PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

GLUCOTRIN XR 500, 750 and 1 000 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg: One extended release tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.
750 mg: One extended release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.
1000 mg: One extended release tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.
These tablets are sugar free.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Extended Release Tablet
500 mg: White to off-white, capsule-shaped, 16.50 mm x 8.20 mm uncoated tablet, debossed with “XR 500” on one side and plain on other side.
750 mg: White to off-white, capsule-shaped, 19.60 mm x 9.30 mm uncoated tablet, debossed with “XR 750” on one side and plain on other side.
1000 mg: White to off-white, capsule-shaped, 21.10 mm x 10.10 mm uncoated tablet, debossed with “XR 1 000” on one side and plain on other side.

4 CLINICAL PARTICULARS

Therapeutic indications

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

Posology and method of administration

Posology

GLUCOTRIN XR 500 mg

Monotherapy and combination with other oral antidiabetic agents:

- The usual starting dose is one tablet of Metformin Hydrochloride 500 mg once daily.
- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. Gastro-intestinal tolerability may improve with a slow increase of dose. The maximum recommended dose is 4 tablets of Metformin Hydrochloride 500 mg daily.
- Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal. If glycaemic control is not accomplished on 4 x GLUCOTRIN XR 500 mg once daily, 2 X GLUCOTRIN XR 500 mg twice daily should be considered. Both doses should be given with food. If glycaemic control is still not accomplished, patients may be converted to standard metformin tablets to a maximum dose of 3000 mg daily.

GLUCOTRIN XR 750 mg

The usual starting dose is one tablet daily given with the evening meal.
After 10 to 15 days the dose should be modified based on blood glucose measurements. Gastro-intestinal tolerability may improve with a slow increase of dose.
The recommended dosage is 2 tablets once daily, with the evening meal.
If glycaemic control is not achieved with GLUCOTRIN XR 750 mg 2 tablets once daily then GLUCOTRIN XR 750 mg may increase to a maximum dose of 3 tablets once daily with the evening meal.
If glycaemic control is not achieved on GLUCOTRIN XR 750 mg 3 tablets once daily, then one tablet of GLUCOTRIN XR 750 mg in the morning and two tablets of GLUCOTRIN XR 750 mg in the evening should be considered. Both doses should be given with food.
If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

GLUCOTRIN XR 1000 mg

GLUCOTRIN XR 1000 mg is aimed as maintenance therapy for patients already treated with either 1000 mg (2 tablets of GLUCOTRIN XR 500) or 2000 mg (4 tablets of GLUCOTRIN XR 500) of extended release metformin hydrochloride. If glycaemic control is not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum daily dose of 3000 mg daily.

Switching patients already treated with metformin tablets

In patients already treated with immediate release metformin tablets, the starting dose of GLUCOTRIN 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, transferring to the extended release tablets is not recommended.

Switching patients from other oral antidiabetic agents

If switching from another oral antidiabetic medicine is intended: discontinue the other medicine and start GLUCOTRIN XR at the dose indicated above.

Combination with insulin:

Metformin prolonged release tablets and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of GLUCOTRIN XR is one 500 mg tablet once daily, with the evening meal, while insulin dosage is altered on the basis of blood glucose measurements. After titration, switch to GLUCOTRIN XR 1000 mg may be considered.

Special populations

Elderly patients: due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Paediatric population

Children: In the absence of sufficient available data, GLUCOTRIN XR range should not be used in children.

Method of administration

GLUCOTRIN XR should be administered with food and swallowed whole with a glass of water. GLUCOTRIN XR should be given with the evening meal when administered once daily. The tablets should not be chewed, split or crushed.

Contraindications

- Hypersensitivity to metformin or to any of the excipients listed in section 6.1.
- Renal dysfunction or failure (creatinine clearance < 60 ml/min, GFR , 30 mL/min).
- Diabetic pre-coma.
- Hepatic insufficiency, alcoholism, acute alcohol intoxication
- Acute conditions with the potential to alter renal function such as: intravascular administration of iodinated contrast media, dehydration, shock and severe infection
- Acute or chronic disease which may cause tissue hypoxia such as: shock, pancreatitis, cardiac or respiratory failure, recent myocardial infarction.
- Any acute metabolic acidosis (diabetic ketoacidosis. Lactic acidosis)
- The use of GLUCOTRIN XR during pregnancy is not advised.

Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a serious metabolic complication that has a high mortality in the absence of prompt treatment, that can occur due to metformin accumulation. Lactic acidosis is a medical emergency that must be treated in hospital. When patients present with a metabolic acidosis and do not have evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and GLUCOTRIN XR range therapy should be stopped.
Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. As GLUCOTRIN XR is excreted by the kidney; regular monitoring of renal function is advised in all diabetic patients with type 2 diabetes mellitus.
The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, prolonged fasting, excessive alcohol intake, ketosis, hepatic insufficiency and any condition associated with hypoxia.
Diagnosis:
The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.
This can be followed by acidotic dyspnea, abdominal pain, hypothermia and coma.
Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels using the Cockcroft-Gault formula) should be determined before initiating treatment and regularly thereafter:

- at least two to four times annually in elderly subjects and in patients with creatinine clearance levels at the limit of normal.
- at least annually in patients with normal renal function.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special care should be employed in situations where renal function may become impaired, for example when initiating diuretic therapy or antihypertensive therapy and when starting therapy with an nonsteroidal anti-inflammatory drug (NSAID).
Therapy should be stopped 2-3 days before clinical investigations and surgery such as intravenous urography and intravenous angiography. Treatment can be reinstated only after control of renal function has been regained.
The use of GLUCOTRIN XR is not advised in conditions which may cause dehydration, or in patients on low calorie intake, suffering from serious infections or trauma.
For Patients on long-term treatment with GLUCOTRIN XR they should have an annual estimation of vitamin B12 levels, as GLUCOTRIN XR may cause mal-absorption of vitamin B12. This could result in megaloblastic anaemia.

Elderly:
Due to the limited efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, GLUCOTRIN XR introduction is not recommended in these patients.

Cardiac function
Patients with heart failure are more at risk of renal insufficiency and hypoxia.
For patients with heart failure, GLUCOTRIN XR is contraindicated. (See section 4.3).

Administration of iodinated contrast media:
The intravascular administration of iodinated contrast media in radiological studies can lead to renal failure. This may lead to metformin accumulation and risk of lactic acidosis. GLUCOTRIN XR must be discontinued prior to, or at the time of the test and not started until 48 hours after, and renal function has been re-evaluated and found to be normal (see section 4.5).

Surgery:

GLUCOTRIN XR should be discontinued 48 hours before elective surgery with general spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition provided normal renal function has been established.
During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combination therapy may cause hypoglycaemia.

Stabilisation of diabetic patients with GLUCOTRIN XR and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been reached.

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.
Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

Interaction with other medicines and other forms of interaction

Concomitant use not recommended

Alcohol
Acute alcohol intoxication is associated with an increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition
- hepatic insufficiency.

Avoid consumption of alcohol-containing medications and alcohol.

Iodinated contrast media
Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.
GLUCOTRIN XR must be discontinued prior to, or at the time of the test and not restarted until 48 hours afterwards, and after renal function has been re-evaluated and found to be normal (see section 4.4).

Combinations requiring precautions for use

Medicines with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes), sympathomimetics (Beta-2-agonists) 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 other medicines and upon its discontinuation.
Some medicines can negatively affect renal function which may increase the risk of lactic acidosis, e.g. including selective cyclo-oxygenase (COX) II inhibitors, NSAIDs, ACE inhibitors, diuretics (especially loop diuretics) and angiotensin II receptor antagonists. Close monitoring of renal function is necessary when initiating or using such products in combination with GLUCOTRIN XR.

Cimetidine
Reduced renal clearance of GLUCOTRIN XR has been reported during cimetidine therapy, a dose reduction can be considered.

Sulphonylurea
Concomitant therapy of GLUCOTRIN XR with sulphonylurea may cause hypoglycaemia.

ACE-inhibitors
May decrease the blood glucose levels. The dosage of the antidiabetic medicine should be adjusted during therapy with the other medicine and upon its discontinuation, if necessary.

Anticoagulants
GLUCOTRIN XR has been reported to decrease the activity of warfarin, and dose adjustments and increased frequency of INR determinations should be considered.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.
Combination therapy of GLUCOTRIN XR 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 dolutegravir, trimethoprim, ranolazine, cimetidine, vandetanib, isavuconazole) may reduce the renal elimination of GLUCOTRIN XR and lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may effect the efficacy and renal elimination of metformin.

Vigilance is therefore advised, specifically in patients with renal impairment, when these medicines are co-administered with GLUCOTRIN XR, as metformin plasma concentration may increase. If required, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Vitamins
Long-term treatment with GLUCOTRIN XR may cause vitamin B12 mal-absorption in the gastro-intestinal tract, thus a dose reduction of GLUCOTRIN XR should be considered.

Fertility, pregnancy and lactation

Pregnancy

The use of GLUCOTRIN XR during pregnancy is not advised (See section 4.3).
Uncontrolled diabetes during pregnancy (permanent or gestational) is associated with increased risk of perinatal mortality and congenital abnormalities.
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, fetal or embryonic development, postnatal or parturition development (see section 5.3).
When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus.

Breastfeeding

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 GLUCOTRIN XR treatment.

Fertility

Fertility female or male rats was unaffected by metformin when given at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Effects on ability to drive and use machines

GLUCOTRIN XR monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.
However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulphonylureas, insulin, or meglinitides).

Undesirable effects

a. Summary of the safety profile

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Metformin Hydrochloride was similar in nature and severity to that reported in patients treated with Metformin Hydrochloride immediate release. During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Less Frequent	Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Concern of such aetiology is recommended if a patient poses with megaloblastic anaemia. Lactic acidosis
Nervous system disorders	Frequent	Taste disturbance
Gastrointestinal disorders	Frequent	Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.
Hepato-biliary disorders	Less Frequent	Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Skin and subcutaneous tissue disorders	Less Frequent	Skin reactions such as erythema, urticaria, pruritus

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Overdose

Concomitant use of GLUCOTRIN XR range with a sulphonylurea, insulin or alcohol can cause hypoglycaemia. Lactic acidosis may develop in excessive dosage, and particularly if there is a possibility of accumulation. Intense supportive and symptomatic therapy is recommended. Therapy should be particularly directed at correcting blood glucose levels and correcting fluid loss.
Treatment of overdosage
There is no specific antidote for overdose with GLUCOTRIN XR range. Treatment is symptomatic and supportive. It should be directed at correcting fluid loss and metabolic disturbances. Haemodialysis is the most effective way to remove metformin and lactate.

5 PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

A21.2 Oral hypoglycaemics
Metformin is a biguanide with antihyperglycaemic effects, lowering both postprandial glucose and basal plasma. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.
Metformin may act via 3 mechanisms:
(1) reduction of hepatic glucose production by inhibiting glycogenolysis and gluconeogenesis
(2) delay of intestinal glucose absorption
(3) and in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.

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

Pharmacokinetic properties

Absorption

Peak plasma levels (Cmax) are achieved with a median value of 7 hours, following a single oral dose of GLUCOTRIN XR 500 mg. A mean plasma concentration of 1193 ng/ml is achieved after a median value of 5 hours (range of 4 to 12 hours), following a single oral dose of 1500 mg of GLUCOTRIN XR 750 mg.
A mean peak plasma concentration of 1214 ng/ml is achieved after a median time of 5 hours (range of 4 to 10 hours), following a single oral administration in the fed state of one tablet of GLUCOTRIN XR 1000 mg. Both Cmax and AUC of metformin at steady-state, do not increase proportionally to the administered dose.
The peak is neither modified nor delayed by fasting conditions, although the AUC is decreased by 30 % when the metformin prolonged release tablet is given under fasting conditions.
Relative to intake in the fasting state the AUC is increased by 77 %, Cmax is increased by 26 % and Tmax is slightly prolonged by about 1 hour when the 1000 mg metformin prolonged release tablet is administered in fed conditions. Although. It is presumed, as there is no information on the exposure after the 500 mg and 750 mg prolonged release tablets, that similar increased exposure occurs when given in the fed-state.

Distribution

Plasma protein binding is insignificant. Metformin partitions into erythrocytes. The plasma peak is higher than the blood peak and appears at approximately the same time. The red blood cells most likely correspond to a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Biotransformation

Metformin is excreted unaffected in the urine. No metabolites have been recognised in humans.

Elimination

Renal clearance of metformin is > 400 ml/min, signifying that metformin is eliminated by tubular secretion and glomerular filtration. After an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.
When renal function is impaired, renal clearance is reduced in proportion to that of creatinine. Therefore, there is an increased level of metformin in plasma as the elimination half-life is prolonged.

Preclinical safety data

Preclinical data reveal no special exposure for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6 PHARMACEUTICAL PARTICULARS

List of excipients

Magnesium stearate, silica colloidal anhydrous, polivinyl pyrrolidone - K30, hypromellose.

Incompatibilities

None

Shelf life

36 months

Special precautions for storage

This medicine does not require any special storage conditions.

Nature and contents of container

Tablets are supplied in transparent PVC/Aluminium blister packs containing 28 or 56 tablets.
Not all pack sizes may be marketed.

Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.
106 16th Road
Midrand
1686

8 REGISTRATION NUMBER(S)

GLUCOTRIN XR 500: 49/21.2/0254
GLUCOTRIN XR 750: 49/21.2/0255
GLUCOTRIN XR 1000: 49/21.2/0256

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 September 2021

10 DATE OF REVISION OF THE TEXT

N.A

TRINITY PHARMA

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PROFESSIONELE INLIGTING

SKEDULERINGSTATUS

S3

1 NAAM VAN DIE MEDISYNE

GLUCOTRIN XR 500, 750 en **1 000 mg**.

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

500 mg: Een verlengde vrystellende tablet bevat 500 mg metformienhidrochloried, gelykstaande aan 390 mg metformienbasis.
750 mg: Een verlengde vrystellende tablet bevat 750 mg metformienhidrochloried, gelykstaande aan 585 mg metformienbasis.
1 000 mg: Een verlengde vrystellende tablet bevat 1 000 mg metformienhidrochloried, gelykstaande aan 780 mg metformienbasis.
Hierdie tablette is suikervry.
Vir ‘n volledige lys van hulpstowwe, sien afdeling 6.1.

3 FARMASEUTIESE VORM

Verlengde Vrystellende Tablet.
500 mg: Wit tot naaswit, kapsulevormige, 16.50 mm x 8.20 mm onbedekte tablet, gebosseleer met “XR 500” aan een kant en plein aan die ander kant.
750 mg: Wit tot naaswit, kapsulevormige, 19.60 mm x 9.30 mm onbedekte tablet, gebosseleer met “XR 750” aan een kant en plein aan die ander kant.
1 000 mg: Wit tot naaswit, kapsulevormige, 21.10 mm x 10.10 mm onbedekte tablet, gebosseleer met “XR 1 000” aan een kant en plein aan die ander kant.

4 KLINIESE BESONDERHEDE

Terapeutiese indikasies

Behandeling van tipe 2 diabetes mellitus in volwassenes, veral in oorgewig pasiënte, wanneer oefening en bestuur van dieet alleen nie voldoende glisemiese beheer gee nie.
GLUCOTRIN XR kan alleen as aanvangsbehandeling gegee word of kan in kombinasie met ander orale antidiabetiese middels of insulien gegee word.

Posologie en metode van toediening

Posologie

GLUCOTRIN XR 500 mg

Monoterapie en kombinasie met ander orale antidiabetiese middels:

- Die gewone aanvangsdosis is een tablet metformienhidrochloried 500 mg een keer per dag.
- Na 10 tot 15 dae moet die dosis op grond van bloedglukosewaardes aangepas word. Gastro-intestinale verdraagbaarheid kan verbeter word deur ‘n stadige verhoging in die dosis. Die maksimum aanbevole dosis is 4 tablette metformienhidrochloried 500 mg daagliks.
- Dosisverhogings moet met inkremente van 500 mg elke 10-15 dae tot ‘n maksimum van 2 000 mg een keer per dag tydens aandete gemaak word. Indien glisemiese beheer nie met 4 x GLUCOTRIN XR 500 mg een keer per dag bereik word nie, kan 2 x GLUCOTRIN XR 500 mg twee keer per dag oorweeg word. Beide doserings moet saam met voedsel gegee word. Indien glisemiese beheer steeds nie bereik word nie, kan pasiënte oorgeskakel word na die standaard metformientablette tot ‘n maksimum dosis van 3 000 mg daagliks.

GLUCOTRIN XR 750 mg

Die gewone aanvangsdosis is een tablet daagliks tydens aandete.
Na 10 tot 15 dae moet die dosis op grond van bloedglukosewaardes aangepas word. Gastro-intestinale verdraagbaarheid kan verbeter word deur ‘n stadige verhoging in die dosis.
Die aanbevole dosis is 2 tablette een keer per dag tydens aandete.
Indien glisemiese beheer nie met GLUCOTRIN XR 750 mg 2 tablette een keer per dag bereik word nie, dan kan GLUCOTRIN XR 750 mg verhoog word tot ‘n maksimum dosis van 3 tablette een keer per dag tydens aandete.
Indien glisemiese beheer nie bereik word met GLUCOTRIN XR 750 mg 3 tablette een keer per dag nie, dan kan een tablet GLUCOTRIN XR 750 mg in die oggend en twee tablette GLUCOTRIN XR 750 mg in die aand oorweeg word. Beide doserings moet saam met voedsel gegee word.
Indien glisemiese beheer steeds nie bereik word nie, kan pasiënte oorgeskakel word na die standaard metformientablette tot ‘n maksimum dosis van 3 000 mg daagliks.

GLUCOTRIN XR 1 000 mg

GLUCOTRIN XR 1 000 mg is bedoel as instandhoudingsbehandeling vir pasiënte wat reeds óf 1 000 mg (2 tablette GLUCOTRIN XR 500) óf 2 000 mg (4 tablette GLUCOTRIN XR 500) verlengde vrystellende metformienhidrochloried kry. Indien glisemiese beheer nie bereik word nie, kan pasiënte oorgeskakel word na standaard metformienhidrochloriedtablette tot ‘n maksimum daaglikse dosis van 3 000 mg daagliks.

Oorskakeling van pasiënte wat reeds behandel word met metformientablette

By pasiënte wat reeds behandel word met onmiddellik vrystellende metformientablette, moet die aanvangsdosis GLUCOTRIN XR gelykstaande wees aan die daaglikse dosis metformien onmiddellik vrystellende tablette.
By pasiënte wat behandel word met metformien teen ‘n dosis bo 2 000 mg daagliks, word oorskakeling na verlengde vrystellende tablette nie aanbeveel nie.

Oorskakeling van pasiënte van ander orale antidiabetiese middels

Indien oorskakeling van ‘n ander orale antidiabetiese middel beplan word, moet die ander middel gestaak en GLUCOTRIN XR teen die dosisse soos hierbo aangedui gegee word.

Kombinasie met insulien:

Metformien verlengde vrystellende tablette en insulien kan in kombinasieterapie gebruik word om beter bloedglukose beheer te bereik. Die gewone aanvangsdosis GLUCOTRIN XR is een 500 mg tablet een keer per dag, met aandete, terwyl die insuliendosis op grond van bloedglukosevlakke aangepas word. Na titrasie kan oorskakeling na GLUCOTRIN XR 1 000 mg oorweeg word.

Spesiale pasiëntgroepe

Bejaarde pasiënte: vanweë die moontlikheid van verlaagde renale funksie in bejaardes, moet die dosis van metformien op grond van renale funksie aangepas word. Gereelde assessering van renale funksie is noodsaaklik (sien afdeling 4.4).

Pediatriese bevolking

Kinders: In die afwesigheid van voldoende beskikbare data, moet GLUCOTRIN XR-reeks nie by kinders gebruik word nie.

Metode van toediening

GLUCOTRIN XR moet saam met voedsel toegedien word en heel ingesluk word met ‘n glas water. GLUCOTRIN XR moet tydens aandete gegee word as dit een keer per dag toegedien word. Die tablette moet nie gekou, gebreek of vergruis word nie.

Kontraïndikasies

- Hipersensitiwiteit teenoor metformien of enige van die hulpstowwe gelys in afdeling 6.1.
- Renale disfunksie of versaking (kreatienopruiming < 60 ml/min, GFR , 30 mL/min).
- Diabetiese pre-koma.
- Hepatiese ontoereikendheid, alkoholisme, akute alkoholvergiftiging.
- Akute toestande wat die potensiaal het om renale funksie te verander, bv.: intravaskulêr toediening van gejodeerde kontrasmiddels, dehidrasie, skok en erge infeksie.
- Akute of kroniese siekte wat weefselhipoksie kan veroorsaak, soos: skok, pankreatitis, kardiale of respiratoriese versaking, onlangse miokardiale infarksie.
- Enige akute metaboliese asidose (diabetiese ketoasidose. Melksuurasidose)
- Die gebruik van GLUCOTRIN XR tydens swangerskap word nie aanbeveel nie.

Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Melksuurasidose:

Melksuurasidose is ‘n ernstige metaboliese komplikasie wat ‘n hoë sterftesyfer het as behandeling nie vinnig gegee word nie, wat kan ontstaan as gevolg van metformien akkumulasie. Melksuurasidose is ‘n mediese noodgeval wat in die hospitaal behandel moet word. Wanneer pasiënte presenteer met ‘n metaboliese asidose sonder tekens van ketoasidose (ketonurie en ketonemie), moet melksuurasidose vermoed word en die behandeling met GLUCOTRIN XR-reeks moet gestaak word.
Aangemelde gevalle van melksuurasidose by pasiënte op metformien het hoofsaaklik voorgekom by diabetiese pasiënte met beduidende renale versaking. Aangesien GLUCOTRIN XR deur die nier uitgeskei word, word gereelde monitering van renale funksie aanbeveel in alle diabetiese pasiënte met tipe 2 diabetes mellitus.
Die voorkoms van melksuurasidose kan en moet verlaag word deur die beoordeling ook van ander verwante risikofaktore, soos swak beheerde diabetes, langdurige vas, oormatige alkoholiname, ketose, hepatiese ontoereikendheid en enige toestand wat met hipoksie verband hou.

Diagnose:
Die risiko van melksuurasidose moet in ag geneem word in die geval van nie-spesifieke tekens soos spierkrampe met spysverteringsversteurings soos abdominale pyn en ernstige astenie.
Dit kan gevolg word deur asidotiese dispnee, abdominale pyn, hipotermie en koma. Diagnostiese laboratoriumbevindings is ‘n daling in pH van die bloed, plasmalaktaatvlakke bo 5 mmol/L, en ‘n groter anioongaping en laktaat/piruvaatverhouding. Indien metaboliese asidose vermoed word, moet metformien gestaak en die pasiënt onmiddellik gehospitaliseer word (sien afdeling 4.9).

Renale funksie:

Aangesien metformien deur die nier uitgeskei word, moet kreatienopruiming (dit kan geskat word uit serumkreatienvlakke met behulp van die Cockcroft-Gault-forule) bepaal word voordat behandeling begin en gereeld daarna:

- minstens twee tot vier keer per jaar by ouer persone en by pasiënte met kreatienopruimingsvlakke teen die limiet van normaal.
- minstens jaarliks in pasiënte met normale renale funksie.

Verlaagde renale funksie by ouer persone kom dikwels voor en is asimptomaties. Wees besonder versigtig in situasies waar renale funksie aangetas kan word, byvoorbeeld as diuretiese terapie of antihipertensiewe terapie geïnisieer word en wanneer terapie met ‘n nie-steroïed anti-inflammatoriese middel (NSAIM) geïnisieer word.
Terapie moet gestaak word 2-3 dae voor kliniese ondersoeke en chirurgie soos intraveneuse urografie en intraveneuse angiografie. Behandeling moet slegs hervat word nadat beheer oor renale funksie herwin is.
Die gebruik van GLUCOTRIN XR word nie aanbeveel in toestande wat dehidrasie kan veroorsaak nie, of in pasiënte met ‘n lae kalorie-inname, of wat aan ernstige infeksies of trauma ly nie.
Vir pasiënte wat op langtermynbehandeling met GLUCOTRIN XR is, moet hulle ‘n jaarlikse bepaling van vitamien B_{12}-vlakke ondergaan, aangesien GLUCOTRIN XR wanabsorpsie van vitamien B_{12} kan veroorsaak. Dit kan lei tot megaloblastiese anemie.

Bejaardes:
Vanweë die beperkte effektiwiteitsdata in die vermindering van die risiko óf die vertraging van tipe 2 diabetes by pasiënte 75 jaar en ouer, word GLUCOTRIN XR nie aanbeveel by hierdie pasiënte nie.

Kardiale funksie
Pasiënte met hartversaking is meer op risiko vir nierontoereikendheid en hipoksie.
Vir pasiënte met hartversaking, is GLUCOTRIN XR gekontra-indikeerd. (Sien afdeling 4.3).

Toediening van gejodeerde kontrasmiddels:
Die intravaskulêr toediening van gejodeerde kontrasmiddels in radiologiese studies kan lei tot renale versaking. Dit kan lei tot metformien akkumulasie en ‘n risiko vir melksuurasidose. GLUCOTRIN XR moet voor of tydens die toets gestaak word en moet nie binne 48 uur daarna hervat word nie, en slegs nadat renale funksie weer geëvalueer en as normaal bevind is (sien afdeling 4.5).

Chirurgie:

GLUCOTRIN XR moet gestaak word 48 uur voor elektiewe chirurgie met algemene spinale of peridurale anestesie. Die behandeling mag hervat word, nie vroeër as 48 uur na chirurgie nie, **ó**f voor hervatting van orale voeding nie, gegewe dat normale renale funksie bevestig is.
Tydens gelyktydige behandeling met ‘n sulfonielureum, moet bloedglukose gemonitor word omdat kombinasieterapie hipoglisemie kan veroorsaak.

Stabilisering van diabetiese pasiënte met GLUCOTRIN XR en insulien moet in die hospitaal uitgevoer word vanweë die moontlikheid van hipoglisemie totdat die verhouding van die twee medisyne bepaal is.

Ander voorsorgmaatreëls:
Alle pasiënte moet voortgaan met hul dieet met ‘n gewone verhouding van koolhidraatinname gedurende die dag. Oorgewig pasiënte moet voortgaan met hul energiebeperkte dieet.
Die gewone laboratoriumtoetse vir diabetes monitering moet gereeld uitgevoer word.
Metformien alleen veroorsaak nooit hipoglisemie nie, alhoewel sorg word aanbeveel wanneer dit in kombinasie gebruik word met insulien of ander orale antidiabetika (bv. sulfonielureums of meglitiniede).

Die tabletdoppe kan in die feses voorkom. Pasiënte moet ingelig word dat dit normaal is.

Interaksie met ander medisyne en ander vorms van interaksie

Kombinasies wat nie aanbeveel word nie

Alkohol
Akute alkoholvergiftiging hou verband met ‘n verhoogde risiko vir melksuurasidose, veral in die geval van:

- vas of wanvoeding
- hepatiese ontoereikendheid.

Vermy die gebruik van alkoholbevattende medikasie en alkohol.

Gejodeerde kontrasmiddels
Intravaskulêre toediening van gejodeerde kontrasmiddels kan lei tot nierversaking, wat kan lei tot die akkumulasie van metformien en ‘n risiko vir melksuurasidose.
GLUCOTRIN XR moet voor of tydens die toets gestaak word en moet nie binne 48 uur daarna hervat word nie, en slegs nadat renale funksie weer geëvalueer en as normaal bevind is (sien afdeling 4.4).

Kombinasies wat voorsorgmaatreëls vir gebruik benodig

Medisyne met intrinsieke hiperglisemiese aktiwiteit (bv. glukokortikoïede (sistemiese en lokale roetes), simpatomimetika (Beta-2-agoniste) en diuretika). Meer gereelde monitering van bloedglukose mag nodig wees, veral aan die begin van die behandeling. Indien nodig, pas die metformien dosis aan tydens terapie met die ander medisyne en as dit gestaak word.
Sommige medisyne kan die renale funksie negatief beïnvloed, wat die risiko vir melksuurasidose kan verhoog, bv. insluitend selektiewe siklo-oksigenase (SOK) II remmers, NSAIM’s, AOE remmers, diuretika (veral lusdiuretika) en angiotensien II reseptorantagoniste. Noukeurige monitering van renale funksie is nodig tydens inisiëring van **ó**f met die gebruik van sulke produkte in kombinasie met GLUCOTRIN XR.

Simetidien
Stadiger renale opruiming van GLUCOTRIN XR is tydens simetidien-behandeling aangemeld, ‘n dosis vermindering mag oorweeg word.

Sulfonielureums
Gelyktydige behandeling met GLUCOTRIN XR met sulfonielureums mag hipoglisemie veroorsaak.

AOE-remmers
Kan die bloedglukosevlakke verlaag. Indien nodig, moet die dosis van die antidiabetiese medisyne aangepas word tydens behandeling met ander medisyne en as dit gestaak word.

Antikoagulante
Dit is gemeld dat GLUCOTRIN XR die aktiwiteit van warfarien verlaag, en dosisaanpassings en meer gereelde INR-bepalings moet oorweeg word.

Organiese katioonvervoerders (OKV)
Metformien is ‘n substraat van beide vervoerders OKV1 en OKV2.
Kombinasieterapie van GLUCOTRIN XR met

- Inhibeerders van OKV1 (soos verapamiel) kan die effektiwiteit van metformien verminder.
- Induseerders van OKV1 (soos rifampisien) kan die gastro-intestinale absorpsie en effektiwiteit van metformien verhoog.
- Inhibeerders van OKV2 (soos dolutegravir, trimetopriem, ranolasien, simetidien, vandetanib, isavukonasool) kan die renale eliminasie van GLUCOTRIN XR verminder en lei tot ‘n toename in metformien plasmakonsentrasie.
- Inhibeerders van beide OKV1 en OKV2 (soos crizotinib, olaparib) kan die effektiwiteit en renale eliminasie van metformien beïnvloed.

Waaksaamheid word dus aanbeveel, spesifiek by pasiënte met renale ontoereikendheid, wanneer hierdie medisyne gelyktydig toegedien word met GLUCOTRIN XR, aangesien die metformien plasmakonsentrasie mag toeneem. Indien nodig, kan ‘n dosisaanpassing van metformien oorweeg word aangesien OKV inhibeerders/induseerders die effektiwiteit van metformien kan verander.

Vitamiene
Langtermynbehandeling met GLUCOTRIN XR kan vitamien B_{12}-wanabsorpsie in die gastro-intestinale weg veroorsaak, dus ‘n dosisverlaging van GLUCOTRIN XR moet oorweeg word.

Vrugbaarheid, swangerskap en borsvoeding

Swangerskap

Die gebruik van GLUCOTRIN XR tydens swangerskap word nie aanbeveel nie (sien afdeling 4.3).
Onbeheerde diabetes tydens swangerskap (permanent of gestasies) hou verband met ‘n verhoogde risiko vir perinatale mortaliteit en kongenitale abnormaliteite.
‘n Beperkte hoeveelheid data oor die gebruik van metformien by swanger vroue dui nie op ‘n verhoogde risiko vir kongenitale abnormaliteite nie. Dierestudies dui nie skadelike gevolge aan ten opsigte van swangerskap, fetale of embrionale ontwikkeling, postnatale ontwikkeling of parturisie nie (sien afdeling 5.3).
Wanneer die pasiënt beplan om swanger te raak en tydens swangerskap, word dit aanbeveel dat diabetes nie behandel word met metformien nie, maar insulien gebruik word vir die handhawing van bloedglukosevlakke so na as moontlik aan normaal om die risiko van misvorming van die fetus te verminder.

Borsvoeding

Metformien word in menslike borsmelk uitgeskei. Geen nadelige gevolge is waargeneem by borsgevoede pasgeborenes/babas nie. Aloewel, aangesien slegs beperkte data beskikbaar is, word borsvoeding nie aanbeveel tydens GLUCOTRIN XR-behandeling nie.

Vrugbaarheid

Vrugbaarheid van vroulike of manlike rotte was ongeaffekteerd deur metformien wanneer dit gegee was teen dosisse so hoog soos 600 mg/kg/dag, wat ongeveer drie keer die maksimum aanbevole menslike daaglikse dosis is, gebaseer op liggaamsoppervlakte vergelykings.

Uitwerking op die vermoë om te bestuur en masjiene te gebruik

GLUCOTRIN XR monoterapie veroorsaak nie hipoglisemie nie en het dus geen effek op die vermoë om te bestuur of om masjiene te gebruik nie.
Alhoewel, pasiënte moet attent gemaak word van die risiko vir hipoglisemie wanneer metformien gebruik word in kombinasie met ander antidiabetiese middels (bv. sulfonielureums, insulien of meglinitide).

Newe-effekte

a. Opsomming van die veiligheidsprofiel

In na-bemarkingsdata en in gekontroleerde kliniese studies, was nadelige insident rapportering by pasiënte wat met Metformienhidrochloried behandel was, soortgelyk aan aard en erns as dié wat gerapporteer was by pasiënte wat behandel was met Metformienhidrochloried onmiddellike vrystelling. Tydens die aanvang van die behandeling is die algemeenste newe-effekte naarheid, braking, diarree, abdominale pyn en verlies van eetlus, wat spontaan oplos in die meeste gevalle.

b. Getabuleerde opsomming van newe-effekte

MedDRA sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Metabolisme- en voedingsversteurings	Minder gereeld	Afname in absorpsie van vitamien B_{12} met ‘n afname in serumvlakke tydens langtermyn gebruik van metformien. Hierdie etiologie moet oorweeg word as ‘n pasiënt met megaloblastiese anemie presenteer. Melksuurasidose.
Senusisteemversteurings	Gereeld	Smaakversteuring
Gastro-intestinale versteurings	Gereeld	Gastro-intestinale versteurings soos naarheid, braking, diarree, abdominale pyn en verlies van eetlus.
Hepato-biliêre versteurings	Minder gereeld	Lewerfunksietoetse abnormaliteite of hepatitis wat oplos met die staking van metformien.
Vel- en Onderhuidse weefselversteurings	Minder gereeld	Velreaksies soos eriteem, urtikarie en pruritus.

Rapportering van vermoedelike newe-effekte
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue observering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die “6.04 Adverse Drug Reactions Reporting Form”, wat aanlyn by SAHPRA se publikasies gevind kan word: https://www.sahpra.org.za/Publications/Index/8

Oordosering

Gelyktydige gebruik van GLUCOTRIN XR-reeks met ‘n sulfonielureum, insulien of alkohol kan hipoglisemie veroorsaak. Melksuurasidose kan ontwikkel in oormatige dosering, en veral as daar ‘n moontlikheid van akkumulasie is. Intensiewe ondersteunende en simptomatiese terapie word aanbeveel. Terapie moet veral gerig wees op die regstelling van bloedglukosevlakke en die regstelling van vloeistofverlies.
Behandeling van oordosering
Daar is geen spesifieke teenmiddel vir oordosering met GLUCOTRIN XR-reeks nie. Behandeling is simptomaties en ondersteunend. Dit moet gerig wees op die regstelling van vloeistofverlies en metaboliese versteurings. Hemodialise is die mees doeltreffende manier om metformien en laktaat te verwyder.

5 FARMAKOLOGIESE EIENSKAPPE

Farmakodinamiese eienskappe

A21.2 Orale hipoglisemiese middels
Metformien is ‘n biguanied met anti-hiperglisemiese effekte, wat beide postprandiale glukose en basale plasma verlaag. Dit stimuleer nie insuliensekresie nie en veroorsaak dus nie hipoglisemie nie.
Metformien kan deur 3 meganismes optree:
(1) verlaging van hepatiese glukoseproduksie deur inhibisie van glukoneogenese en glikogenolise
(2) vertraging van intestinale glukose absorpsie
(3) en in spiere, deur insulien sensitiwiteit te verhoog, verbetering van perifere glukose opname en benutting.

Metformien verhoog die vervoerkapasiteit van alle tipe membraanglukosetransporters (GLUT).
Metformien stimuleer intrasellulêre glikogeensintese deur op glikogeensintase te werk.

Farmakokinetiese eienskappe

Absorpsie

Piek plasmavlakke (K_{maks}) word bereik met ‘n mediaantyd van 7 uur, na ‘n enkele orale dosis GLUCOTRIN XR 500 mg. ‘n Gemiddelde plasmakonsentrasie van 1 193 ng/ml word bereik na ‘n mediaantyd van 5 uur (gebied van 4 tot 12 uur), na ‘n enkele orale dosis van 1 500 mg GLUCOTRIN XR 750 mg.
‘n Gemiddelde piek plasmakonsentrasie van 1 214 ng/ml word bereik na ‘n mediaan tyd van 5 uur (gebied van 4 tot 10 uur), na ‘n enkele orale toediening van een tablet GLUCOTRIN XR 1 000 mg in die gevoede toestand.
Beide K_{maks} en AOK van metformien by gelykvlak neem nie proporsioneel toe met die toegediende dosis nie.
Die piek word nie verander of vertraag deur vastende toestande nie, hoewel die AOK 30 % minder is wanneer die metformien verlengde vrystellende tablet onder vastende toestande gegee word.
Relatief tot die inname in die vastende toestand word die AOK met 77 % verhoog, K_{maks} met 26 % verhoog en T_{maks} effens verleng met ongeveer 1 uur wanneer die 1 000 mg metformien verlengde vrystellende tablet onder gevoerde toestande toegedien word. Alhoewel, dit word vermoed, aangesien daar geen inligting oor die blootstelling na die 500 mg en 750 mg verlengde vrystellende tablette is nie, dat soortgelyke verhoogde blootstelling voorkom wanneer dit in die gevoede staat gegee word.

Verspreiding

Plasmaproteïenbinding is weglaatbaar. Metformien dring in eritrosiete in. Die plasma piek is hoër as die bloed piek en verskyn ongeveer op dieselfde tyd. Die rooibloedselle stem waarskynlik ooreen met ‘n sekondêre kompartement van verspreiding. Die gemiddelde Vd het gewissel tussen 63-276 L

Biotransformasie

Metformien word onveranderde in die urien uitgeskei. Geen metaboliete is in die mens geïdentifiseer nie.

Eliminasie

Renale opruiming van metformien is > 400 ml/min, wat daarop dui dat metformien geëlimineer word deur tubulêre sekresie en glomerulêre filtrasie. Na ‘n orale dosis is die oënskynlike terminale eliminasiehalfleeftyd ongeveer 6,5 uur.
Wanneer renale funksie ingekort is, is die renale opruiming verminderd in verhouding tot die van kreatinien. Daarom is daar ‘n verhoogde vlak van metformien in plasma, en verlengde eliminasiehalfleeftyd.

Pre-kliniese veiligheids data

Pre-kliniese data toon geen spesiale blootstelling aan mense op grond van konvensionele studies oor veiligheidsfarmakologie, herhaalde dosis toksisiteit, genotoksisiteit, karsinogeniese potensiaal, reproduksie van toksisiteit nie.

6 FARMSEUTIESE BESONDERHEDE

Lys van hulpstowwe

Hipromellose, magnesiumstearaat, polivinielpirrolidoon - K30, anhidriese kolloïdale silika.

Onverenigbaarheid

Geen.

Rakleeftyd

36 maande.

Spesiale voorsorgmaatreëls tydens berging

Hierdie medisyne benodig nie enige spesiale bergingstoestande nie.

Aard en inhoud van die houer

Tablette word verskaf in deursigtige PVC/Aluminium stolpverpakkings wat 28 of 56 tablette bevat.
Nie alle verpakkingsgroottes mag moontlik bemark word nie.

Spesiale voorsorgmaatreëls vir wegdoening en ander hantering

Geen spesiale vereistes vir wegdoen. Enige ongebruikte medisyne of afvalstowwe moet weggedoen word volgens die plaaslike vereistes.

7 HOUER VAN REGISTRASIESERTIFIKAAT

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8 REGISTRASIENOMMER(S)

GLUCOTRIN XR 500: 49/21.2/0254
GLUCOTRIN XR 750: 49/21.2/0255
GLUCOTRIN XR 1000: 49/21.2/0256

9 DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING

14 September 2021

10 DATUM VAN HERSIENING VAN DIE TEKS

N.V.T