XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use
Xigduo XR 5mg/500mg extended release tablets
Xigduo XR 5mg/1000mg extended release tablets
Xigduo XR 10mg/500mg extended release tablets
Xigduo XR 10mg/1000mg extended release tablets

WARNING: LACTIC ACIDOSIS

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL *[see Warnings and Precautions (5.1)]*.**

- **Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.**
- **Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the full prescribing information *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue XIGDUO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.1)]*.**

. 1. Therapeutic indications

XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate [see *Clinical Studies (14)*].

1.1 Limitations of Use

XIGDUO XR is not recommended for patients with type 1 diabetes mellitus or diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of XIGDUO XR

- Assess renal function before initiating XIGDUO XR therapy and periodically thereafter *[see Warnings and Precautions (5.1, 5.4)]*.
- In patients with volume depletion, correct this condition prior to initiation of XIGDUO XR *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5)]*.

2.2 Recommended Dosage

- Take Xigduo XR once daily in the morning with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin.
- Swallow XIGDUO XR tablets whole and never crush, cut, or chew. Occasionally, the inactive ingredients of XIGDUO XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.
- Individualize the starting dose of XIGDUO XR based upon the patient's current regimen
- Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2000 mg metformin HCl.
- Patients taking an evening dose of metformin XR should skip their last dose before starting XIGDUO XR.

- In patients with volume depletion, correcting this condition prior to initiation of XIGDUO XR is recommended [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.5)*, and *Patient Counseling Information (17)*].

2.3 Patients with Renal Impairment

No dosage adjustment for XIGDUO XR is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2 .

XIGDUO XR is not recommended in patients with an eGFR below 45 mL/min/1.73 m^2.

3 DOSAGE FORMS AND STRENGTHS

XIGDUO XR (dapagliflozin and metformin HCl) extended-release. tablets are available as follows:

- 5 mg/500 mg tablets are orange, biconvex, capsule-shaped, and film-coated tablets with "1070" and "5/500" debossed on one side and plain on the reverse side.
- 5 mg/1000 mg tablets are pink to dark pink, biconvex, oval-shaped, and film-coated tablets with "1071" and "5/1000" debossed on one side and plain on the reverse side.

- 10 mg/500 mg tablets are pink, biconvex, capsule-shaped, and film-coated tablets with "1072" and "10/500" debossed on one side and plain on the reverse side.
- 10 mg/1000 mg tablets are yellow to dark yellow, biconvex, oval-shaped, and film-coated tablets with "1073" and "10/1000" debossed on one side and plain on the reverse side.

4 CONTRAINDICATIONS

XIGDUO XR is contraindicated in patients with:

- severe renal impairment (eGFR below 30 mL/min/1.73 m^2 end stage renal disease or patients on dialysis [see *Warnings and Precautions (5.1)*].
- History of a serious hypersensitivity reaction to dapagliflozin or hypersensitivity to metformin hydrochloride [see *Adverse Reactions (6.1)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis,

including fatal cases. These cases

had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence, ; however, hypothermia, hypotension, and resistant bradyarrhythmias have accorred with severe acidosis

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5mmol/L), anion gap acidosis (without evidence of (ketonuria or ketonemia).

), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis especially in patients at risk.

If metformin, -associated lactic acidosis is suspected, general supportive measures should be instituted. promptly in a hospital setting, along with immediate discontinuation of XIGDUO XR.

In XIGDUO XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin. (metformin HCl is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery

Hypoxic States *:* Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur , discontinue XIGDUO XR.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin associated lactic acidosis Warn patients against excessive alcohol intake while receiving XIGDUO XR.

Hepatic Impairment : Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. . Therefore, avoid use of XIGDUO XR in patients with . clinical or laboratory evidence of hepatic disease.

5.2 Hypotension

Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin [see *Adverse Reactions (6.1)*], particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics.

Before initiating XIGDUO XR in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

5.3 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus taking sodium glucose co-transporter-2 (SGLT2) inhibitors, including dapagliflozin. XIGDUO XR is not indicated for the treatment of patients with type 1 diabetes mellitus [see *Indications and Usage (1.1)*].

Patients treated with XIGDUO XR who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood glucose levels as ketoacidsosis associated with XIGDUO XR may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, XIGDUO XR should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe

metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating XIGDUO XR, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing XIGDUO XR for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)].*

consider monitoring for ketoacidosis and temporarily discontinuing XIGDUO XR in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting XIGDUO XR.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue XIGDUO XR and seek medical attention immediately if signs and symptoms occur.

5.4 Acute Kidney Injury and Impairment in Renal Function

Dapagliflozin causes intravascular volume contraction *[see Warning and Precautions (5.1)]*, and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin. some reports involved patients younger than 65 years of age.

Before initiating XIGDUO XR, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing XIGDUO XR in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue XIGDUO XR promptly and institute treatment.

Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating XIGDUO XR *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiation of XIGDUO XR and monitored periodically thereafter.

Use of XIGDUO XR is not recommended when the eGFR is less than 45 mL/min/1.73 m^2.

XIGDUO XR is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)]*.

5.5 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections;. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. [see *Adverse Reactions (6.2)*].

5.6 Use with Medications Known to Cause Hypoglycemia

Dapagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin can increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue [see *Adverse Reactions (6.1)*]. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with XIGDUO XR.

Metformin hydrochloride Hypoglycemia 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 hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking betaadrenergic blocking drugs.

5.7 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with XIGDUO XR presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue XIGDUO XR, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.8Vitamin B_{12} Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. This decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex is, however, very rarely associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on XIGDUO XR and any apparent abnormalities should be appropriately investigated and managed [see *Adverse Reactions (6.1)*].

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

5.9 Genital Mycotic Infections

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections [see *Adverse Reactions (6.1)*]. Monitor and treat appropriately.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hypotension [see *Warnings and Precautions (5.2)*]
- Ketoacidosis [*see Warnings and Precautions (5.3)*]
  - Acute Kidney Injury *[see Warnings and Precautions (5.4)]*
- Urosepsis and Pyelonephritis [*see Warnings and Precautions (5.5)*]
- Use with Medications Known to Cause Hypoglycemia [see *Warnings and Precautions (5.6)*]
  - Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.7)]*
- Vitamin B_{12} Concentrations [see *Warnings and Precautions (5.8)*]
- Genital Mycotic Infections [see *Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Dapagliflozin and Metformin hydrochloride

Data from a prespecified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin coadministered with metformin immediate- or extended-release was used to evaluate safety. This pool included several add-on studies (metformin alone and in combination with a dipeptidyl peptidase-4 [DPP4] inhibitor and metformin, or insulin and metformin, 2 initial combination with metformin studies, and 2 studies of patients with cardiovascular disease [CVD] and type 2 diabetes who received their usual treatment [with metformin as background therapy]). For studies that included background therapy with and without metformin, only patients who received metformin were included in the 8-study placebo-controlled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 mg and metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean duration of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years. Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or African American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients.

The overall incidence of adverse events for the 8-study, short-term, placebo-controlled pool in patients treated with dapagliflozin 10 mg and metformin was 60.3% compared to 58.2% for the placebo and metformin group. Discontinuation of therapy due to adverse events in patients who received dapagliflozin 10 mg and metformin was 4% compared to 3.3% for the placebo and metformin group. The most commonly reported events leading to discontinuation and reported in at least 3 patients treated with dapagliflozin 10 mg and metformin were renal impairment (0.7%), increased blood creatinine (0.2%), decreased renal creatinine clearance (0.2%), and urinary tract infection (0.2%).

Table 1 shows common adverse reactions associated with the use of dapagliflozin and metformin. These adverse reactions were not present at baseline, occurred more commonly on dapagliflozin and metformin than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.

Table 1: Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin and Metformin

Adverse Reaction	**% of Patients**		
	Pool of 8 Placebo-Controlled Studies		
	Placebo and Metformin N=1185	**Dapagliflozin 5 mg and Metformin N=410**	**Dapagliflozin 10 mg and Metformin N=983**
Female genital mycotic infections[1]	1.5	9.4	9.3
Nasopharyngitis	5.9	6.3	5.2
Urinary tract infections[2]	3.6	6.1	5.5
Diarrhea	5.6	5.9	4.2
Headache	2.8	5.4	3.3
Male genital mycotic infections[3]	0	4.3	3.6
Influenza	2.4	4.1	2.6
Nausea	2.0	3.9	2.6
Adverse Reaction	**% of Patients**		
	Pool of 8 Placebo-Controlled Studies		
	Placebo and Metformin N=1185	**Dapagliflozin 5 mg and Metformin N=410**	**Dapagliflozin 10 mg and Metformin N=983**
Back pain	3.2	3.4	2.5
Dizziness	2.2	3.2	1.8
Cough	1.9	3.2	1.4
Constipation	1.6	2.9	1.9
Dyslipidemia	1.4	2.7	1.5
Pharyngitis	1.1	2.7	1.5
Increased urination[4]	1.4	2.4	2.6
Discomfort with urination	1.1	2.2	1.6

1. Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, genital infection, vulvovaginitis, fungal genital infection, vulvovaginal candidiasis, vulval abscess, genital candidiasis, and vaginitis bacterial. (N for females: Placebo and metformin=534, dapagliflozin 5 mg and metformin=223, dapagliflozin 10 mg and metformin=430).
2. Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, pyelonephritis, urethritis, and prostatitis.
3. Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, balanoposthitis. (N for males: Placebo and metformin=651, dapagliflozin 5 mg and metformin=187, dapagliflozin 10 mg and metformin=553).
4. Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

Metformin hydrochloride

In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with metformin extended-release.

Pool of 12 Placebo-Controlled Studies for Dapagliflozin 5 and 10 mg

Dapagliflozin

The data in Table 2 are derived from 12 placebo-controlled studies ranging from 12 to 24 weeks. In 4 studies dapagliflozin was used as monotherapy, and in 8 studies dapagliflozin was used as add-on to background antidiabetic therapy or as combination therapy with metformin [see *Clinical Studies (14.1)*].

These data reflect exposure of 2338 patients to dapagliflozin with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), dapagliflozin 5 mg (N=1145), or dapagliflozin 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean HbA1c of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m^2).

Table 2 shows common adverse reactions associated with the use of dapagliflozin. These adverse reactions were not present at baseline, occurred more commonly on dapagliflozin than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.

Table 2: Adverse Reactions in Placebo- Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin

Adverse Reaction	**% of Patients**		
	Pool of 12 Placebo-Controlled Studies		
	Placebo **N=1393**	**Dapagliflozin 5 mg N=1145**	**Dapagliflozin 10 mg N=1193**
Female genital mycotic infections[1]	1.5	8.4	6.9

Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections[2]	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination[3]	1.7	2.9	3.8
Male genital mycotic infections[4]	0.3	2.8	2.7
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

1. Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, dapagliflozin 5 mg=581, dapagliflozin 10 mg=598).
2. Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.
3. Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.
4. Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis. (N for males: Placebo=716, dapagliflozin 5 mg=564, dapagliflozin 10 mg=595).

Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg

dapagliflozin 10 mg was also evaluated in a larger placebo-controlled study pool. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with dapagliflozin 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m^2).

Volume Depletion

Dapagliflozin causes an osmotic diuresis, which may lead to reductions in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) are shown in Table 3 for the 12-study and 13-study, short-term, placebo-controlled pools [see *Warnings and Precautions (5.2)*].

Table 3: Adverse Reactions of Volume Depletion[1] in Clinical Studies with Dapagliflozin

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies	
	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies	
	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)
Patient Subgroup n (%)					
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m^2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)

1. Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Impairment of Renal Function

Use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 4). In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline values at Week 24. Renal-related adverse reactions, including renal failure and blood creatinine increase, were more frequent in patients treated with dapagliflozin (see Table 5). Elderly patients and patients with impaired renal function were more susceptible to these adverse reactions (see Table 5). Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2).

Table 4: Changes in Serum Creatinine and eGFR Associated with Dapagliflozin in the Pool of 12 Placebo-Controlled Studies and Moderate Renal Impairment Studies

		Pool of 12 Placebo-Controlled Studies		
		Placebo N=1393	Dapagliflozin 5 mg N=1145	Dapagliflozin 10 mg N=1193
Baseline Mean	Serum Creatinine (mg/dL)	0.853	0.860	0.847
	eGFR (mL/min/1.73 m^2)	86.0	85.3	86.7
Week 1 Change	Serum Creatinine (mg/dL)	−0.003	0.029	0.041
	eGFR (mL/min/1.73 m^2)	0.4	−2.9	−4.1
Week 24 Change	Serum Creatinine (mg/dL)	−0.005	−0.001	0.001
	eGFR (mL/min/1.73 m^2)	0.8	0.8	0.3
		Moderate Renal Impairment Study (eGFR 30 to less than 60 mL/min/1.73 m^2)		
		Placebo N=84	Dapagliflozin 5 mg N=83	Dapagliflozin 10 mg N=85
Baseline Mean	Serum Creatinine (mg/dL)	1.46	1.53	1.52

	eGFR (mL/min/1.73 m^2)	45.6	44.2	43.9
Week 1 Change	Serum Creatinine (mg/dL)	0.01	0.13	0.18
	eGFR (mL/min/1.73 m^2)	0.5	−3.8	−5.5
Week 24 Change	Serum Creatinine (mg/dL)	0.02	0.08	0.16
	eGFR (mL/min/1.73 m^2)	0.03	−4.0	−7.4
Week 52 Change	Serum Creatinine (mg/dL)	0.10	0.06	0.15
	eGFR (mL/min/1.73 m^2)	−2.6	−4.2	−7.3

		Moderate Renal Impairment Study (eGFR 45 to less than 60 mL/min/1.73 m^2)	
		Placebo N=161	**Dapagliflozin 10 mg N=160**
Baseline Mean	Serum Creatinine (mg/dL)	1.25	1.25
	eGFR (mL/min/1.73 m^2)	53.6	53.3
Week 4 Change	Serum Creatinine (mg/dL)	-0.02	0.09
	eGFR (mL/min/1.73 m^2)	1.3	-3.8
Week 12 Change	Serum Creatinine (mg/dL)	-0.02	0.08
	eGFR (mL/min/1.73 m^2)	1.5	-3.2
Week 24 Change	Serum Creatinine (mg/dL)	-0.003	0.06
	eGFR (mL/min/1.73 m^2)	0.8	-2.0

Table 5: Proportion of Patients with at Least One Renal Impairment-Related Adverse Reaction

	Pool of 6 Placebo-Controlled Studies (up to 104 weeks)[1]			**Pool of 9 Placebo-Controlled Studies (up to 104 weeks)[2]**	
Baseline Characteristic	**Placebo**	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**
Overall population Patients (%) with at least one event	n=785 13 (1.7%)	n=767 14 (1.8%)	n=859 16 (1.9%)	n=1956 82 (4.2%)	n=2026 136 (6.7%)
65 years of age and older Patients (%) with at least one event	n=190 4 (2.1%)	n=162 5 (3.1%)	n=159 6 (3.8%)	n=655 52 (7.9%)	n=620 87 (14.0%)
eGFR ≥30 and <60 mL/min/1.73 m^2 Patients (%) with at least one event	n=77 5 (6.5%)	n=88 7 (8.0%)	n=75 9 (12.0%)	n=249 40 (16.1%)	n=251 71 (28.3%)
65 years of age and older and eGFR ≥30 and <60 mL/min/1.73 m^2 Patients (%) with at least one event	n=41 2 (4.9%)	n=43 3 (7.0%)	n=35 4 (11.4%)	n=141 27 (19.1%)	n=134 47 (35.1%)

1. Subset of patients from the pool of 12 placebo-controlled studies with long-term extensions.
2. Subset of patients from the pool of 13 placebo-controlled studies with long-term extensions.

In the pool of 12 clinical studies, a subgroup analysis assessed thesafety of patients with (eGFR between 30 to less than 60 mL/min/1.73 m^2). At Week 24, the safety was similar to that seen in the overall program, although a higher proportion of patients had at least one event related to renal impairment or failure.

Fractures

In a study of patients with eGFR 30 to less than 60 mL/min/1.73 m^2

13 patients experienced bone fractures for treatment durations up to 104 weeks. No fractures occurred in the placebo group, 5 occurred in the dapagliflozin 5 mg group, and 8 occurred in the dapagliflozin 10 mg group. Eight of these 13 fractures were in patients who had a baseline eGFR of 30 to 45 mL/min/1.73 m^2. Ten of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the anatomic site of fracture.

Hypoglycemia

The frequency of hypoglycemia by study [see *Clinical Studies (14)*] is shown in Table 6. Hypoglycemia was more frequent when dapagliflozin was added to sulfonylurea or insulin [see *Warnings and Precautions (5.11)*].

Table 6: Incidence of Major[1] and Minor[2] Hypoglycemia in Placebo-Controlled Studies

	Placebo	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**
Add-on to Metformin[1] (24 weeks)	**N=137**	**N=137**	**N=135**
Major [n (%)]	0	0	0
Minor [n (%)]	0	2 (1.5)	1 (0.7)
Active Control Add-on to Metformin versus Glipizide (52 weeks)	**N=408**	–	**N=406**
Major [n (%)]	3 (0.7)	–	0
Minor [n (%)]	147 (36.0)	–	7 (1.7)
	Placebo	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**
Add-on to DPP4 inhibitor (with or without Metformin) (24 weeks)	**N=226**	–	**N=225**
Major [n (%)]	0	–	1 (0.4)
Minor [n (%)]	3 (1.3)	–	4 (1.8)
Add-on to Insulin with or without other OADs[3] (24 weeks)	**N=197**	**N=212**	**N=196**
Major [n (%)]	1 (0.5)	1 (0.5)	1 (0.5)
Minor [n (%)]	67 (34.0)	92 (43.4)	79 (40.3)

1. Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration.
2. Minor episodes of hypoglycemia were defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.
3. OAD = oral antidiabetic therapy.

Genital Mycotic Infections

Genital mycotic infections were more frequent with dapagliflozin treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on dapagliflozin 5 mg, and 4.8% on dapagliflozin 10 mg, in the 12-study placebocontrolled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with dapagliflozin 10 mg. Infections were more frequently reported in females than in males (see Table 2). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively).

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with dapagliflozin treatment. Across the clinical program, serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of dapagliflozin-treated patients. If hypersensitivity reactions occur, discontinue use of dapagliflozin; treat per standard of care and monitor until signs and symptoms resolve.

Laboratory Tests

Increase in Hematocrit

Dapagliflozin

In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were −0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg–treated patients.

Increase in Serum Inorganic Phosphorus

Dapagliflozin

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg–treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL versus −0.04 mg/dL, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1

mg/dL if age ≥66) were reported in the dapagliflozin 10 mg group versus the placebo group at Week 24 (1.7% versus 0.9%, respectively).

Increase in Low-Density Lipoprotein Cholesterol

Dapagliflozin

In the pool of 13 placebo-controlled studies, changes from baseline in mean lipid values were reported in dapagliflozintreated patients compared to placebo-treated patients. Mean percent change from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol and −1.0% versus 2.9% for LDL cholesterol in the placebo and dapagliflozin 10 mg groups, respectively.

Vitamin B_{12} Concentrations

Metformin hydrochloride

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on XIGDUO XR and any apparent abnormalities should be appropriately investigated and managed [see *Warnings and Precautions (5.14)*].

6.2 Postmarketing Experience

Dapagliflozin

Additional adverse reactions have been identified during postapproval use of dapagliflozin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
  - Acute Kidney Injury and Impairment in Renal Function
- Urosepsis and Pyelonephritis
  - Necrotizing Fasciitis of the Perineum (Fournier’ s Gangrene)
  - Rash

Metformin hydrochloride

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 Positive Urine Glucose Test

Dapagliflozin

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

7.2 Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Dapagliflozin

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

7.3 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with XIGDUO XR may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

7.4 Drugs that Reduce Metformin Clearance

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Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors, such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*. Consider the benefits and risks of concomitant use.

7.5 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving XIGDUO XR.

7.6 Drugs affecting Glycemic Control

Metformin hydrochloride

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These medications 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 XIGDUO XR, the patient should be observed closely for loss of glycemic control. When such drugs are withdrawn from a patient receiving XIGDUO XR, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, XIGDUO XR is not recommended during the second and third trimesters of pregnancy.

Limited data with XIGDUO XR or dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to Based on animal data showing adverse renal effects, XIGDUO XR is not recommended during the second and third trimesters of pregnancy.

Limited data with XIGDUO XR or dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to

the late second and third trimesters of human pregnancy.

at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose *(see Data)*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was

used during pregnancy

However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Dapagliflozin

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15 times the 10mg clinical dose, (based on AUC.) The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the aa 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415 times and 137 times, respectively, the human values at the 10mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greated or equal to 29 times the 10mg clinical dose(based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day, (19 times the 10mg clinical dose , based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.

In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441 times the 10mg clinical dose , based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only. At higher dosages, equal to or greater than 150 mg/kg 2344 times the 10 mg clinical dose , based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed.

in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

Metformin HCl

Metformin HCl did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/dayduring the period of organogenesis. This represents an exposure of about 2 and 6 times a 2000 mg clinical dose based on body surface area (mg/m^2) for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

8.2 Lactation

Risk Summary

there no information regarding the presence of XIGDUO XR or dapaglifozin in human milk. the effects on the breastfed infant, or the effects on milk production.

Limited published studies report that metformin is present in human milk *(see Data)*. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Dapagliflozin is presentin the milk of lactating rats.

(see Data). However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of XIGDUO XR is not recommended while breastfeeding

Data in

Dapagliflozin

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49 indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile

rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Metformin hydrochloride

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma

ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

8.4 Pediatric Use

Safety and effectiveness of XIGDUO XR in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

XIGDUO XR

No XIGDUO XR dosage change is recommended based on age.

Dapagliflozin

A total of 1424 (24%) of the 5936 dapagliflozin-treated patients were 65 years and over and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical safety and efficacy studies of dapagliflozin. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with dapagliflozin had adverse reactions related to volume depletion and renal impairment or failure compared to patients treated with placebo [see *Warnings and Precautions (5.4)* and *Adverse Reactions (6.1)*].

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently than 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 lactic acidosis with metformin is greater in patients with moderately to severely impaired renal function, XIGDUO XR should only be used in patients with normal or mildly impaired renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function [see *Contraindications (4)*, *Warnings and Precautions (5.1, 5.3)*, and *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Dapagliflozin

In clinical studies (dapagliflozin was associated with increases in serum creatinine and decreases in eGFR *[see Adverse Reactions (6.1)]*. Use of dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (2.3), Warnings and Precautions (5.4), and Adverse Reactions (6.1)]* and is contraindicated in patients with renal impairment. (eGFR less than 30 mL/min/1.73 m^2) or ESRD *[see Contraindications (4)]*.

patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2, and an eGFR of 30 to less than 60 mL/min/1.73 m^2) *[see Clinical Studies (14.4)]*. The safety profile of dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 was similar to the general population. of patients with type 2 diabetes. Although patients in the dapagliflozin arm had reduction in eGFR compared to the placebo arm, eGFR generally returned towards baseline after treatment discontinuation.

Metformin hydrochloride

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. XIGDUO XR is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.2)]*.

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. XIGDUO XR is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

Dapagliflozin

There were no reports of overdose during the clinical development program for dapagliflozin. In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts >50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin

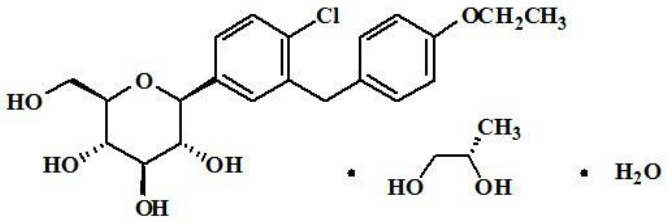
hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions (5.1)*]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

11 DESCRIPTION

XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets contain two oral antihyperglycemic medications used in the management of type 2 diabetes: dapagliflozin and metformin hydrochloride.

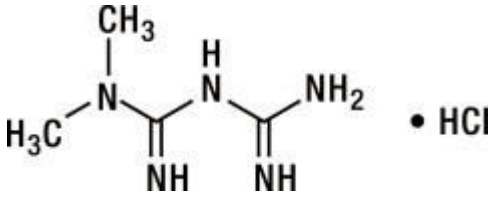
Dapagliflozin

Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ and the formula weight is 502.98. The structural formula is:



Metformin hydrochloride

Metformin hydrochloride (*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \bullet HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



XIGDUO XR

XIGDUO XR is available for oral administration as tablets containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin hydrochloride (XIGDUO XR 5 mg/500 mg), the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 5 mg/1000 mg), the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin hydrochloride (XIGDUO XR 10 mg/500 mg), or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 10 mg/1000 mg).

Each film-coated tablet of XIGDUO XR contains the following inactive ingredients: microcrystalline cellulose PH302, lactose anhydrous, crospovidone, silicon dioxide, magnesium stearate, carboxymethylcellulose sodium, and hypromellose 2208. The 5 mg/500 mg and 10 mg/500 mg strength tablets of XIGDUO XR also contain microcrystalline cellulose PH102 and hypromellose 2910.

The film coatings contain the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. Additionally, the film coating for the XIGDUO XR 5 mg/500 mg tablets contains FD&C Yellow No. 6/Sunset Yellow FCF aluminum lake and the film coating for the XIGDUO XR 5 mg/1000 mg, 10 mg/500 mg, and 10 mg/1000 mg tablets contains iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XIGDUO XR

XIGDUO XR combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a biguanide.

Dapagliflozin

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Metformin hydrochloride

Metformin 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 utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or in healthy subjects, except in unusual circumstances [see *Warnings and Precautions (5.10)*], and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

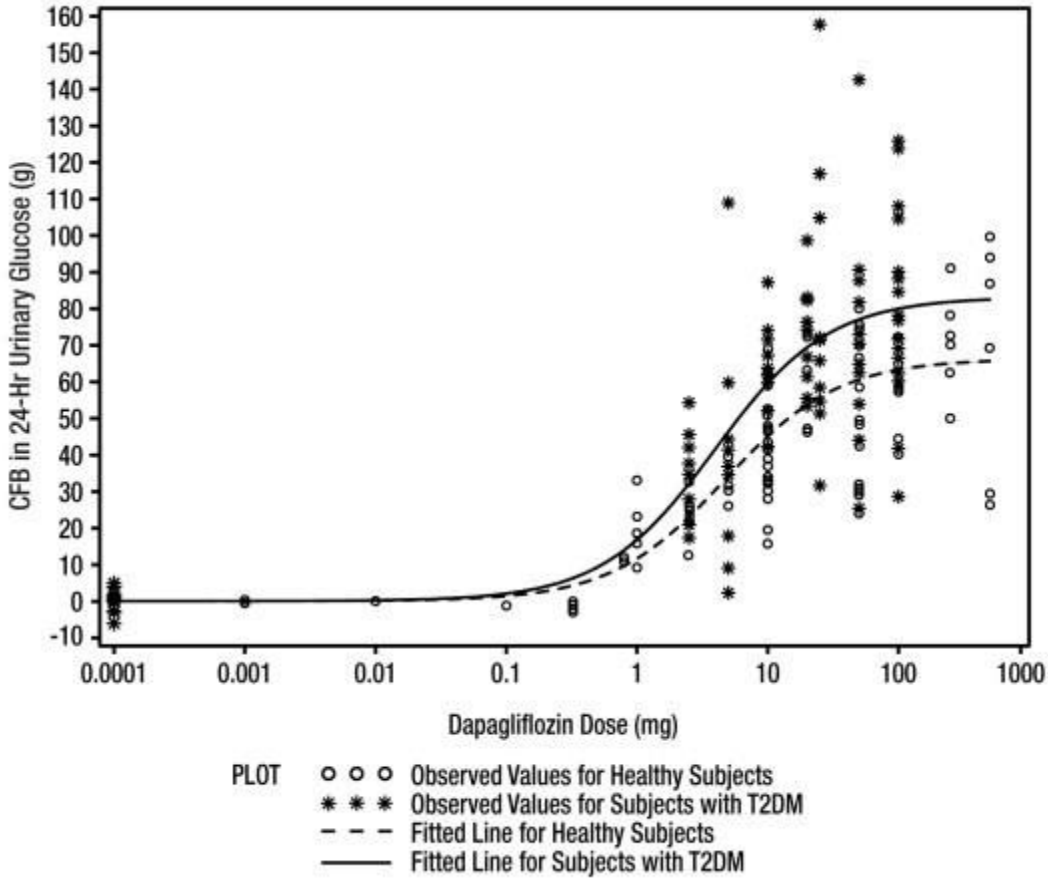
12.2 Pharmacodynamics

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 (see Figure 1). Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume [see *Adverse Reactions (6.1)*].

Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-Hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM) (Semi-Log Plot)



Cardiac Electrophysiology

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.

12.3 Pharmacokinetics

XIGDUO XR

XIGDUO XR combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin (FARXIGA™) and metformin hydrochloride extended-release (GLUCOPHAGE® XR) administered together as individual tablets.

The administration of XIGDUO XR in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin extended-release.

Compared to the fasted state, the standard meal resulted in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of metformin when administered as XIGDUO XR combination tablets.

Absorption

Dapagliflozin

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

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. 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. **Distribution**

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with 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. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Metformin hydrochloride

Intravenous single-dose studies in healthy 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.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg. *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.

Specific Populations

Renal Impairment

Dapagliflozin

At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5.3)*, and *Use in Specific Populations (8.6)*].

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

XIGDUO XR

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Because XIGDUO XR contains metformin, XIGDUO XR should generally be avoided in patients with hepatic impairment [see *Warnings and Precautions (5.7)*].

Dapagliflozin

In patients with mild and moderate hepatic impairment (Child-Pugh Classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh Class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Metformin hydrochloride

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

Geriatric

Dapagliflozin

Based on a population pharmacokinetic analysis, age does not have a clinically meaningful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggests 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.

XIGDUO XR should not be initiated in patients of any age unless measurement of creatinine clearance demonstrates that renal function is only normal or mildly impaired [see *Warnings and Precautions (5.1, 5.3)* and *Use in Specific Populations (8.6)*].

Pediatric

Pharmacokinetics of XIGDUO XR in the pediatric population has not been studied.

Gender

Dapagliflozin

Based on a population pharmacokinetic analysis, gender does not have a clinically meaningful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Race

Dapagliflozin

Based on a population pharmacokinetic analysis, race (White, Black, or Asian) does not have a clinically meaningful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.

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 antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Body Weight

Dapagliflozin

Based on a population pharmacokinetic analysis, body weight does not have a clinically meaningful effect on systemic exposures of dapagliflozin; thus, no dose adjustment is recommended.

Drug Interactions

Specific pharmacokinetic drug interaction studies with XIGDUO XR have not been performed, although such studies have been conducted with the individual dapagliflozin and metformin components.

In Vitro Assessment of Drug Interactions

Dapagliflozin

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP 1A2, 2B6, or 3A4. 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-Oglucuronide 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.

Effects of Other Drugs on Metformin

Table 7 shows the effect of other coadministered drugs on metformin.

Table 7: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Metformin (Dose	Metformin

(Dose Regimen)[1]	Regimen)[1]	Change[2] in AUC[3]	Change[2] in C_{max}
No dosing adjustments required for the following:			
Glyburide (5 mg)	850 mg	[4] ↓9%	[4] ↓7%
Furosemide (40 mg)	850 mg	[4] ↑15%	[4] ↑22%
Nifedipine (10 mg)	850 mg	↑9%	↑20%
Propranolol (40 mg)	850 mg	↓10%	↓6%
Ibuprofen (400 mg)	850 mg	[4] ↑5%	[4] ↑7%
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution [see *Warnings and Precautions (5.10)* and *Drug Interactions (7.3)*].			
Cimetidine (400 mg)	850 mg	↑40%	↑60%

1. All metformin and coadministered drugs were given as single doses.
2. Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
3. AUC = AUC(INF).
4. Ratio of arithmetic means.

Effects of Metformin on Other Drugs

Table 8 shows the effect of metformin on other coadministered drugs.

Table 8: Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug (Dose Regimen)[1]	Metformin (Dose Regimen)[1]	Coadministered Drug	
		Change[2] in AUC[3]	Change[2] in C_{max}
No dosing adjustments required for the following:			
Glyburide (5 mg)	850 mg	[4] ↓22%	[4] ↓37%
Furosemide (40 mg)	850 mg	[4] ↓12%	[4] ↓31%
Nifedipine (10 mg)	850 mg	[5] ↑10%	↑8%
Propranolol (40 mg)	850 mg	[5] ↑1%	↑2%
Ibuprofen (400 mg)	850 mg	[6] ↓3%	[6] ↑1%
Coadministered Drug (Dose Regimen)[1]	**Metformin (Dose Regimen)[1]**	**Coadministered Drug**	
		Change[2] in AUC[3]	**Change[2] in C_{max}**
Cimetidine (400 mg)	850 mg	[5] ↓5%	↑1%

1. All metformin and coadministered drugs were given as single doses.
2. Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
3. AUC = AUC(INF) unless otherwise noted.
4. Ratio of arithmetic means, p-value of difference <0.05.

5. AUC(0-24 hr) reported.

6. Ratio of arithmetic means.

Effects of Other Drugs on Dapagliflozin

Table 9 shows the effect of coadministered drugs on dapagliflozin. No dose adjustments are recommended for dapagliflozin.

Table 9: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)[1]	**Dapagliflozin (Dose Regimen)[1]**	**Dapagliflozin**	
		Change[2] in AUC[3]	**Change[2] in C_{max}**
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	↓1%	↓7%
Pioglitazone (45 mg)	50 mg	0%	↑9%
Sitagliptin (100 mg)	20 mg	↑8%	↓4%
Glimepiride (4 mg)	20 mg	↓1%	↑1%
Voglibose (0.2 mg three times daily)	10 mg	↑1%	↑4%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↑7%	↓1%
Bumetanide (1 mg)	10 mg once daily for 7 days	↑5%	↑8%
Valsartan (320 mg)	20 mg	↑2%	↓12%
Simvastatin (40 mg)	20 mg	↓1%	↓2%
Anti-infective Agent			
Rifampin (600 mg once daily for 6 days)	10 mg	↓22%	↓7%
Non-Steroidal Anti-inflammatory Agent			
Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10 mg	↑51%	↑13%

1. Single dose unless otherwise noted.

2. Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

3. AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

Effects of Dapagliflozin on Other Drugs

Table 10 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

Table 10: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)[1]	**Dapagliflozin (Dose Regimen)**[1]	**Coadministered Drug**	
		Change[2] **in AUC** [3]	**Change**[2] **in C_{max}**
Coadministered Drug (Dose Regimen)[1]	**Dapagliflozin (Dose Regimen)**[1]	**Coadministered Drug**	
		Change[2] **in AUC** [3]	**Change**[2] **in C_{max}**
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	0%	↓5%
Pioglitazone (45 mg)	50 mg	0%	↓7%
Sitagliptin (100 mg)	20 mg	↑1%	↓11%
Glimepiride (4 mg)	20 mg	↑13%	↑4%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↓1%	↓5%
Bumetanide (1 mg)	10 mg once daily for 7 days	↑13%	↑13%
Valsartan (320 mg)	20 mg	↑5%	↓6%
Simvastatin (40 mg)	20 mg	↑19%	↓6%
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	0%	↓1%
Warfarin (25 mg) S-warfarin R-warfarin	20 mg loading dose then 10 mg once daily for 7 days	 ↑3% ↑6%	 ↑7% ↑8%

1. Single dose unless otherwise noted.
2. Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
3. AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

XIGDUO XR

No animal studies have been conducted with XIGDUO XR to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with dapagliflozin and metformin individually.

Dapagliflozin

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72 times (males) and 105 times (females) the clinical dose of 10 mg/day based on AUC exposure. In rats, the highest dose was approximately 131 times (males) and 186 times (females) the clinical dose of 10 mg perday based on AUC exposure.
Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrationsgreater than or equal to 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiplesgreater than2100 times the clinical dose.

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708 times and 998 times the maximum recommended human doses in males and females, respectively.

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 and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human 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.

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.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human dosebased on body surface area comparisons.

14 CLINICAL STUDIES

There have been no clinical efficacy studies conducted with XIGDUO XR combination tablets to characterize its effect on HbA1c reduction. XIGDUO XR is considered to be bioequivalent to coadministered dapagliflozin and metformin hydrochloride extended-release (XR) tablets [see *Clinical Pharmacology (12.3)*]. Relative bioavailability studies between XIGDUO XR and coadministered dapagliflozin and metformin hydrochloride immediate-release (IR) tablets have not been conducted. The metformin hydrochloride XR tablets and metformin hydrochloride IR tablets have a similar extent of absorption (as measured by AUC), while peak plasma levels of XR tablets are approximately 20% lower than those of IR tablets at the same dose.

The coadministration of dapagliflozin and metformin XR tablets has been studied in treatment-naive patients inadequately controlled on diet and exercise alone. The coadministration of dapagliflozin and metformin IR or XR tablets has been studied in patients with type 2 diabetes inadequately controlled on metformin and compared with a sulfonylurea (glipizide) in combination with metformin. Treatment with dapagliflozin plus metformin at all doses produced clinically relevant and statistically significant improvements in HbA1c and fasting plasma glucose (FPG) compared to placebo in combination with metformin (initial or add-on therapy). HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline BMI.

14.1 Initial Combination Therapy with Metformin Extended-Release

A total of 1241 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥7.5% and ≤12%) participated in 2 active-controlled studies of 24-week duration to evaluate the safety and efficacy of initial therapy with dapagliflozin 5 mg or 10 mg in combination with metformin XR formulation.

In one study, 638 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: dapagliflozin 10 mg plus metformin XR (up to 2000 mg/day), dapagliflozin 10 mg plus placebo, or metformin XR (up to 2000 mg/day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 10 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 11 and Figure 2). Dapagliflozin 10 mg as monotherapy also provided statistically significant improvements in FPG and statistically significant reduction in body weight compared with metformin alone and was noninferior to metformin XR monotherapy in lowering HbA1c.

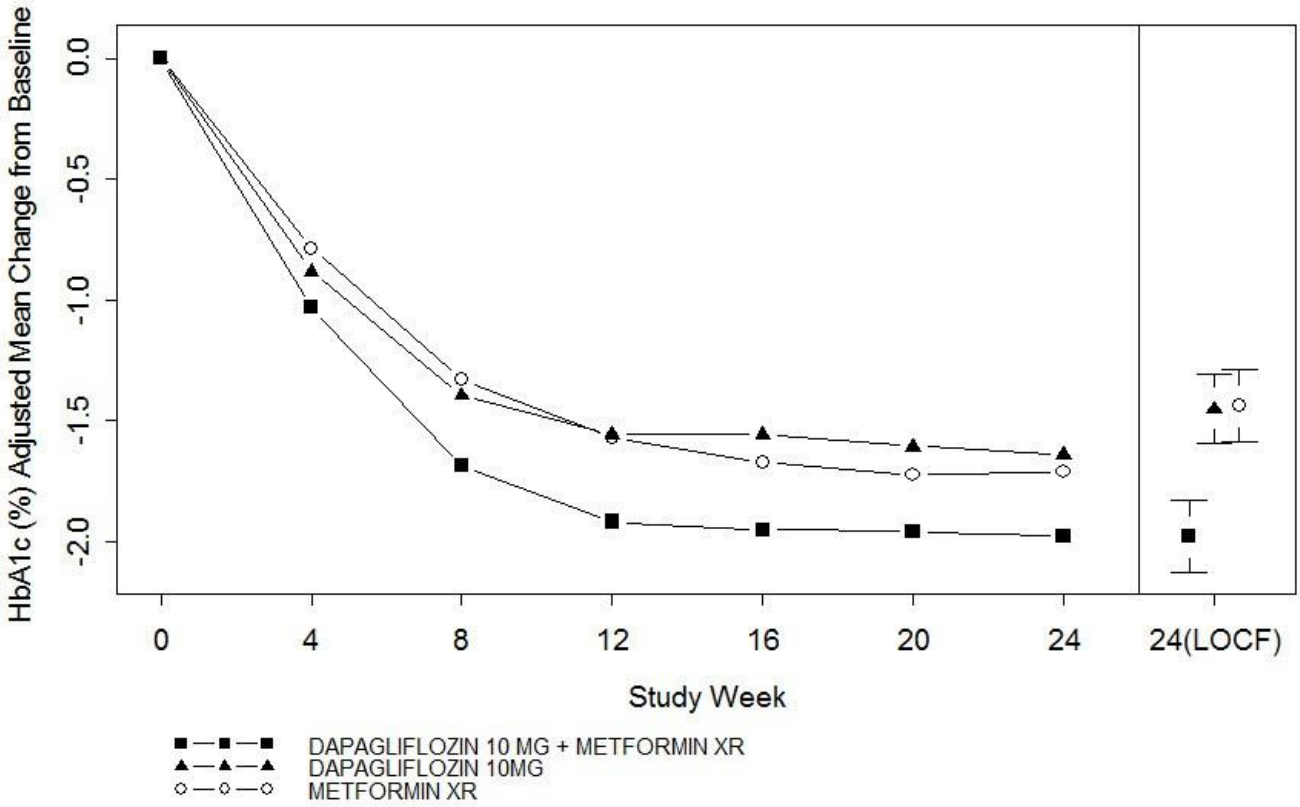
Table 11: Results at Week 24 (LOCF[1]) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter	**Dapagliflozin 10 mg + Metformin XR N=211[2]**	**Dapagliflozin 10 mg N=219[2]**	**Metformin XR N=208[2]**
HbA1c (%)			
Baseline (mean)	9.1	9.0	9.0

Change from baseline (adjusted mean[3])	−2.0	−1.5	−1.4
Difference from dapagliflozin (adjusted mean[3]) (95% CI)	−0.5 [4] (−0.7, −0.3)		
Difference from metformin XR (adjusted mean[3]) (95% CI)	−0.5 [4] (−0.8, −0.3)	0.0[5] (−0.2, 0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6%	31.7%	35.2%
FPG (mg/dL)			
Baseline (mean)	189.6	197.5	189.9
Change from baseline (adjusted mean[3])	−60.4	−46.4	−34.8
Difference from dapagliflozin (adjusted mean[3]) (95% CI)	−13.9 [4] (−20.9, −7.0)		
Difference from metformin XR (adjusted mean[3]) (95% CI)	−25.5 [4] (−32.6, −18.5)	−11.6 [6] (−18.6, −4.6)	
Body Weight (kg)			
Baseline (mean)	88.6	88.5	87.2
Change from baseline (adjusted mean[3])	−3.3	−2.7	−1.4
Difference from metformin XR (adjusted mean[3]) (95% CI)	−2.0 [4] (−2.6, −1.3)	−1.4 [4] (−2.0, −0.7)	

1. LOCF: last observation (prior to rescue for rescued patients) carried forward.
2. All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
3. Least squares mean adjusted for baseline value.
4. p-value <0.0001.
5. Noninferior versus metformin XR.
6. p-value <0.05.

Figure 2: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed the study with both baseline and Week 24 HbA1C values without rescue.
Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

In the second study, 603 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: dapagliflozin 5 mg plus metformin XR (up to 2000 mg/day), dapagliflozin 5 mg plus placebo, or metformin XR (up to 2000 mg/day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 5 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 12).

Table 12: Results at Week 24 (LOCF[1]) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter	Dapagliflozin 5 mg + Metformin XR N=194[2]	Dapagliflozin 5 mg N=203[2]	Metformin XR N=201[2]
HbA1c (%)			
Baseline (mean)	9.2	9.1	9.1
Change from baseline (adjusted mean[3])	−2.1	−1.2	−1.4
Difference from dapagliflozin (adjusted mean[3]) (95% CI)	−0.9 [4] (−1.1, −0.6)		
Difference from metformin XR (adjusted mean[3]) (95% CI)	−0.7 [4] (−0.9, −0.5)		
Percent of patients achieving HbA1c <7% adjusted for baseline	52.4%[5]	22.5%	34.6%
FPG (mg/dL)			
Baseline (mean)	193.4	190.8	196.7
Change from baseline (adjusted mean[3])	−61.0	−42.0	−33.6
Difference from dapagliflozin (adjusted mean[3]) (95% CI)	−19.1 [4] (−26.7, −11.4)		
Difference from metformin XR (adjusted mean[3]) (95% CI)	−27.5 [4] (−35.1, −19.8)		
Body Weight (kg)			
Baseline (mean)	84.2	86.2	85.8
Change from baseline (adjusted mean[3])	−2.7	−2.6	−1.3
Difference from metformin XR (adjusted mean[3]) (95% CI)	−1.4 [4] (−2.0, −0.7)		

1. LOCF: last observation (prior to rescue for rescued patients) carried forward.
2. All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
3. Least squares mean adjusted for baseline value.
4. p-value <0.0001.
5. p-value <0.05.

14.2 Add-On to Metformin Immediate-Release

A total of 546 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled study to evaluate dapagliflozin in combination with metformin. Patients on metformin at a dose of at least 1500 mg/day were randomized after completing a 2-week, single-blind, placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo in addition to their current dose of metformin.

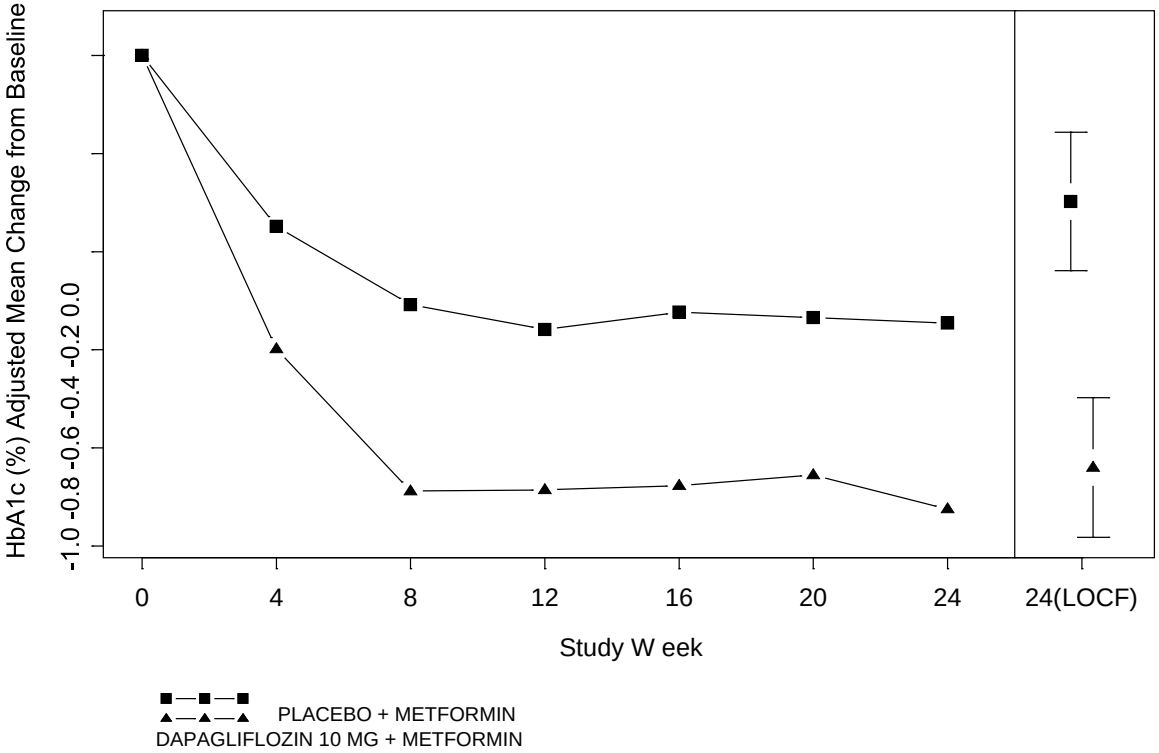
As add-on treatment to metformin, dapagliflozin 10 mg provided statistically significant improvements in HbA1c and FPG, and statistically significant reduction in body weight compared with placebo at Week 24 (see Table 13 and Figure 3). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus metformin were −4.5 mmHg and −5.3 mmHg with dapagliflozin 5 mg and 10 mg plus metformin, respectively.

Table 13: Results of a 24-Week (LOCF[1]) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin

Efficacy Parameter	Dapagliflozin 10 mg + Metformin N=1352	Dapagliflozin 5 mg + Metformin N=1372	Placebo + Metformin N=1372
HbA1c (%)			
Baseline (mean)	7.9	8.2	8.1
Change from baseline (adjusted mean[3])	−0.8	−0.7	−0.3
Difference from placebo (adjusted mean[3]) (95% CI)	−0.54 (−0.7, −0.3)	−0.44 (−0.6, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%[5]	37.5%[5]	25.9%
FPG (mg/dL)			
Baseline (mean)	156.0	169.2	165.6
Change from baseline at Week 24 (adjusted mean[3])	−23.5	−21.5	−6.0
Difference from placebo (adjusted mean[3]) (95% CI)	−17.54 (−25.0, −10.0)	−15.54 (−22.9, −8.1)	
Change from baseline at Week 1 (adjusted mean[3])	−16.54 (N=115)	−12.04 (N=121)	1.2 (N=126)
Body Weight (kg)			
Baseline (mean)	86.3	84.7	87.7
Change from baseline (adjusted mean[3])	−2.9	−3.0	−0.9
Difference from placebo (adjusted mean[3]) (95% CI)	−2.04 (−2.6, −1.3)	−2.24 (−2.8, −1.5)	

1. LOCF: last observation (prior to rescue for rescued patients) carried forward.
2. All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
3. Least squares mean adjusted for baseline value.
4. p-value <0.00001 versus placebo + metformin.
5. p-value <0.05 versus placebo + metformin.

Figure 3: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Placebo-Controlled Study of Dapagliflozin in Combination with Metformin



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed Short-Term Period with both baseline and Week 24 HbA1C values without rescue. Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

14.3 Active Glipizide-Controlled Study Add-On to Metformin Immediate-Release

A total of 816 patients with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, glipizide-controlled, noninferiority study to evaluate dapagliflozin as add-on therapy to metformin. Patients on metformin at a dose of at least 1500 mg/day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and dapagliflozin 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia.

At the end of the titration period, 87% of patients treated with dapagliflozin had been titrated to the maximum study dose (10 mg) versus 73% treated with glipizide (20 mg). Dapagliflozin treatment led to a similar mean reduction in HbA1c from baseline at Week 52, compared with glipizide, thus demonstrating noninferiority (see Table 14). Dapagliflozin treatment led to a statistically significant mean reduction in body weight from baseline at Week 52 compared with a mean increase in body

weight in the glipizide group. Statistically significant (p<0.0001) mean change from baseline in systolic blood pressure relative to glipizide plus metformin was −5.0 mmHg with dapagliflozin plus metformin.

Table 14: Results at Week 52 (LOCF[1]) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-On to Metformin

Efficacy Parameter	Dapagliflozin + Metformin N=400[2]	Glipizide + Metformin N=401[2]
HbA1c (%)		
Baseline (mean)	7.7	7.7
Change from baseline (adjusted mean[3])	−0.5	−0.5
Difference from glipizide + metformin (adjusted mean[3]) (95% CI)	0.0[4] (−0.1, 0.1)	
Body Weight (kg)		
Baseline (mean)	88.4	87.6
Change from baseline (adjusted mean[3])	−3.2	1.4
Difference from glipizide + metformin (adjusted mean[3]) (95% CI)	−4.7 [5] (−5.1, −4.2)	

1. LOCF: last observation carried forward.
2. Randomized and treated patients with baseline and at least 1 postbaseline efficacy measurement.
3. Least squares mean adjusted for baseline value.
4. Noninferior to glipizide + metformin.
5. p-value <0.0001.

14.4 Use in Patients with Type 2 Diabetes and Moderate Renal Impairment

Dapagliflozin was assessed in two placebo-controlled studies of patients with type 2 diabetes and moderate renal impairment.

Patients with type 2 diabetes and an eGFR between 45 to less than 60 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy participated in a 24-week, double-blind, placebo-controlled clinical study (NCT02413398). Patients were randomized to either dapagliflozin 10 mg or placebo, administered orally once daily. At Week 24, dapagliflozin provided statistically significant reductions in HbA1c compared with placebo (Table 15).

Table 15: Results at Week 24 of Placebo-Controlled Study for Dapagliflozin in Patients with Type 2 Diabetes and Renal Impairment (eGFR 45 to less than 60 mL/min/1.73 m^2)

	Dapagliflozin 10 mg	Placebo
Number of patients:	**N=160**	**N=161**
HbA1c (%)		
Baseline (mean)	8.3	8.0
Change from baseline (adjusted mean*)	-0.4†	-0.1

	Dapagliflozin 10 mg	Placebo
Number of patients:	**N=160**	**N=161**
Difference from placebo (adjusted mean*) (95% CI)	-0.3† (-0.5, - 0.1)	

* Least squares mean adjusted for baseline value; at Week 24, HbA1c was missing for 5.6% and 6.8% of individuals treated with dapagliflozin and placebo, respectively. Retrieved dropouts, i.e. observed HbA1c at Week 24 from subjects who discontinued treatment, were used to impute missing values in HbA1c.

† p-value <0.001 versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

XIGDUO™ XR (dapagliflozin and metformin HCl extended-release) tablets have markings on one side, are plain on the reverse side, and are available in the strengths and packages listed in Table 15.

Table 16: XIGDUO XR Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Pack Size
5/500 mg	orange, biconvex, capsule-shaped	"1070" and "5/500" debossed on one side and plain on the reverse side.	Alu/Alu blister 7, 14, 28, 56 tablets
5/1000 mg	pink to dark pink, biconvex, oval-shaped	"1071" and "5/1000" debossed on one side and plain on the reverse side.	Alu/Alu blister 7, 14, 28, 56 tablets
10/500 mg	pink, biconvex, capsule-shaped	"1072" and "10/500" debossed on one side and plain on the reverse side.	Alu/Alu blister 7, 14, 28, 56 tablets

10/1000 mg	yellow to dark yellow, biconvex, oval-shaped	"1073" and "10/1000" debossed on one side and plain on the reverse side	Alu/Alu blister 7, 14, 28, 56 tablets

Storage and Handling

Store below 30°C

Manufacturer: Bristol-Myers Squibb Manufacturing Company, State Road#3, Km 77.5 Humacao, Puerto Rico 00791

License Holder and importer: AstraZeneca (Israel) Ltd., 1 Atirei Yeda St., Kfar Saba 4464301

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