs. Extended release exenatide (95% CI)	-1.54* (-2.10 -0.98)		
Seated systolic blood pressure (mmHg)			
Baseline (mean)[a]	130.7	129.5	129.3
Change from baseline	-4.3	-1.8	-1.2
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-2.4[#] (-4.5 -0.4)		
Mean difference in change from baseline vs. Extended release exenatide (95% CI)	-3.0** (-5.2 -0.9)		

QD=once daily, QW=once weekly, N=number of patients in treatment group, CI=confidence interval, FPG= fasting plasma glucose, PPG= postprandial glucose.
[a] Adjusted least squares means (LS Means) and treatment group difference(s) in the change from baseline values at Week 28 are modeled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (< 9.0% or ≥ 9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.
[b] Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders. Treatment comparison is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline HbA1c (< 9.0% or ≥ 9.0%). P-values are from the general association statistics.
[c] Patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.
*p < 0.001, **p < 0.01, [#]p < 0.05.
P values are all adjusted p values for multiplicity.
Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication discontinuation, except for systolic blood pressure analysis, which includes measurements post rescue therapy but excludes data post premature discontinuation of study medication discontinuation.

Post prandial glucose

Treatment with dapagliflozin 10 mg as an add on to sitagliptin (with or without metformin) resulted in reductions in 2 hour post prandial glucose at 24 weeks that were maintained up to Week 48.

Body weight

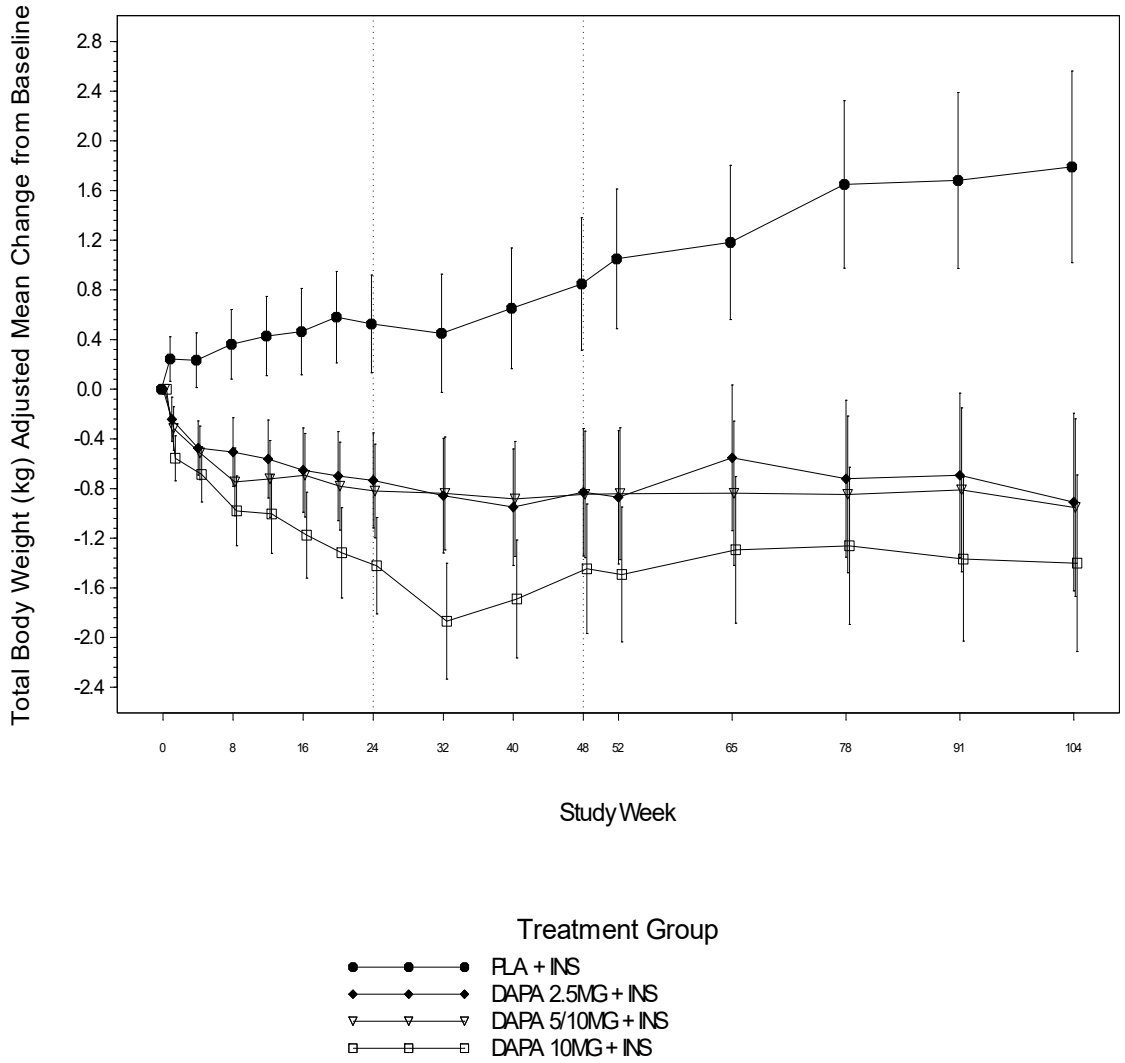
Dapagliflozin 10 mg as an add on to metformin, metformin and a sulfonylurea, sitagliptin (with metformin) or insulin resulted in a statistically significant body weight reduction at 24 weeks (Tables 4, 6, 8and 9) with placebo-corrected reductions of 1.97 kg (2.43%), 2.07 kg (2.25%), 1.87 kg (2.08%) and 1.68 kg (1.83%), respectively. These effects were sustained in longer-term trials (see Fig 6 for add-on to insulin). At 48 weeks, the difference for dapagliflozin as add on to sitagliptin (with or without metformin) compared to placebo was -2.22 kg. At 102 weeks, the differences for dapagliflozin as add on to metformin compared to

placebo, or as add on to insulin (at 104 weeks) compared to placebo were -2.14 kg and -2.88 kg, respectively.

As an add on therapy to metformin in an active controlled non inferiority study, dapagliflozin resulted in a statistically significant body weight reduction compared with glipizide of 4.65kg at 52 weeks (Table 5) compared to glipizide, that was sustained at 104 and 208 weeks (-5.06 kg and -4.38 kg respectively) (see Fig 7).

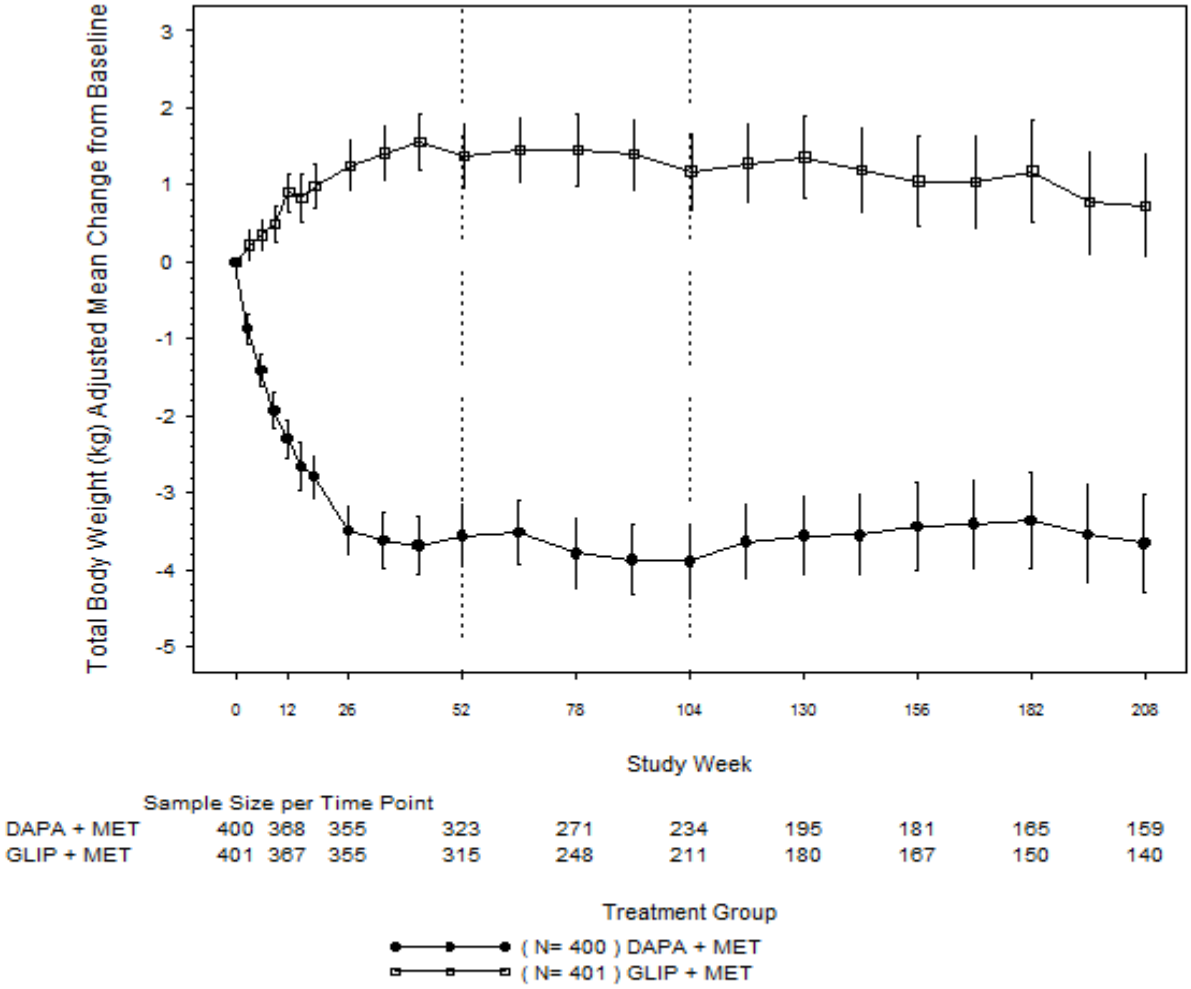
The adjusted mean change from baseline in body weight at Week-24 when dapagliflozin 10 mg and saxagliptin were added concomitantly to metformin was −2.05 kg (-2.27%) in the saxagliptin plus dapagliflozin 10 mg plus metformin group and −2.39 kg (-2.67%) in the dapagliflozin 10 mg plus metformin group, while the saxagliptin plus metformin group had no change (0.00) (See also Table 10). At Week 24 In the dapagliflozin 10 mg as add-on to saxagliptin with metformin study, change from baseline in body weight was -1.91 kg (-2.23%) in the dapagliflozin 10 mg plus saxagliptin plus metformin group (see Table 7).

Figure 6: Total Body Weight (kg) Adjusted Mean Change from Baseline Over Time in a Placebo-controlled Study of Dapagliflozin in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Short-term and Long-term Treatment Period Including Data After Insulin Up-titration



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 7: **Adjusted Mean Change from Baseline Over Time in Body Weight (kg) in a 208-Week Active-Controlled Study Comparing FORXIGA to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)**



Subjects in the full analysis set.
Mean value based on repeated measures analysis model:
post-baseline = baseline treatment week rescue week*treatment week*baseline.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Cardiovascular outcomes

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicenter, randomized, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on cardiovascular (CV) and renal outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension or current tobacco use) without having had a CV event at baseline (primary prevention) or established CV disease (secondary prevention).

Of 17160 randomized patients, 6974 (40.6%) had established CV disease and 10186 (59.4%) did not have established CV disease. 8582 patients were randomized to dapagliflozin 10 mg and 8578 to placebo, and were followed for a median of 4.2 years.

The mean age of the study population was 63.9 years, 37.4% were female, 79.6% were White, 3.5% Black or African-American and 13.4% Asian. In total, 22.4% had had diabetes for ≤5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

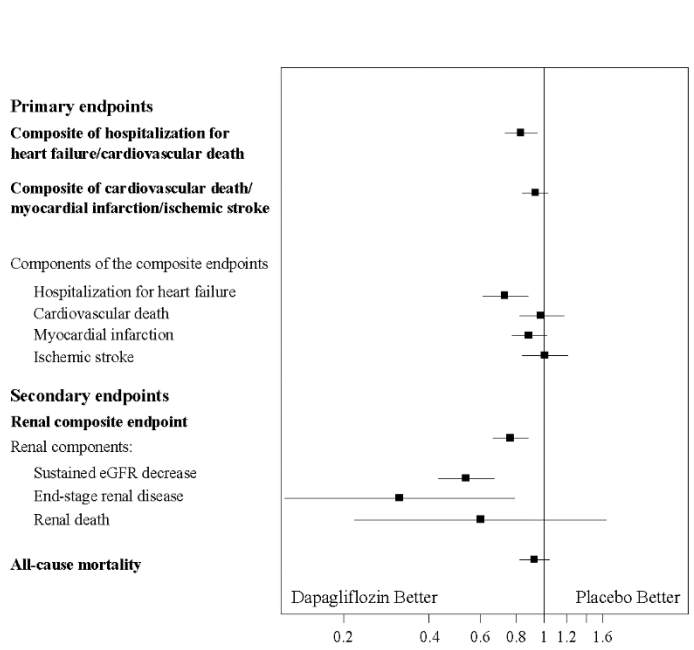
At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR <60mL/min/1.73 m^2 and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ration [UACR] ≥30 to ≤300 mg/g or >300 mg/g, respectively).

Most patients (98.1%) used one or more diabetic medications at baseline, 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 agonist.

Approximately 81.3% of patients were treated with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics and 10.5% with loop diuretics.

Results on primary and secondary endpoints are displayed in Figure 8.

Figure 8 Treatment effects for the primary composite endpoints and their components and the secondary endpoints and components



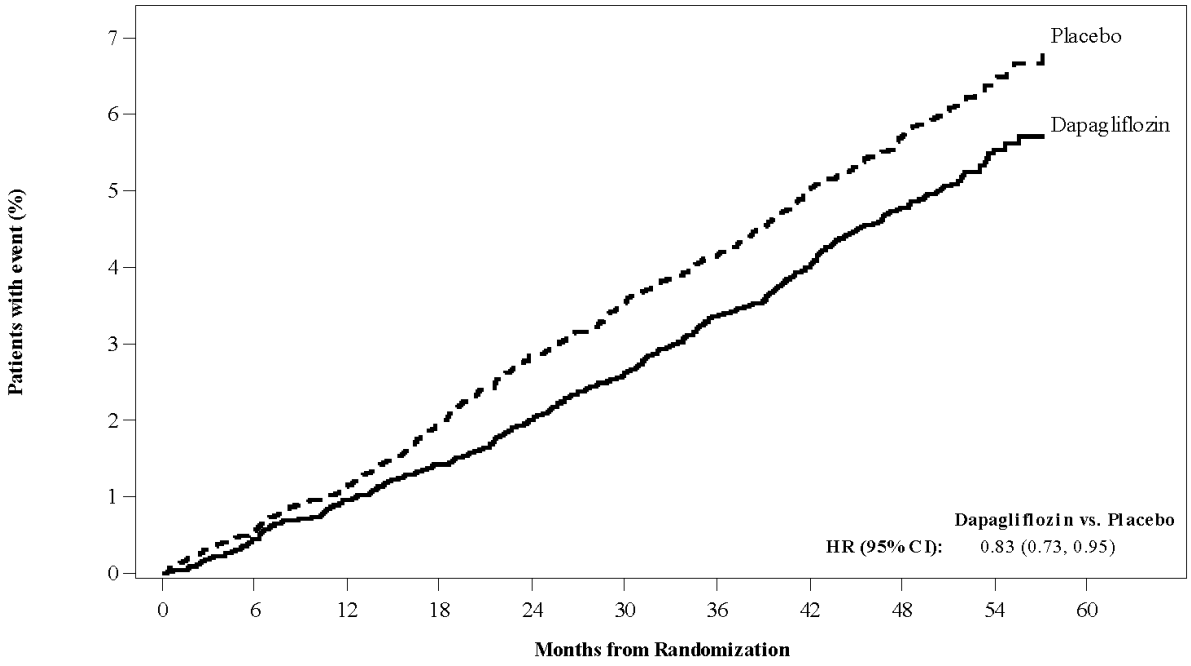
p-values are two-sided p-values for primary endpoints and nominal p-values for secondary endpoints and single components. Time to first event was analyzed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.
Renal composite endpoint is defined as sustained confirmed ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73m^2) and/or renal or CV death.
CI=confidence interval.

Hospitalisation for heart failure or cardiovascular death

Dapagliflozin 10 mg was superior to placebo in preventing the primary composite endpoint of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]; p=0.005) (Figure 9).

Exploratory analyses of the single components suggest that the difference in treatment effect was driven by hospitalization for heart failure (HR 0.73 [95% CI 0.61, 0.88]) (Figure 8), with no clear difference in CV death (HR 0.98 [95% CI 0.82 to 1.17]).

Figure 9 Time to first occurrence of hospitalization for heart failure or cardiovascular death



Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

Patients at risk is the number of patients at risk at the beginning of the period.
CI Confidence interval, HR Hazard ratio

Major adverse cardiovascular events

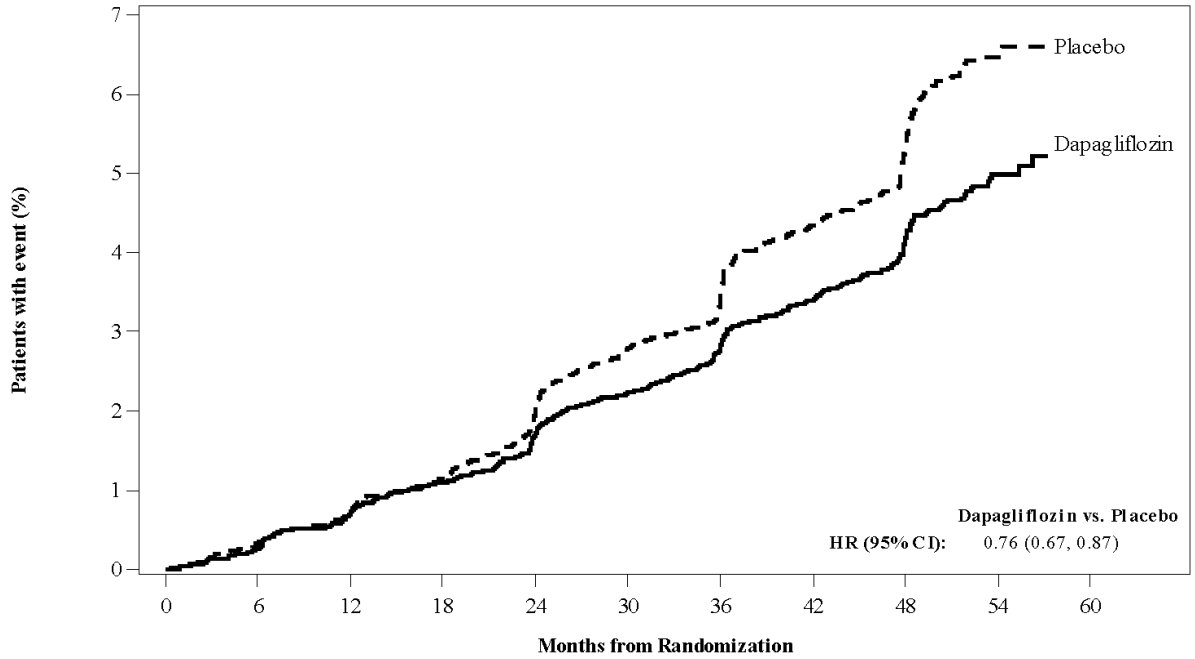
Dapagliflozin demonstrated cardiovascular safety (tested as non-inferiority versus placebo for the composite of CV death, myocardial infarction or ischemic stroke [MACE]; one-sided p <0.001).

Nephropathy

The composite of confirmed sustained eGFR decrease, ESRD, renal or CV death was a secondary variable in the DECLARE study. Because confirmatory testing stopped before the secondary variables were assessed, the analyses of the secondary variables should be considered exploratory.

Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, ESRD, renal or CV death (HR 0.76 [95% CI 0.67, 0.87], Figure 10). The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESRD and renal death (Figure 8), and was observed both in patients with and without CV disease.

Figure 10 Time to first occurrence of sustained eGFR decrease, ESRD, renal or CV death



Patients at risk

Dapagliflozin:	8582	8533	8436	8347	8248	8136	8009	7534	5472	1637
Placebo:	8578	8508	8422	8326	8200	8056	7932	7409	5389	1589

Patients at risk is the number of patients at risk at the beginning of the period.

Renal composite endpoint defined as sustained confirmed eGFR decrease ≥40% to eGFR <60 mL/min/1.73m^2 and/or ESRD and/or renal or CV death.

CI Confidence interval; HR Hazard ratio.

When evaluating the renal components, there were 127 and 238 events of new or worsening nephropathy (sustained eGFR decrease, ESRD or renal death) in patients in the dapagliflozin and placebo groups, respectively. The HR for time to nephropathy was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

Beneficial effects of dapagliflozin on renal outcomes were also observed for albuminuria, e.g.,

- In patients without pre-existing albuminuria, dapagliflozin reduced the incidence of sustained albuminuria (UACR >30 mg/g) compared with placebo (HR 0.79 [95% CI 0.72, 0.87]).
- In patients without pre-existing macroalbuminuria, new onset of macroalbuminuria (UACR >300 mg/g) was reduced in the dapagliflozin group compared with the placebo group (HR 0.54 [95% CI 0.45, 0.65]).
- In patients with pre-existing macroalbuminuria, regression of macroalbuminuria was greater in the dapagliflozin group compared with the placebo group (HR 1.82 [95% CI 1.51, 2.20]).

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without existing renal impairment.

Supportive Studies

Dual Energy X-ray Absorptiometry in Patients with Diabetes

Due to the mechanism of action of dapagliflozin a study was done to evaluate body composition and bone mineral density. Dapagliflozin 10 mg added on to metformin in 182 patients with type 2 diabetes over a 24 week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: -2.96 kg v. -0.88 kg); waist circumference (mean change from baseline: -2.51 cm v. -0.99 cm), and body fat mass as measured by DXA (mean change from baseline -2.22 kg v. -0.74 kg) rather than lean tissue or fluid loss. Dapagliflozin plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (change from baseline -322.6 cm^3 vs. -8.7 cm^3) in an MRI substudy. In an ongoing extension of this study to week 50, there was no important change in bone mineral density for the lumbar spine, femoral neck or total hip seen in either treatment group (mean change from baseline for all anatomical regions <0.5%, 7/89 dapagliflozin and 4/91 comparator subjects showed a decrease of 5% or more). These effects were sustained in a further extension of the study to 102 weeks where no important changes in BMD for the lumbar spine, femoral neck or total hip in either treatment group were observed.

Special Populations

Renal Impairment

Dapagliflozin

Patients with mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2)

In the clinical trial program more than 3000 patients with mild renal impairment were treated with dapagliflozin. Efficacy was assessed in a pooled analysis across 9 clinical studies consisting of 2226 patients with mild renal impairment. The mean change from baseline in haemoglobin A1c (HbA1c) and the placebo-corrected mean HbA1c change at 24 weeks was -1.03% and -0.54%, respectively for FORXIGA 10 mg (n=562). The safety profile in patients with mild renal impairment is similar to that in the overall population.

Patients with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2)

The efficacy and safety of dapagliflozin was evaluated in two dedicated studies of patients with moderate renal impairment.

In a randomized, double blind, placebo-controlled trial a total of 321 adult patients with type 2 diabetes mellitus and eGFR ≥45 to <60 mL/min/1.73 m2 (moderate renal impairment subgroup Chronic Kidney Disease [CKD 3A]), with inadequate glycaemic control on current treatment regimen, were treated with dapagliflozin 10 mg or placebo. At Week 24, dapagliflozin 10 mg (n=159) provided significant improvements in HbA1c, FPG, Body Weight and SBP compared with placebo (n=161) (Table 12). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change was −0.37% and −0.34%, respectively. The mean change from baseline in FPG and the placebo-corrected mean FPG was -1.19 mmol/L and -0.92 mmol/L, respectively. The mean body weight reduction (percentage) and the placebo-corrected mean body weight reduction was -3.42% and -1.43%, respectively. The mean reduction in seated systolic blood pressure (SBP) and the placebo-corrected mean reduction in SBP was -4.8 mmHg and -3.1 mmHg, respectively.

Table 12: Results at Week 24 in a Placebo-Controlled Study of dapagliflozin Treatment in Diabetic Patients with Moderate Renal Impairment (Class 3A, eGFR ≥45 to <60 mL/min/1.73 m2)

Efficacy Parameter	**Dapagliflozin 10 mg N=159**	**Placebo N=161**
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline (adjusted mean*)	-0.37§	-0.03
Difference from placebo (adjusted mean*) (95% CI)	-0.34§ (-0.53, -0.15)	
FPG (mmol/L)		
Baseline (mean)	10.16	9.62
Change from baseline (adjusted mean*)	-1.19§	-0.27

Efficacy Parameter	Dapagliflozin 10 mg N=159	Placebo N=161
Difference from placebo (adjusted mean*) (95% CI)	-0.92§ (-1.48, -0.36)	
Body Weight (percentage)		
Baseline (mean)	92.51	88.30
% Change from baseline (adjusted mean*)	-3.42§	-2.02
Difference from placebo (adjusted mean*) (95% CI)	-1.43§ (-2.15, -0.69)	
Seated Systolic Blood Pressure (mmHg)		
Baseline (mean)	135.7	135.0
Change from baseline (adjusted mean*)	-4.8¶	-1.7
Difference from placebo (adjusted mean*) (95% CI)	-3.1¶ (-6.3, 0.0)	

* Least squares mean adjusted for baseline value.

§ p-value <0.001.

¶ p-value <0.05.

The safety profile of dapagliflozin in the study was consistent with that in the general population of patients with type 2 diabetes. Mean eGFR decreased initially during the treatment period in the dapagliflozin group and subsequently remained stable during the 24-week treatment period (dapagliflozin: -3.39 mL/min/1.73 m^2 and placebo: -0.90 mL/min/1.73 m^2). At 3 weeks after termination of dapagliflozin, the mean change from baseline in eGFR in the dapagliflozin group was similar to the mean change in the placebo group (dapagliflozin: 0.57 mL/min/1.73 m^2 and placebo: -0.04 mL/min/1.73 m^2).

The efficacy and safety of dapagliflozin was also assessed in a study of 252 patients with diabetes with eGFR ≥30 to <60 mL/min/1.73 m^2 (moderate renal impairment subgroup CKD 3A, eGFR ≥45 to <60 mL/minute/1.73 m^2 and CKD 3B, eGFR ≥30 to <45 mL/minute/1.73 m^2). Dapagliflozin treatment did not show a significant placebo corrected change in HbA1c in the overall study population (CKD 3A and CKD 3B combined) at 24 weeks. At Week 52, dapagliflozin was associated with a greater reduction in mean eGFR (dapagliflozin 10 mg −4.46 mL/min/1.73 m^2 and placebo −2.58 mL/min/1.73 m^2). At Week 104, these changes persisted (eGFR: dapagliflozin 10 mg −3.50 mL/min/1.73 m^2 and placebo −2.38 mL/min/1.73 m^2) With dapagliflozin 10 mg, this eGFR reduction were evident at Week 1 and remained stable through Week 104, while placebo-treated patients had a slow continuous decline through Week 52 that stabilized through Week 104.

At Week 52 and persisting through Week 104, greater increases in mean parathyroid hormone (PTH) and serum phosphorus were observed in this study with dapagliflozin 10 mg compared to placebo, where baseline values of these analytes were higher. Elevations of

potassium of ≥6 mEq/L were more common in patients treated with placebo (12.0%) than those treated with dapagliflozin 10 mg (4.8%) during the cumulative 104-week treatment period. The proportion of patients discontinued for elevated potassium, adjusted for baseline potassium, was higher for the placebo group (14.3%) than for the dapagliflozin 10mg group (6.7%).

Overall, there were 13 patients with an adverse event of bone fracture reported in the dapagliflozin group. Eight (8) of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1.73 m^2 and 10 of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the site of fracture. No bone fractures were reported in the dedicated study of patients with eGFR ≥45 to <60 mL/min/1.73 m^2 (CKD 3A). No fractures were reported in the placebo group.

Blood Pressure

In the pre specified pooled analysis of 13 placebo-controlled studies (see section 4.8 Adverse effects (Undesirable effects)), treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of –3.7 mmHg and diastolic blood pressure of –1.8 mmHg versus –0.5 mmHg systolic and 0.5 mmHg diastolic blood pressure for the placebo group at Week 24. Similar reductions were observed up to 104 weeks.

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with dapagliflozin 10 mg or placebo. At Week 12 for both studies, dapagliflozin 10 mg plus usual antidiabetic treatment provided improvement in HbA1c and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively.

5.2 PHARMACOKINETIC PROPERTIES

The results of bioequivalence studies in healthy subjects demonstrated that XIGDUO XR combination tablets are bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride modified-release as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of XIGDUO XR.

Absorption

Dapagliflozin

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects.

Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Metformin hydrochloride

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 µg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. Although the extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin extended-release.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (eg, renal or hepatic impairment).

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. After repeated administration of metformin extended-release, metformin did not accumulate in plasma. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time.

Metabolism

Dapagliflozin

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide. Dapagliflozin 3-O-glucuronide, with a molar plasma AUC 52% higher than that of dapagliflozin itself at the clinical dose, is an inactive metabolite and does not contribute to the glucose lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP mediated metabolism was a minor clearance pathway in humans.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Excretion

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After oral administration of 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Special Populations

Renal Impairment

XIGDUO XR should not be used in patients with eGFR persistently <45 mL/min/1.73 m^2 (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

Dapagliflozin

At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes and mild, moderate or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60% and 87% higher, respectively, than those of patients with type 2 diabetes and normal renal function. At dapagliflozin 20 mg once-daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24 hour glucose excretion. The renal glucose clearance and 24 hour glucose excretion was lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-h urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin exposure is not known. Dapagliflozin should not be used in patients with eGFR persistently <45 mL/min/1.73 m^2 (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

Metformin hydrochloride

In patients with renal impairment function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged in proportion to the decrease in renal function.

Hepatic Impairment

Dapagliflozin

A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively. Dapagliflozin should not be used in patients with severe hepatic impairment (see section 4.4 Special warnings and precautions for use).

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Age

Dapagliflozin

No dosage adjustment for dapagliflozin is recommended on the basis of age. The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group [90% CI: 87.9, 92.2%] and 25% higher in elderly patients compared to the reference group [90% CI: 123, 129%]. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients >70 years old.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it

appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Paediatric and Adolescent

Dapagliflozin

Pharmacokinetics in the paediatric and adolescent population have not been studied.

Metformin hydrochloride

After administration of a single oral metformin 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between paediatric type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function.

Gender

Dapagliflozin

No dosage adjustment from the dose of 10 mg once daily is recommended for dapagliflozin on the basis of gender. Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUC_{ss} in females (n=619) was estimated to be 22% higher than in males (n=634) [90% CI: 117,124].

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin was comparable in males and females.

Race

Dapagliflozin

No dosage adjustment from the dapagliflozin dose of 10 mg once daily is recommended on the basis of race. Race (white, black [African descent] or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures [90% CI range 3.7% lower, 1% higher]. Compared to whites, black (African descent) subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures [90% CI range 7.7% lower, 3.7% lower].

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycaemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Body Weight

Dapagliflozin

No dose adjustment is recommended on the basis of weight.

In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high body weight subjects (≥120 kg, n=91) were estimated to be 78.3% [90% CI: 78.2, 83.2%] of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥120 kg) is recommended.

Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low body weight subjects were estimated to be 29% higher than subjects with the reference group body weight. This difference is considered to be small and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in patients with type 2 diabetes mellitus with low body weight (<50 kg) is recommended.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Dapagliflozin

Dapagliflozin was positive in an in-vitro clastogenicity assay in the presence of metabolic activation. However, dapagliflozin was negative in the Ames mutagenicity assay and in a series of *in-vivo* clastogenicity studies evaluating micronuclei or DNA repair in rats at exposure multiples at least 2100 times the human exposure at the MRHD. The weight of evidence from these studies, along with the absence of tumour findings in the rat and mouse carcinogenicity studies, support that dapagliflozin is not genotoxic.

Metformin hydrochloride

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Carcinogenicity

Dapagliflozin

Dapagliflozin did not induce tumours in two-year carcinogenicity studies in mice or rats at oral doses up to 40 mg/kg/day and 10 mg/kg/day respectively. These doses correspond to AUC exposure levels at least 78 times the human AUC at the MRHD of 10 mg/day.

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet of XIGDUO XR contains the following inactive ingredients: carmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, lactose, crospovidone, silicon dioxide, polyvinyl alcohol, macrogol 3350, titanium dioxide, purified talc, iron oxide red (XIGDUO XR 10/500 and XIGDUO XR 5/1000 tablets), iron oxide yellow (XIGDUO XR 10/1000 tablets).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine .

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

The tablets should be stored below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

- XIGDUO XR 10/500: available in aluminium/ aluminium blister packs of 7 and 28 tablets.
- XIGDUO XR 10/1000: available in aluminium/ aluminium blister packs of 7 and 28 tablets.
- XIGDUO XR 5/1000: available in aluminium/ aluminium blister packs of 14 and 56 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

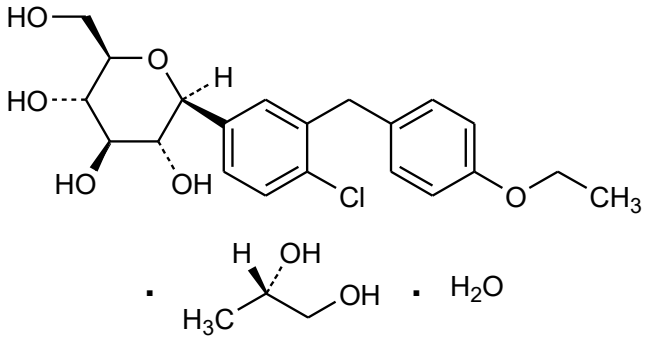
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Dapagliflozin

Dapagliflozin propanediol monohydrate is an orally-active inhibitor of the human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin is described chemically as (1*S*)-1,5-Anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol, (*S*)-propylene glycol, monohydrate.

The chemical structure of dapagliflozin propanediol monohydrate is:



Molecular formula: $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$

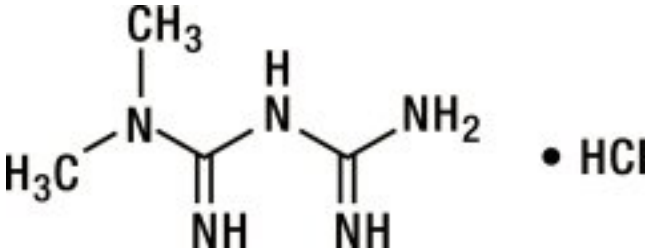
Molecular weight: 502.98

CAS number: 960404-48-2

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide with antihyperglycaemic effects.

The chemical structure of metformin hydrochloride is:



Molecular formula: $C_4H_{11}N_5 \bullet HCl$

Molecular weight: 165.63

CAS number: 1115-70-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

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Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

18 July 2014

10 DATE OF REVISION

30 April 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Changes to warning statement in relation to ketoacidosis and surgery. Addition of increased haematocrit as a warning. Addition of warning for patients on metformin with known/suspected mitochondrial diseases.
4.8	Inclusion of text in relation to adverse events: increased haematocrit, phimosis and tubulointerstitial nephritis

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