

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.

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 CI77491 (XIGDUO XR 10/500 and XIGDUO XR 5/1000 tablets), iron oxide yellow CI77492 (XIGDUO XR 10/1000 tablets).

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 (dapagliflozin 10 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

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

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

No dose adjustment of XIGDUO XR is required for patients with mild renal impairment. XIGDUO XR is contraindicated in patients with moderate or severe renal impairment (CrCl persistently <60 mL/min or eGFR persistently <60 mL/min/1.73 m²). See section 4.3 Contraindications and section 4.4 Special warnings and precautions for use.

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 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. Due to the limited therapeutic experience with dapagliflozin in patients 75 years and older, initiation of therapy with XIGDUO XR is not recommended in this patient group. (See section 4.4 Special warnings and precautions for use).

4.3 CONTRAINDICATIONS

XIGDUO XR is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients; (See section 4.4 Special warnings and precautions for use);
- diabetic ketoacidosis, diabetic pre-coma;
- moderate or severe renal impairment (creatinine clearance < 60 ml/min or eGFR < 60 mL/min/1.73 m²) (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 rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with XIGDUO XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterised by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive

heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle and accompanied only by non-specific symptoms such as malaise, myalgias, 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. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilised on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal, but less than 5 mmol/L, in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See section 4.3 Contraindications).

Use in renal impairment

XIGDUO XR is not recommended in patients with moderate renal impairment (see section 4.3 Contraindications).

Dapagliflozin

The efficacy of dapagliflozin is dependent on renal function. XIGDUO XR should not be used in patients with moderate renal impairment (eGFR persistently <60 mL/min/1.73 m² by MDRD or CrCl persistently <60 mL/min by Cockcroft-Gault) as it will be less efficacious. (See sections 4.2 Dose and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)).

Dapagliflozin has not been studied in patients with severe renal impairment (eGFR <30 mL/min/1.73m² by MDRD or CrCl 30 mL/min by Cockcroft-Gault) or end stage renal disease (ESRD) and should, therefore, also not be used in this population. Based on the mechanism of action, dapagliflozin was not anticipated to be effective in these populations.

Metformin hydrochloride

As metformin is excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function, patients with serum creatinine levels above the upper limit of normal for their age should not receive XIGDUO XR.

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 approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls persistently below CrCl < 60 mL/min or eGFR < 60 mL/min/1.73 m², treatment with XIGDUO XR should be discontinued (see section 4.3 Contraindications).

Decreased renal function in elderly patients is frequent and asymptomatic. In the elderly, XIGDUO XR should be carefully titrated to establish the minimum dose for adequate glycaemic effect because aging is associated with reduced renal function. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, XIGDUO XR should not be titrated to the maximum dose of the metformin component. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy, or when starting treatment with a nonsteroidal anti-inflammatory drug (NSAID).

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

Metformin hydrochloride

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 lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis 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 lactic acidosis in patients taking metformin, XIGDUO XR should not be used in patients with clinical or laboratory evidence of hepatic disease.

Administration of Iodinated contrast agent

Metformin hydrochloride

The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving metformin. Therefore, XIGDUO XR should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.3 Contraindications).

Hypoxic States

Metformin hydrochloride

Cardiovascular collapse (shock), from whatever cause, 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. When such events occur in patients on XIGDUO XR therapy, the drug should be promptly discontinued.

Surgery

Treatment with XIGDUO XR should be ceased at least 48 hours prior to major surgery (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, Hypotension and/or Electrolyte Imbalances

Dapagliflozin

The diuretic effect of dapagliflozin is a potential concern for volume depleted patients. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted.

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.

For patients receiving dapagliflozin, 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 haematocrit) and 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

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving 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).

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 diabetic patients on routine preventative footcare.

Vitamin B12 Levels

Metformin hydrochloride

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on XIGDUO XR and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at 2- to 3-year intervals may be useful.

Alcohol Intake

Metformin hydrochloride

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving XIGDUO XR.

Ketoacidosis

There have been postmarketing reports of ketoacidosis, including diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalisation in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. XIGDUO XR is not indicated for the treatment of patients with type 1 diabetes mellitus.

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.

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 reinstated after the acute episode is resolved.

Use with Medications Known to Cause Hypoglycaemia

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)).

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

As dapagliflozin and metformin are eliminated in part 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.

Dapagliflozin

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti hypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see

section 4.4 Special warnings and precautions for use - Use in renal impairment and section 4.2 Dose and method of administration).

In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse events related to renal impairment or failure compared with placebo. The most commonly reported adverse event related to renal function was increased blood serum creatinine increases, the majority of which were transient and reversible (see section 5.2 Pharmacokinetic properties - Special Populations and section 4.2 Dose and method of administration).

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse events related to volume depletion (see section 4.8 Adverse effects (Undesirable effects)).

Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended (see section 4.8 Adverse effects (Undesirable effects) and section 5.2 Pharmacokinetic properties - Special Populations).

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 because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, metformin should only be used in patients with normal 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).

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with dapagliflozin or any other antidiabetic drug. In a prospective meta-analysis of 21 clinical studies, dapagliflozin use was not associated with an increased risk for adverse cardiovascular events (see section 4.8 Adverse effects (Undesirable effects)).

Cardiac failure

Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV.

Use in patients treated with pioglitazone

While a causal relationship between dapagliflozin and bladder cancer is unlikely (see section 4.8 Adverse effects (Undesirable effects)), as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Available

epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone.

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.

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%.

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 studies conducted in healthy subjects, the pharmacokinetics of dapagliflozin were not altered by metformin, pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate, and P-glycoprotein substrate), glimepiride, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. Dapagliflozin also did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin, or warfarin. 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 type 2 diabetes patients, 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

embryofetal 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.

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 $\geq 2\%$ of patients treated with dapagliflozin 10 mg and $\geq 1\%$ more and at least 3 patients more than treated with placebo are shown in Table 1.

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

	% of patients	
	Dapagliflozin 10mg N=2360	Placebo N=2295
<i>Infections and infestations</i>		
Genital Infection [§]	5.5	0.6
Urinary tract infection*	4.7	3.5
<i>Musculoskeletal and Connective Tissue Disorders</i>		
Back pain	3.5	2.4
<i>Renal and Urinary disorders</i>		

Polyuria [¶]	3.3	1.2
<i>Metabolism and nutrition disorders</i>		
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 $\geq 5\%$ of patients treated with dapagliflozin 10 mg, $\geq 1\%$ 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).

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 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulfonylurea and in 3.7% 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 ($\leq 1.8\%$ 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.

Volume depletion

In the pooled analysis of 13 short-term, placebo-controlled studies, events related to 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 $\leq 0.2\%$ of patients and were balanced between dapagliflozin 10 mg and comparator (see section 4.4 Special warnings and precautions for use).

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.

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.

Events related to decreased renal function

In the 13 study, short-term, placebo controlled pool, adverse effects related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 mL/min/1.73m²) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73m² (18.5% dapagliflozin 10 mg vs 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 44 μ mol/L from baseline. The increases in creatinine were

generally transient during continuous treatment or reversible after discontinuation of treatment.

Malignancies

During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.50%) and placebo/comparator (1.50%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 4.4 Special warnings and precautions for use). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post-authorisation studies.

Cardiovascular Safety

A meta-analysis of cardiovascular events in the clinical program was performed. In the clinical program, 34.4% of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 67.9% had hypertension. Cardiovascular events were adjudicated by an independent adjudication committee. The primary endpoint was the time to first event of the following outcomes: cardiovascular death, stroke, myocardial infarction, and hospitalisation for unstable angina. Primary events occurred at a rate of 1.62% per patient-year in patients treated with dapagliflozin and 2.06% in comparator-treatment patients, per patient-year. The hazard ratio comparing dapagliflozin to comparator was 0.79 (95% confidence interval: 0.58, 1.07), indicating that in this analysis, dapagliflozin is not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus. Cardiovascular death, MI and stroke were observed with a hazard ratio of 0.77 (95% CI: 0.54, 1.10).

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

Very rare: A decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long term with metformin (< 1/10,000). 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.

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

Infections and infestations – Pyelonephritis, urosepsis

Skin and subcutaneous tissue disorders – Rash

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 type 2 diabetes patients, 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). Dapagliflozin is orally available and requires once daily dosing.

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 $\mu\text{mol/L}$.

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, DPP4 inhibitor or insulin, in treatment-naïve 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 type 2 diabetes patients with cardiovascular disease (approximately 37% of patients across 2 studies received dapagliflozin 10 mg or placebo plus metformin alone [with or without insulin]) and type 2 diabetes patients 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 HbA1c and FPG, compared with either of the monotherapy treatments and significant improvements in body weight compared with metformin alone (Table 2). 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 2. 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)		
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

Table 2. 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)	-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 3).

Table 3. 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)
Body Weight (kg)		
Baseline mean	86.28	87.74
Change from baseline (adjusted mean [‡])	-2.86	-0.89
Difference from placebo (adjusted mean [‡]) (95% CI)	-1.97 [§] (-2.63, -1.31)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

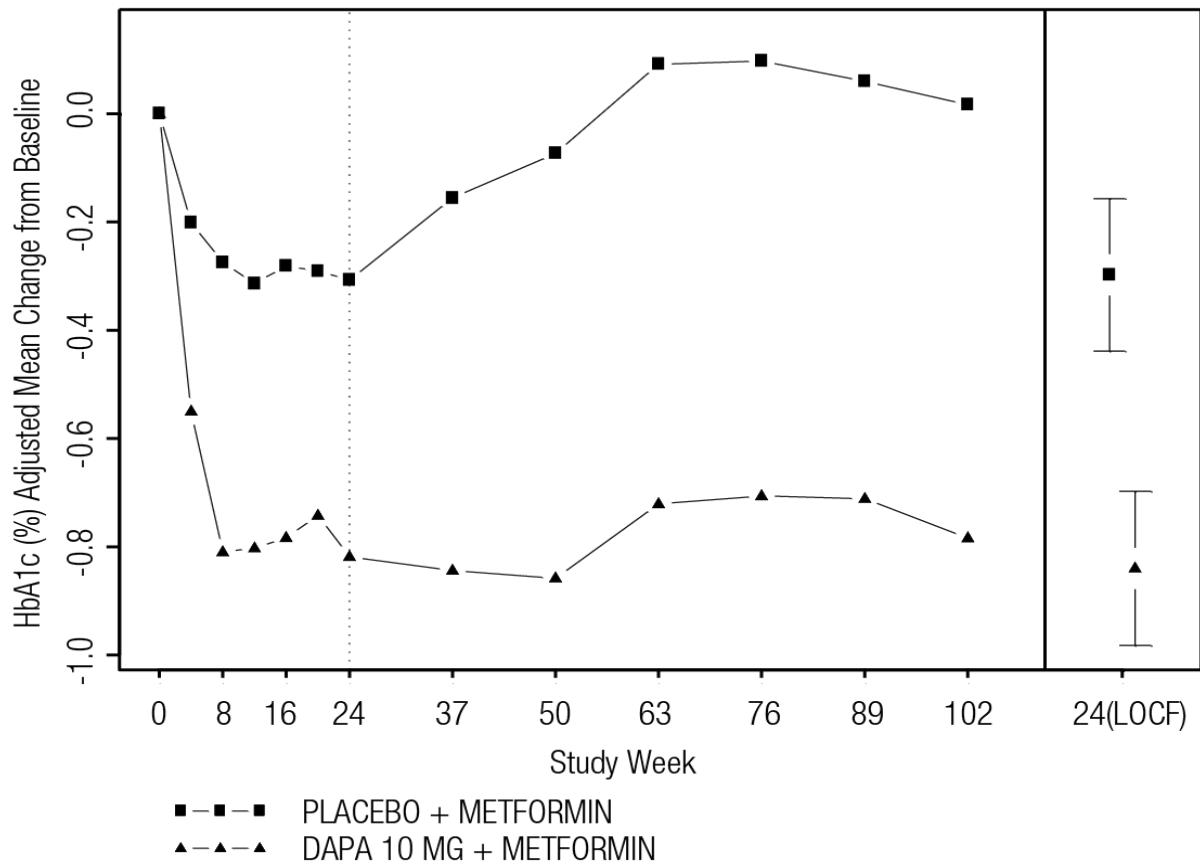
† All randomised patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ 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 4). 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 4. 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 [‡]) (95% CI)	0.00 [¶] (-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 [‡]) (95% CI)	-4.65 [§] (-5.14, -4.17)	2.5%

*LOCF: last observation carried forward.

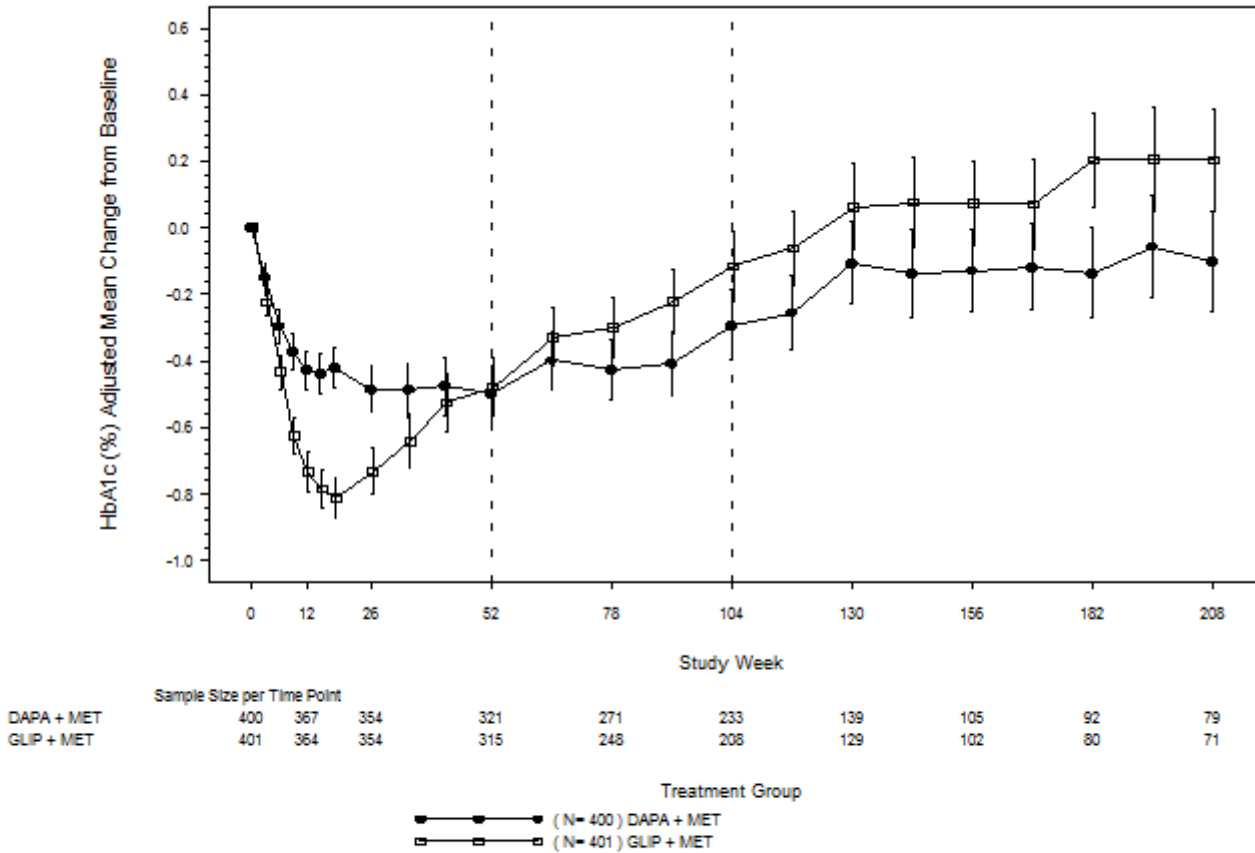
[†] Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[‡] 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 5, 6, 7 and 8).

Table 5. 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 [‡]) (95% CI)	-0.40 [§] (-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 [‡]) (95% CI)	-1.87 [§] (-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 6. 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 (95% CI)	-0.72 [*] (-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 (95% CI)	-1.50 [*] (-2.12, -0.89)	

¹Metformin ≥1500 mg/day; ³saxagliptin 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

^cLeast squares mean adjusted for baseline value

^{*}p-value <0.0001 versus placebo + oral glucose-lowering medicinal product

Table 7. 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 [‡]) (95% CI)	-0.69 [§] (-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 [‡]) (95% CI)	-2.07 [§] (-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 8. 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 [‡]) (95% CI)	-0.60 [§] (-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 [‡] (95% CI)	-6.23 [§] (-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 [‡]) (95% CI)	-1.68 [§] (-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.

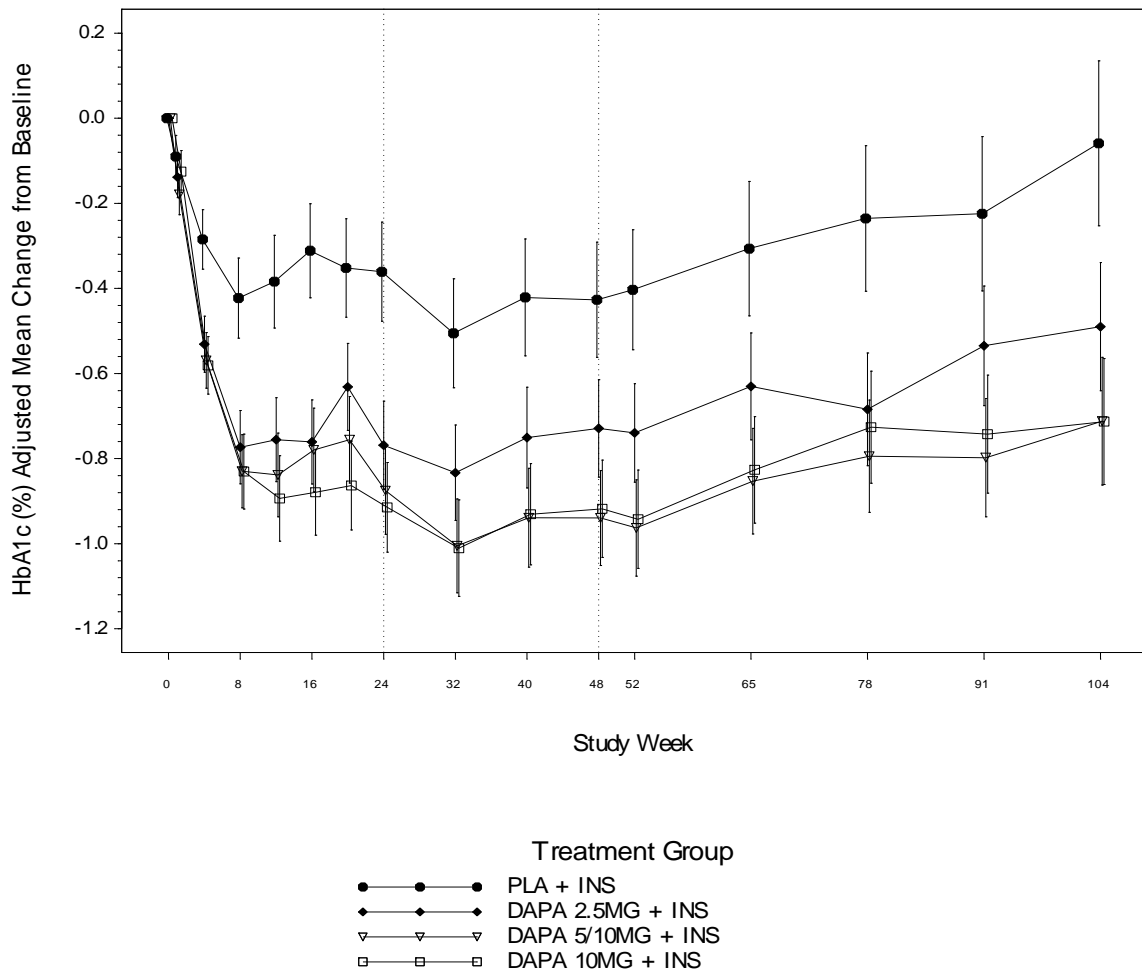
[^] Fifty percent of subjects were on insulin therapy monotherapy at baseline: 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group 80% were on metformin alone, 12 % were on metformin plus sulfonylurea therapy and the rest were on other oral glucose-lowering 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

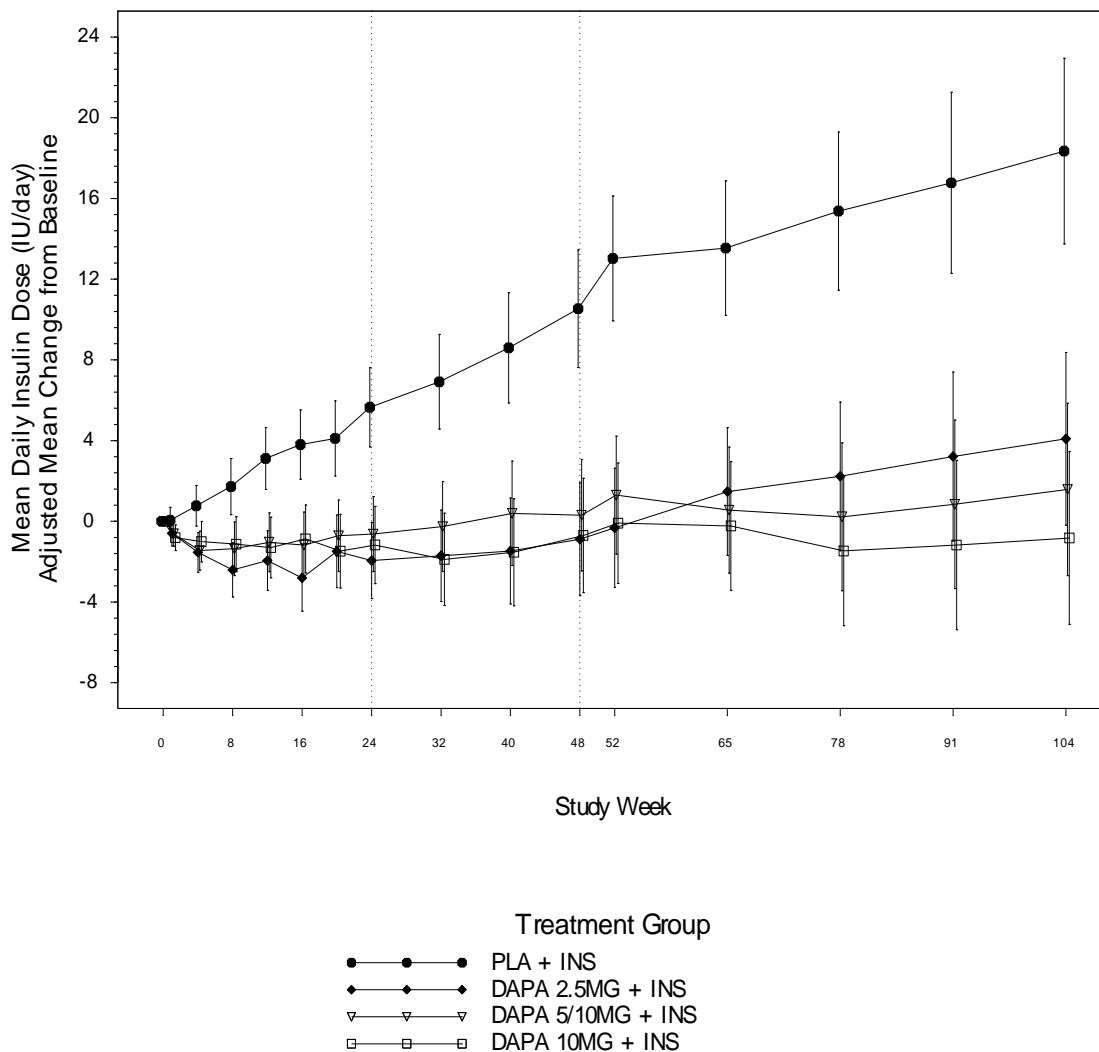
placebo group there was a mean increase of 10.5 IU/day and 18.3 IU/day from baseline at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4% for the group treated with dapagliflozin 10 mg and 54.8% for the placebo group.

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 $\geq 8\%$ and $\leq 12\%$). The saxagliptin and dapagliflozin group achieved significantly greater reductions in HbA1c versus either the saxagliptin group or dapagliflozin group at 24 weeks (see Table 9).

Table 9. 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.

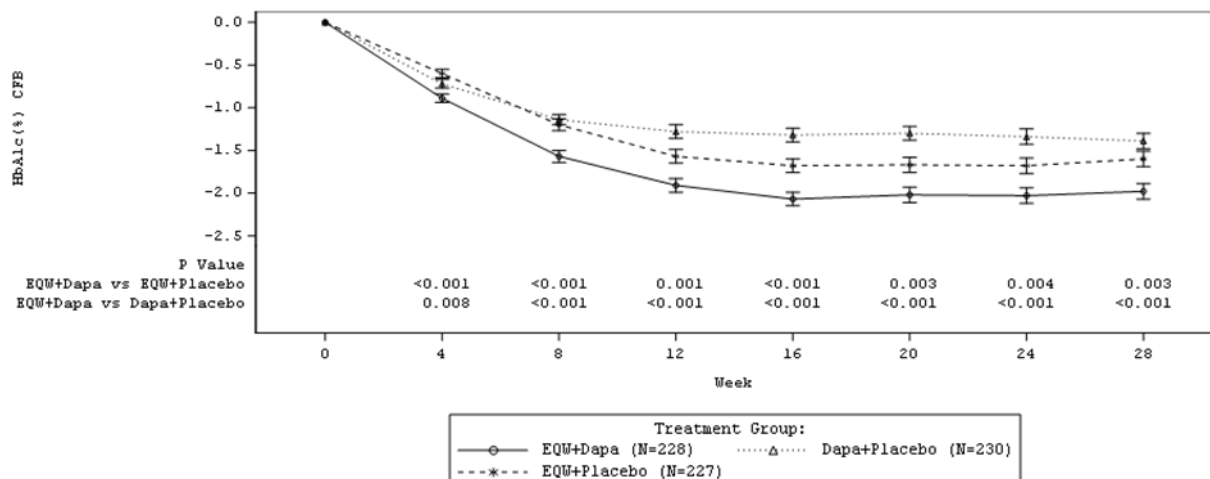
^e p-value=0.0166
^f LOCF = Last Observation Carried Forward

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 $\leq 12.0\%$) on metformin alone ($\geq 1,500$ 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 $\geq 9.0\%$) 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 10).

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 10. 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 10. 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 <u>exenatide</u> (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

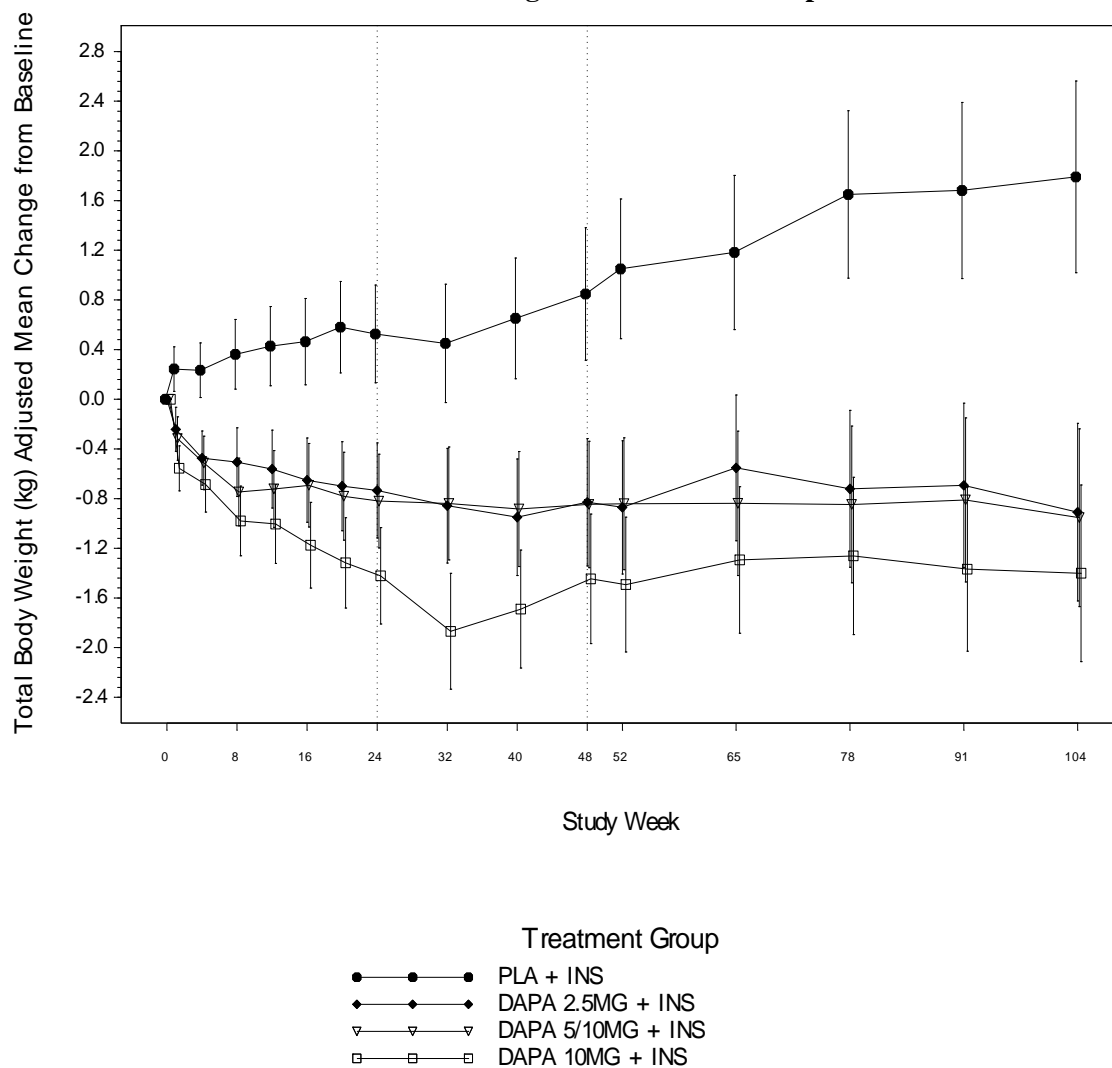
Dapagliflozin 10 mg as an add on to metformin, metformin and a sulfonylurea, sitagliptin (with metformin) or insulin resulted in a statistically significant body weight reduction at 24 weeks (Tables 3, 5, 7 and 8) with placebo-corrected reductions of 1.97 kg (2.43%), 2.07 kg (2.25%), 1.87 kg (2.08%) 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 4) compared to glipizide, that was sustained at 104 and 208 weeks (-5.06 kg and -4.38 kg respectively) (see Fig 7).

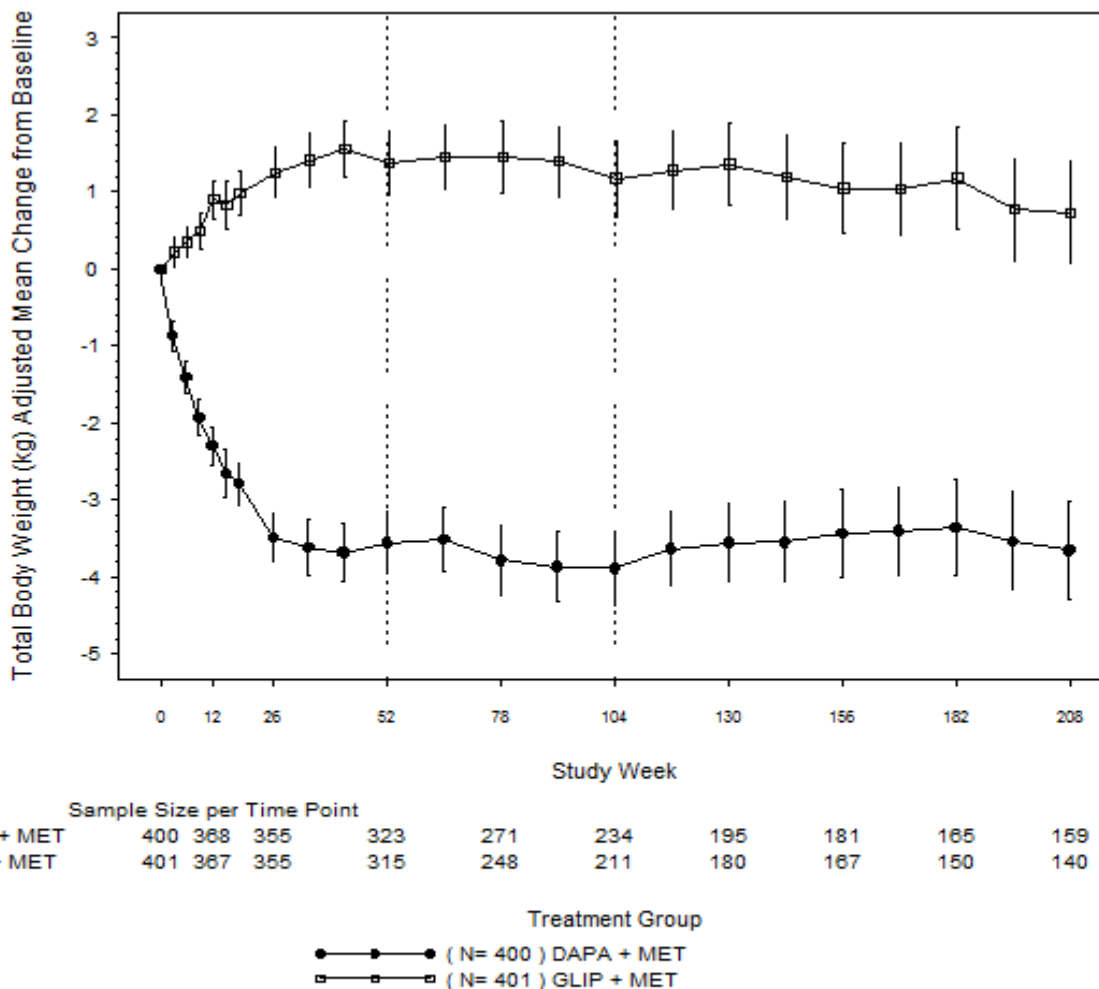
The adjusted mean change from baseline in body weight at Week-24 when dapagliflozin 10 mg and saxagliptin were added concomitantly to metformin was -2.05 kg (-2.27%) in the saxagliptin plus dapagliflozin 10 mg plus metformin group and -2.39 kg (-2.67%) in the dapagliflozin 10 mg plus metformin group, while the saxagliptin plus metformin group had no change (0.00) (See also Table 9). 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 6).

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.

Supportive Studies

Dual Energy X-ray Absorptiometry in Diabetic Patients

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 cm³ vs. -8.7 cm³) 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.

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 $\mu\text{g/mL}$ 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 moderate or severe renal impairment (CrCl <60 mL/min or eGFR <60 mL/min/1.73 m²). 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 moderate or severe renal impairment (CrCl persistently <60 mL/min or eGFR persistently <60 mL/min/1.73m²), see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use.

Metformin hydrochloride

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

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.

Elderly Patients

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 type 2 diabetes mellitus patients 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

Refer to Section 2-Qualitative and quantitative composition.

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.

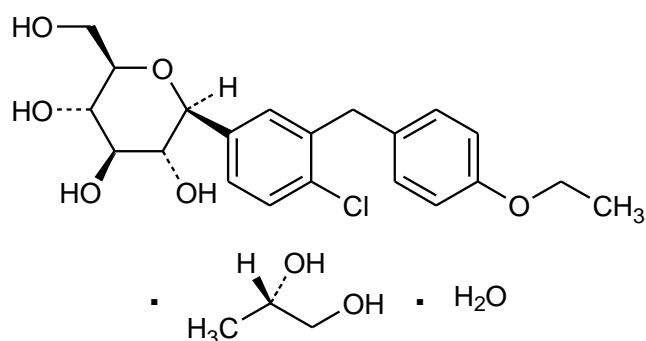
6.7 PHYSICOCHEMICAL PROPERTIES

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: $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$

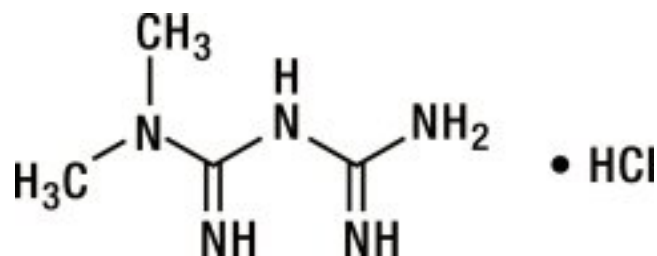
Molecular weight: 502.98

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: $C_4H_{11}N_5 \cdot HCl$

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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9 DATE OF FIRST APPROVAL

18 July 2014

10 DATE OF REVISION

07 September 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Updated Ketoacidosis section Updated Surgery section

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Doc ID-003000267 v7.0