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

Amaryl® MP 1mg
Amaryl® MP 2mg
Metformin Hydrochloride Sustained Release, Glimepiride & Pioglitazone Hydrochloride Tablets

For Pioglitazone :

The drug should not be used as first line therapy for diabetes.

Advice for healthcare professionals:

1. **Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone.**
2. **Prescribers should review the safety and efficacy of pioglitazone in individuals after 3-6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequately to treatment (eg, reduction in glycosylated haemoglobin, HbA1c).**
3. **Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals : age, current or past history of smoking, exposure to some occupational or chemotherapy agents such as cyclophosphamide, or previous irradiation of the pelvic region.**
4. **Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.**

DESCRIPTION

Active Ingredients

Glimepiride (sulfonylurea), Pioglitazone hydrochloride (thiazolidinedione) and Metformin Hydrochloride (biguanide)

Therapeutic or Pharmacological Class

Antidiabetic

Pharmaceutical Form(s)

Uncoated bilayered Tablet

COMPOSITION

Amaryl® MP 1mg

Each uncoated bilayered tablet contains

Metformin Hydrochloride I.P…… 500 mg (in Sustained release form)

Glimepiride IP…… 1mg

Pioglitazone Hydrochloride I.P. equivalent to Pioglitazone……15 mg
Excipients qs
Colour : Ferric Oxide Red

Amaryl® MP 2mg
Each uncoated bilayered tablet contains
Metformin Hydrochloride I.P…… 500 mg (in Sustained release form)
Glimepiride IP…… 2mg
Pioglitazone Hydrochloride I.P. equivalent to Pioglitazone……15 mg
Excipients qs
Colour : Ferric Oxide Yellow

INDICATION
As third line treatment of Type II diabetes mellitus in adult patients when diet, exercise and the single agents and second line therapy with two drugs do not result in adequate glycemic control.

DOSAGE AND ADMINISTRATION
Amaryl® MP should be given once daily with the first meal of the day. The maximum recommended daily dose of Amaryl® MP in adults should not exceed 3 tablets.

Amaryl® MP tablet should not be crushed or chewed and should be taken as a whole with water.

Use in special population
Pediatrics : Safety and effectiveness of Amaryl® MP has not been established.

Females of reproductive potential: Discuss the potential of unintended pregnancy with premenopausal females as therapy with pioglitazone, like other thiazolidinediones may result in ovulation in some anovulatory women..

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 Amaryl MP 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. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated	Change-over to insulin is indicated, not least to achieve optimal metabolic control

CONTRAINDICATIONS:

For Glimepiride:

- in patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, or any of the excipients of Amaryl® MP
- 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.

For Metformin:

- 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
  - 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
  - shock
- Hepatic insufficiency.
- Acute alcohol intoxication, alcoholism.
- Lactation.

For Pioglitazone:

- Initiation of Pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.
- Use in patients with known hypersensitivity to pioglitazone, metformin or any other component of Amaryl MP.

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 alter 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.

For Pioglitazone:
Congestive Heart Failure: Pioglitazone, like other thiazolidinediones, can cause dose – related fluid retention when used alone or in combination with other antihyperglycemic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of pioglitazone must be considered (See Contraindications and Adverse Reactions). Not recommended in patients with symptomatic heart failure.

Hypoglycemia: When used with insulin or an insulin secretagogue, a lower dose of the insulin or insulin secretagogue may be needed to reduce the risk of hypoglycemia.

Bladder cancer: Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. Amaryl MP should not be used in patients with active bladder cancer or with history of bladder cancer and those with uninvestigated haematuria (see boxed warning).

Fractures: The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care.

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 patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency 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.

For Pioglitazone hydrochloride

Hepatic effects:
There have been postmarketing reports of fatal and non fatal hepatic failure in patients taking pioglitazone. Causality cannot be excluded. If liver injury is detected, promptly interrupt treatment and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart Amaryl MP if liver injury is confirmed and no alternate etiology can be found.

Edema:
Pioglitazone should be used with caution in patients with oedema. In clinical trials with pioglitazone, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and appears to be dose related. Since thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, Amaryl®MP should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure.

Macular Edema:
Macular edema has been reported in post-marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist. Patient who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings.

Macrovascular Outcomes:
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Amaryl MP or any other oral antidiabetic drug.

DRUG 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; para-aminosalicylic 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, guanethidine and reserpine, the signs of adrenergic counter-regulation 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 observed when glimepiride was taken at least 4 hours before colesevelam. 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.

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 re-evaluated and found to be stable (See Section Dosage and Administration and warnings).

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 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 glucose 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 phenprocoumon. 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, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an 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

For Pioglitazone Hydrochloride:
Strong CYP2C8 Inhibitors
An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the serum concentration-time curve or AUC) and half-life (t½) of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors

CYP2C8 Inducers
An inducer of CYP2C8 (e.g., rifampin) may significantly decrease the exposure (AUC) of pioglitazone. Therefore, if an inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response.

Topiramate
A decrease in the exposure of pioglitazone and its active metabolites were noted with concomitant administration of pioglitazone with topiramate. The clinical relevance of this decrease is unknown, monitor patients for adequate glycemic control.

PREGNANCY
Amaryl® MP must not be taken during pregnancy. Otherwise there is risk of harm to the child. The patient must change over to insulin during pregnancy. Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

LACTATION
To prevent possible ingestion with the breast milk and possible harm to the child, Amaryl® MP must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

ADVERSE REACTIONS
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:

- Metabolism and nutrition disorders

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 to and including coma, 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)

- 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/µl and thrombocytopenic purpura have been reported in post-marketing experience (frequency not known).

- Skin and subcutaneous tissue disorders

Alopecia (frequency not known)

- General disorders

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)
- Reduction of thyrotropin level in patients with hypothyroidism (see Precautions) (frequency unknown)
- Hypomagnesemia in the context of diarrhea (frequency unknown)
- Encephalopathy (frequency unknown)
- Photosensitivity (frequency unknown)
- Hepatobiliary disorders: Reports of liver function tests abnormalities and hepatitis resolving upon metformin discontinuation.

For Pioglitazone Hydrochloride

For following serious adverse reactions, see Warnings & Precautions :

- Congestive Heart Failure

- Oedema
- Fractures

The most common adverse events (≥ 5%) are upper respiratory tract infection, headache, sinusitis, myalgia and pharyngitis.

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

- New onset or worsening diabetic macular edema with decreased visual acuity [see Warnings and Precautions].
- Fatal and nonfatal hepatic failure [see Warnings and Precautions].

Postmarketing reports of congestive heart failure have been reported in patients treated with pioglitazone, both with and without previously known heart disease and both with and without concomitant insulin administration.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure (see Warnings and Precautions)

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 glimepiride 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 precautionary measure.
In particular, significant overdoses and severe reactions with signs such as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment and admission to hospital.

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 considered.

In particular when treating hypoglycaemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be very carefully adjusted in view of the

possibility of producing dangerous hyperglycaemia, and must be controlled by close monitoring of blood glucose.

Patients who have ingested life-threatening amounts of glimepiride require 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 recur. 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:
Hypoglycaemia 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. The most effective method to remove lactate and metformin is haemodialysis.
Pancreatitis may occur in the context of a metformin overdose.

For Pioglitazone Hydrochloride:
In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

STORAGE CONDITIONS
Store below +25ºC in a dry place.
Keep out of reach of children.

MANUFACTURED BY:
Sanofi India Limited
3501,3503-15,6310 B-14
G.I.D.C Estate, Ankleshwar-393002

Updated: December 2017

Reference:
CCDS version 11 dated October 2017 for Glimepiride plus Metformin Fixed Dose Combination
Actos leaflet dated December 2017