GLUCIENT XR

Extended-release tablet

Compositions:
GLUCIENT XR 500
Each extended-release tablet contains
Metformin HCl 500 mg

GLUCIENT XR 750
Each extended-release tablet contains
Metformin HCl 750 mg

GLUCIENT XR 1000
Each extended-release tablet contains
Metformin HCl 1000 mg

List of Excipients:
GLUCIENT XR 500:
Carmellose sodium 2000, hypromellose 100M, purified water, colloidal anhydrous silica, magnesium stearate.

GLUCIENT XR 750:
Carmellose sodium 2000, hypromellose 100M, purified water, colloidal anhydrous silica, magnesium stearate.

GLUCIENT XR 1000:
Carmellose sodium 2000, hypromellose 100M, purified water, colloidal anhydrous silica, magnesium stearate.

Product Descriptions:
GLUCIENT XR 500:
White tablet, round shallow, diameter 12 mm, with marking “XR” on one side and without marking on the other side.

GLUCIENT XR 750:
White tablet, shallow convex, dimension 20 x 9 mm, with marking “SR1” on one side and without marking on the other side.

GLUCIENT XR 1000:
White tablet, shallow convex, dimension 22.25 x 9 mm, with marking “SR2” on one side and without marking on the other side.

Pharmacology:
ATC code: A10BA02
Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.
Mechanism of action, metformin may act via 3 mechanisms:
- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis,
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization,
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Pharmacokinetics:
Absorption:
After an oral dose of metformin XR 500 mg, metformin absorption is significantly delayed compared to the immediate-release tablet (T_{max} at 2.5 hours) with a T_{max} at 7 hours.
Following a single oral administration of 1500 mg of metformin XR 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours. Metformin XR 750 mg was shown to be bioequivalent to metformin XR 500 mg at a 1500 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.
Following a single oral administration in the fed state of one tablet of metformin XR 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours). Metformin XR 1000 mg was shown to be bioequivalent to metformin XR 500 mg at a 1000 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.
At steady state, similar to the immediate-release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg metformin prolonged-release is similar to that observed after administration of 1000 mg metformin immediate-release twice daily.
Intrasubject variability of C_{max} and AUC of metformin prolonged-release is comparable to that observed with metformin immediate-release. When 2 tablets of 500 mg metformin prolonged-release is administered in fed conditions the AUC is increased by approximately 70% (both C_{max} and T_{max} are only slightly increased). When the 1000 mg prolonged-release tablets are administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and T_{max} is slightly prolonged by about 1 hour).

Metformin absorption from the prolonged-release formulation is not altered by meal composition.
No accumulation is observed after repeated administration of up to 2000 mg metformin prolonged-release.

Distribution:
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (V_d) ranged between 63–276 l.

Metabolism:
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:
Renal clearance of metformin is >400 ml/minute, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. 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.

Indications:
Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic control. GLUCIENT XR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

Recommended Dosage:
Adult with normal renal function (GFR ≥90 ml/minute)

Reduction in the risk or delay of the onset of type 2 diabetes
- Metformin should only be considered where intensive lifestyle modifications are not feasible.
- The therapy should be initiated with one tablet GLUCIENT XR 500 mg once daily with the evening meal.
- After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose is 2000 mg once daily with the evening meal.
- It is recommended to regularly monitor (every 3-6 months) the glycemic status (OGTT and/or FPG and/or HbA1c value) as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued.
- A decision to reevaluate therapy is also required if the patient subsequently implements improvements to diet and/or exercise, or if changes to the medical condition will allow increased lifestyle interventions to be possible.

Monotherapy and combination with other oral antidiabetic agents in type 2 diabetes mellitus:
GLUCIENT XR 500
- The usual starting dose of GLUCIENT XR 500 is one tablet once daily with the evening meal.
- GLUCIENT XR must be swallowed whole and never crushed or chewed.
- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements.
- To improve gastrointestinal tolerability, dosage increase is recommended in increments of 500 mg every 10 to 15 days, up to 2000 mg once daily with the evening meal. If glycemic control is not achieved on GLUCIENT XR 2000 mg once daily, GLUCIENT XR 1000 mg twice daily should be considered, with both doses being given with food. If glycemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.
- In patients already treated with metformin tablets, the starting dose of GLUCIENT XR should be equivalent to the daily dose of metformin immediate-release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to GLUCIENT XR is not recommended.

GLUCIENT XR 750
- GLUCIENT XR 750 is intended for patients who are already treated with metformin tablets (extended- or immediate-release). The dose of GLUCIENT XR 750 should be equivalent to the daily dose of metformin tablets (extended- or immediate-release), up to a maximum dose of 1500 mg given with the evening meal.
- After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended. A slow increase of dose may improve gastrointestinal tolerability. The recommended dose of GLUCIENT XR 750 is 2 tablets once daily. If glycemic control is not achieved on GLUCIENT XR 1500 mg once daily, the dose may be increased to a maximum dose of 2000 mg once daily. If glycemic control is not achieved on GLUCIENT XR 2000 mg once daily, GLUCIENT XR 1000 mg twice daily should be considered, with both doses being given with food. If glycemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

GLUCIENT XR 1000
- GLUCIENT XR 1000 is intended as a maintenance therapy for patients treated with either 1000 mg or 2000 mg of metformin hydrochloride. On switch, the daily dose of GLUCIENT XR should be equivalent to the current daily dose of metformin hydrochloride.
- GLUCIENT XR 1000 should be taken once daily with the evening meal at a maximum recommended dose of 2 tablets per day. If glycemic control is not achieved on GLUCIENT XR 2000 mg once daily, GLUCIENT XR 1000 mg twice daily should be considered, with both doses being given with food. If glycemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

Combining GLUCIENT XR dosage strengths
The combined use of different strengths of GLUCIENT XR 500, GLUCIENT XR 750 or GLUCIENT XR 1000 is not recommended. Only one strength (GLUCIENT XR 500, GLUCIENT XR 750 or GLUCIENT XR 1000) should be used at a time in order to avoid accidentally exceeding the recommended upper daily dose limit of 2000 mg.

Transfer from another oral antidiabetic agent
If transfer from another oral antidiabetic agent is intended, discontinue the other agent and initiate GLUCIENT XR 500 at the dose indicated above, before switching to GLUCIENT XR 750 or GLUCIENT XR 1000.

Combination with insulin
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of GLUCIENT XR is 500 mg once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly
Due to the potential for decreased renal function in elderly patients, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see **Warnings and Precautions**). Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older and metformin initiation is therefore not recommended in these patients (see **Warnings and Precautions**).

Patient with renal impairment
A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3–6 months.

GFR (ml/minute)	Total maximum daily dose	Additional considerations
60-89	2000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis (see **Warnings and precautions**) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

Pediatric population
In the absence of available data, GLUCIENT XR should not be used in children.

Contraindications:
- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).

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- Diabetic precoma.
- Severe renal failure (GFR <30 ml/minute).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

Warnings and Precautions:
Lactic acidosis:
Lactic acidosis is a very rare, but serious metabolic complication, most often occurs at worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (severe diarrhea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.
Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics, and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see **Contraindications** and **Interaction with Other Medicines and Other Forms of Interaction**).
Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterized by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention.
Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/l), and an increased anion gap and lactate/pyruvate ratio.

Renal function:
GFR should be assessed before treatment initiation and regularly thereafter (see **Recommended Dosage**). Metformin is contraindicated in patients with GFR <30 ml/minute and should be temporarily discontinued in the presence of conditions that after renal function (see **Contraindications**).

Cardiac function:
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.
For patients with acute and unstable heart failure, metformin is contraindicated.

Hepatic function:
Because impaired hepatic function may significantly limit the ability to clear lactate and has been associated with some cases of lactic acidosis, GLUCIENT XR is contraindicated in patients with clinical and laboratory evidence of hepatic disease.

Hypoxic states:
Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCIENT XR therapy, the drug should be promptly discontinued.

Hypoglycemia:
Hypoglycemia does not occur in patients receiving GLUCIENT XR 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, meglitinides 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 beta-adrenergic blocking drugs.

Administration of iodinated contrast agent:
Intravascular administration of iodinated contrast agents may lead to contrast included nephropathy, resulting in metformin accumulation and may increase the risk for lactic acidosis. Metformin should be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been reevaluated and found to be stable (see **Recommended Dosage** and **Interactions with Other Medicines and Other Forms of Interaction**).

Surgery:
Metformin must be discontinued 48 hours before elective surgery under general, spinal or peridural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

Other precautions:
- All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- It is recommended that vitamin B_{12} serum levels are monitored annually. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency (see **Adverse Effects**).
- The tablet shells may be present in the feces. Patients should be advised that this is normal.

Effects on ability to drive and use machines:
Metformin monotherapy does not cause hypoglycemia and therefore has no effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin, meglitinides).

Interactions with Other Medicines and Other Forms of Interaction:
Concomitant use not recommended:
Alcohol:
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition, or hepatic impairment.

Iodinated contrast materials:
Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been reevaluated and found to be stable (see **Recommended Dosage** and **Warnings and Precautions**).

Combinations requiring precautions for use:
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonist, and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycemic activity (e.g. glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonist, danazol, chlorpromazine at high dosages of 100 mg per day, and diuretics):
More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon discontinuation.

Organic cation transporter (OCT):
Metformin is a substrate of both transporters OCT1 and OCT2.
Coadministration of metformin with:
- inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to increase in metformin plasma concentration.
- inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Use during Pregnancy and Lactation:
Pregnancy:
Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.
A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development.
When the patient plans to become pregnant and during pregnancy, it is recommended that impaired glycemic control or diabetes are not treated with metformin. For diabetes it is recommended that insulin should be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the fetus.

Lactation:
Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breastfeeding should be made, taking into account benefit of breastfeeding and the potential risk to adverse effect on the child.

Adverse Effects:
The following adverse effects may occur with metformin.
Frequencies are defined as follows: very common >1/10; common ≥1/100, <1/10; uncommon ≥1/1000, <1/100; rare ≥1/10,000, <1/1000; very rare <1/10,000.

Nervous system disorders:
Common: taste disturbance.

Gastrointestinal disorders:
Very common: gastrointestinal disorders such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.

Skin and subcutaneous tissue disorders:
Very rare: skin reactions such as erythema, pruritus, urticaria.

Metabolism and nutrition disorders:
Common: vitamin B_{12} deficiency. Consideration of such etiology is recommended if a patient presents with megaloblastic anemia (see **Warnings and Precautions**).
Very rare: lactic acidosis (see **Warnings and Precautions**).

Hepatobiliary disorders:
Very rare: liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Overdose and Treatment:
Hypoglycemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. In a patient with lactic acidosis who is taking GLUCIENT XR, the drug should be discontinued immediately and general supportive measures promptly instituted. The most effective method to remove lactate and metformin is hemodialysis.

Presentations and registration numbers:
GLUCIENT XR 500:
Box, 4 PVC/PVDC-Alu blisters x 15 extended-release tablets; SIN15416P
GLUCIENT XR 750:
Box, 4 PVC/PVDC-Alu blisters x 15 extended-release tablets; SIN16095P
GLUCIENT XR 1000:
Box, 4 PVC/PVDC-Alu blisters x 15 extended-release tablets; SIN16096P

ON MEDICAL PRESCRIPTION ONLY.

STORE AT TEMPERATURE BELOW 30ºC.

Manufactured by
PT Ferron Par Pharmaceuticals
Cikarang-Indonesia

For
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia

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