

TAJ PHARMA



Metformin Hydrochloride Prolonged Release & Glimepiride Tablets I.P. Glucotai® M 1mg Glucotai® M 2mg DESCRIPTION

Active Ingredients Glimepiride and Metformin Hydrochloride (in prolonged release form) Therapeutic or Pharmacological Class

Pharmaceutical Form(s) Bilayer Tablet (one layer prolonged release)

COMPOSITION

Glucotaj M 1mg

Each uncoated bilayered tablet contains: Glimepiride IP 1mg

Metformin hydrochloride IP (in prolonged release form) 500mg Excipients q.s.

Colours : Red Iron Oxide

Glucotaj M 2mg

Each uncoated bilayered tablet contains :

Glimeniride IP 2mg Metformin hydrochloride IP (in prolonged release form) 500mg

Excipients q.s. Colours: Yellow Iron Oxide & Indigo Carmine

INDICATION For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in

DOSAGE AND ADMINISTRATION

adequate glycemic control

General

In principle, the dosage of Glucotaj M is governed by the desired blood glucose level. The dosage

of Glucotaj M must be the lowest which is sufficient to achieve the desired

During treatment with Glucotaj M glucose levels in blood and urine, must be measured regularly.

In addition, it is recommended that regular determinations of the proportion of glycated haemoglobin be carried out .Mistakes, e.g. forgetting to take a dose, must never be corrected by subsequently taking a larger dose. Measures for dealing with such mistakes (in particular forgetting a dose or skipping a meal) or situations where a dose cannot be

taken at the prescribed time must be discussed and agreed between physician and patient

For the use only of a Registered Medical Practitioner or Hospital or a Laboratory

This package insert is continually updated. Please read carefully before using a new pack

As an improvement in control of diabetes is, in itself, associated with

higher insulin sensitivity, glimepiride requirements may fall as treatment proceeds. To avoid hypoglycemia timely dose reduction or cessation of Glucotaj M therapy

must therefore be considered. Glucotaj M is to be administered once per day during breakfast or the first

The highest recommended dose per day should be 8mg of glimepiride and 2000mg of metformin.

Daily doses of glimepiride of more than 6mg are more effective only in a minority of patients. In order to avoid hypoglycemia the starting dose of Glucotaj M should not exceed the daily doses of glimepiride or metformin already being taken.

When switching from combination therapy of glimeniride plus metforming as separate tablets, Glucotaj M should be administered on the basis of dosage currently being taken Titration:

The daily dose should be titrated based on the glycemic control ,in increments of 1 tablet only, corresponding to the lowest strength. Duration of therapy: Treatment with Glucotaj M is normally a long-term therapy

Special Populations

Children

Data are insufficient to recommend pediatric use of Glucotaj M. Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at 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. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses.

Factors that may increase the risk of lactic acidosis (see Section Warnings) should be

reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

If no adequate strength of Glucotaj M is available, individual monocomponents should be

used instead of the fixed dose combination. GFR ml/min Metformin Glimepride 60-89 Maximum daily dose is 3000 mg

Dose reduction may be considered in relation to declining renal function. The highest recommended dose per

day should be 8 mg of glimepiride 45-59 Maximum daily dose is 2000 mg The starting dose is at most half of the maximum dose. 30-44 Maximum daily dose is 1000 mg.

30 Metformin is contraindicated Change-over to insulin is indicated. not least to achieve optimal metabolic

The starting dose is at most half of the maximum dose

control ADMINISTRATION

Due to prolonged release formulation, Glucotaj M must be swallowed whole and not crushed or chewed.

CONTRAINDICATIONS:

For Glimepiride: in patients hypersensitive to glimepiride, other sulfonylureas, other

sulfonamides, or any of the excipients of Glucotaj® M

in pregnant women.

in breast-feeding women. No experience has been gained concerning the use of glimepiride in patients with severe impairment of liver function and in dialysis patients. In

patients with severe impairment of hepatic function, change-over to insulin is indicated, not least to achieve optimal metabolic control

Hypersensitivity to metformin or any of the excipients.

Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma).

Severe renal failure (GFR 30ml/min) Acute conditions with the potential to alter renal function such as:

- Dehydration

For Metformin:

- severe infection
- shock

- Intravascular administration of iodinated contrast agents (see Precautions)

Acute or chronic disease which may cause tissue hypoxia such as: -cardiac or respiratory failure

- recent myocardial infarction

Hepatic insufficiency. Acute alcohol intoxication, alcoholism.

Lactation. WARNINGS

For Glimepiride:

In exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. For Metformin:

Lactic acidosis

Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea 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 associated to 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 Section

Contraindications and Section Interactions) Diagnosis: Patients and/or care-givers should be informed of the risk of lactic acidosis. 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 Section Dosage and Administration) Metformin is contraindicated in patients with GFR < 30 ml/min and should

be temporarily discontinued in the presence of conditions that after renal function, (see Section Contraindications)

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for

example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent:

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis

Metformin should be discontinued prior to, or at the time of the imaging procedure and not restarted until 48 hours after, provided that renal function has been re-evaluated and found to be stable (see Section Dosage and Administration and Section Interactions) Surgery:

Metformin must be discontinued at the time of surgery under general spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. **PRECAUTIONS**

For Glimepiride: In the initial weeks of treatment, the risk of hypoglycaemia may be increased and necessitates especially careful monitoring. Factors favouring hypoglycaemia include:

unwillingness or (more commonly in older patients) incapacity of the patient to cooperate

undernourishment, irregular mealtimes or skipped meals. imbalance between physical exertion and carbohydrate intake alterations of diet. consumption of alcohol, especially in combination with skipped meals

impaired renal function.

severe impairment of liver function. overdosage with glimepiride.

certain uncompensated disorders of the endocrine system affecting

carbohydrate metabolism or counter-regulation of hypoglycaemia (as for example in certain disorders of thyroid function and in anterior pituitary or corticoadrenal

insufficiency). concurrent administration of certain other medicines (see Interactions).

treatment with glimepiride in the absence of any indication.

If such risk factors for hypoglycaemia are present, it may be necessary to adjust the dosage of

glimepiride or the entire therapy. This also applies whenever illness occurs during therapy or the patient's life-style changes. Those symptoms of hypoglycaemia which reflect the body's

adrenergic counter regulation (see Adverse Reactions) may be milder or absent where hypoglycaemia develops gradually, in the elderly, and where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers,

clonidine, reserpine, guanethidine or other sympatholytic drugs. Hypoglycaemia can almost always be promptly controlled by immediate intake of carbohydrates(glucose or sugar). It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore,

remain under close observation. Severe hypoglycaemia further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care. Treatment of natients with G6PD-deficiency with sulfonylurea agents can

lead to hemolytic anaemia. Since alimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PDdeficiency and a non-sulfonylurea alternative should be considered. For Metformin: Regular monitoring of thyroid-stimulating hormone (TSH) levels is

recommended in patients with hypothyroidism (see Adverse reactions) Long-term treatment with metformin has been associated with a decrease in vitamin B12 serum

levels which may cause peripheral neuropathy. Monitoring of the vitamin B12 level is recommended (see Adverse reactions) 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 sulfonylureas INTERACTIONS

For Glimepiride:

Based on experience with glimepiride and on what is known of other sulfonylureas, the following interactions must be considered: Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is coadministered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP2C9.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following drugs is taken, for example: insulin

and other oral antidiabetics; ACE inhibitors; anabolic steroids and male sex hormones: chloramphenicol: coumarin derivatives; cyclophosphamide; disopyramide; fenfluramine;

fenyramidol; fibrates; fluoxetine; guanethidine; ifosfamide; MAO inhibitors; miconazole; fluconazole; paraaminosalicylic acid; pentoxifylline (high dose parenteral): phenylbutazone: azapropazone: oxyphenbutazone: probenecid: quinolones; salicylates; sulfinpyrazone; clarithromycin; sulfonamide antibiotics; tetracyclines; tritoqualine; trofosfamide

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following drugs is taken, for example: acetazolamide; barbiturates; corticosteroids; diazoxide; diuretics

epinephrine (adrenaline) and other sympathomimetic agents; glucagon; laxatives (after protracted use); nicotinic acid (in high doses); oestrogens and progestogens; phenothiazines; phenytoin; rifampicin; thyroid hormones.

H2 receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose-lowering effect. Under the influence of sympatholytic drugs such as beta-blockers, clonidine, quanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent. Both acute and chronic alcohol intake may potentiate or weaken the blood glucose-lowering action of glimepiride in an unpredictable fashion. The effect of coumarin derivatives may be potentiated or weakened. Bile acid sequestrant: Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was

Therefore glimepiride should be administered at least 4 hours prior to colesevelam

For Metformin: Concomitant use not recommended:

Alcohol: Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting or malnutrition or hepatic insufficiency.

observed when glimepiride was taken at least 4 hours before colesevelam.

Avoid consumption of alcohol and alcohol-containing medications. Iodinated contrast agents Metformin must be discontinued prior to or at the time of the image

procedure and not restarted until at least 48 hours after, provided that renal function has been reevaluated and found to be

stable(See Section Dosage and Administration and Warnings) imbinations requiring precautions for usi

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II

inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin,

close monitoring of renal function is necessary. Glucocorticoids (systemic and local routes), beta-2-agonists and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood alucose monitoring.

especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation. ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

Metformin may decrease the anticoagulant effect of phenorocoumon. Therefore, a close monitoring of the INR is recommended. Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated or stopped, and the dosage of metformin must be adjusted if

necessary. Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2

Co-administration 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, trimethoprime,

concentration. · Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma

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 metforming PREGNANCY

Glimepiride must not be taken during pregnancy. Otherwise there is risk of harm to the child. The patient must change over to insulin during

For Glimepiride:

pregnancy. Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin For Metformin:

To date, no relevant epidemiological data are available. 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, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to

lower the risk of fetal malformations associated with abnormal blood

alucose levels.

For Glimepiride: To prevent possible ingestion with the breast milk and possible harm to the child, glimepiride must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-

For Metformin

Metformin is excreted into milk in lactating rats. Similar data is not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother. INIVING A VEHICLE OR PERFORMING OTHER HAZARI

For Glimepiride: Alertness and reactions may be impaired due to hypo- or hyperglycemia, especially when beginning or after altering treatment or when glimepiride is not taken regularly. This may, for example, affect the ability to drive or to

operate machinery. For Metformin: Metformin 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 (sulfonylureas, insulin, repaglinide)

The following CIOMS frequency rating is used, when applicable Very common ≥10%; Common ≥1 and <10%; Uncommon ≥0.1 and <1%; Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%, Unknown (cannot be estimated from available data)

For Glimepiride and Metformin The use of a combination of both compounds, either as a free combination or as a fixed combination, is associated with the same safety

separately. For Glimepiride:

to and including coma,

ADVERSE REACTIONS

Metabolism and nutrition disorders

characteristics as the use of each compound

As a result of the blood-glucose-lowering action of glimepiride, hypoglycaemia may occur, which may also be prolonged. Possible symptoms of hypoglycaemia include headache, ravenous hunger,

nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration impaired alertness and reactions, depression, confusion, speech

disorders, aphasia, visual disorders, tremor, pareses, sensory disturbances, dizziness, helplessness, loss of self-control. delirium, cerebral convulsions, somnolence and loss of consciousness up

shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as

sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris, and

cardiac arrhythmias The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke

The symptoms nearly always subside when hypoglycaemia is corrected. Eye disorders Especially at the start of treatment, there may be temporary visual impairment due to the change in blood glucose levels. The cause is a temporary alteration in the turgidity

and hence the refractive index of the lens, this being dependent on blood glucose level.

Gastrointestinal disorders

Occasionally, gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fulness in the epigastrium, abdominal pain and diarrhoea may occur. In isolated cases, there may be hepatitis, elevation of liver enzyme levels

and/or cholestasis and jaundice, which may progress to life-threatening liver failure but can regress after withdrawal of glimepiride.

Dysgeusia (frequency not known)

experience (frequency not known).

Alopecia (frequency not known)

General disorders

Skin and subcutaneous tissue disorders

Blood and lymphatic system disorders Changes in the blood picture may occur: Rarely, thrombocytopenia and, in isolated cases, leucopenia, haemolytic anaemia, erythrocytopenia, granulocytopenia, agranulocytosis or pancytopenia may develop. Cases of severe thrombocytopenia with platelet count less than 10,000/ I and thrombocytopenic purpura have been reported in post-marketing

Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching, urticaria or rashes. Such mild reactions may develop into serious reactions with dyspnoea and a fall in blood pressure, sometimes progressing to shock. In the event of urticaria a physician must

therefore be notified immediately. In isolated cases, a decrease in serum sodium concentration and allergic vasculitis or hypersensitivity of the skin to light may occur.

Investigations Glimepiride, like all sulfonylureas, can cause weight gain (frequency not known)

For Metformin: Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite (>10%) are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal

tolerability. - Metallic taste (3%) is common.

· Mild erythema has been reported in some hypersensitive individuals. The incidence of such effects is regarded as very rare (<0.01%)

- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (<0.01%). However, cases of peripheral neuropathy in patients with vitamin B12 deficiency have been reported in post-marketing experience (frequency not

known) (see Precautions) -Lactic acidosis (0.03 cases/1000 patient-years) is very rare (see

Warnings). - Hemolytic anemia (frequency unknown)

Photosensitivity (frequency unknown)

- Reduction of thyrotropin level in patients with hypothyroidism (see Precautions) (frequency unknown) - Hypomagnesemia in the context of diarrhea (frequency unknown) Encephalopathy (frequency unknown)

Hepatobiliary disorders: Reports of liver function tests abnormalities and

hepatitis resolving upon metformin discontinuation OVERDOSAGE: For Glimepiride:

Signs and Symptoms:

Acute overdosage as well as long-term treatment with too high a dose of glimepiride may lead to severe life-threatening hypoglycaemia

Management: As soon as an overdose of alimepiride has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible in the form of glucose, unless a physician has already undertaken responsibility for treating the overdose. Careful monitoring is essential until the physician is confident that the patient is out of danger. It must be remembered that hypoglycaemia may recur after initial recovery Admission to hospital may sometimes be necessary - even as a

as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital.

considered. In particular when treating hypoglycaemia due to accidental intake of olimepiride in infants and young children, the dose of glucose given must be very carefully adjusted in view of the possibility of producing dangerous

detoxification (e.g. by gastric lavage and medicinal charcoal). After acute glucose replacement has been completed it is usually necessary to give an intravenous glucose infusion in lower concentration so as to ensure that the hypoglycaemia does not recui The patient's blood glucose level should be carefully monitored for at least

24 hours. In severe cases with a protracted course, hypoglycaemia, or the danger of slipping back into hypoglycaemia, may persist for several days For Metformin:

has occurred in such circumstances. High overdose or concomitant risks of metformin may lead

STORAGE CONDITIONS Store below +25°C in a dry place. Keep out of reach of children. Manufactured in India by TAJ PHARMACEUTICALS LTD Mumbai India Unit no 214.0ld Bake House

Maharashtra Chambers of Commerce Lan Fort Mumbai - 400001 at : Ahmedabad-382213, Guiarat, INDIA

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Reference: CCDS Version 11 dated 17th October 2017 for Glimepiride plus Metformin Fixed Dose Combination



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precautionary measure. In particular, significant overdoses and severe reactions with signs such

If, for example, the patient is unconscious, an intravenous injection of concentrated glucose solution is indicated (for adults starting with 40 ml of 20% solution, for example). Alternatively in adults, administration of glucagon, e.g. in doses of 0.5 to 1 mg i.v., s.c. or i.m. may be

hyperglycaemia, and must be controlled by close monitoring

of blood alucose. Patients who have ingested life-threatening amounts of glimepiride require

Hypoglycaemia has not been seen with metformin doses of up to 85 g. although lactic acidosis

to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis. Pancreatitis may occur in the context of a metformin overdose