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

## Glimepiride, Pioglitazone & Metformin Hydrochloride Extended release 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)**

Bilayered uncoated tablet

**COMPOSITION**

**Amaryl® MP 1mg**

Each bilayered uncoated tablet contains

Glimepiride IP…… 1mg

Pioglitazone Hydrochloride I.P. equivalent to Pioglitazone……15 mg

Metformin Hydrochloride I.P…… 500 mg (as extended release)

Excipients qs
Colour : Ferric Oxide Red

**Amaryl® MP 2mg**
Each bilayered uncoated tablet contains
Glimepiride IP…… 2mg
Pioglitazone Hydrochloride I.P. equivalent to Pioglitazone……15 mg
Metformin Hydrochloride I.P…… 500 mg (as extended release)

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 in children and adolescents under 18 years of age has not been established.

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**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<br>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<br>The starting dose is at most half of the maximum dose. | |
| 30-44 | Maximum daily dose is 1000 mg.<br>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 |

No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min). No information is available from dialysed patients therefore pioglitazone should not be used in such patients.

Hepatic impairment
Pioglitazone should not be used in patients with hepatic impairment (See Contraindications)

**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:***

- cardiac failure or history of cardiac failure (NYHA stages I to IV) .
- Use in patients with known hypersensitivity to pioglitazone, metformin or any other component of Amaryl MP.
  - hepatic impairment,
  - diabetic ketoacidosis,
  - current bladder cancer or a history of bladder cancer,
  - uninvestigated macroscopic haematuria

**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:***

**Fluid retention and cardiac failure:** Pioglitazone, like other thiazolidinediones, can cause fluid retention. Fluid retention may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of oedema. Post marketing cases of peripheral oedema and cardiac failure have also been reported in patients with concomitant use of pioglitazone and nonsteroidal anti-inflammatory drugs, including selective COX-2 inhibitors. Pioglitazone should be discontinued if any deterioration in cardiac status occurs. A cardiovascular outcome study of pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing antidiabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study.

**Hypoglycemia:**
As a consequence of increased insulin sensitivity, patients receiving pioglitazone in dual or triple oral therapy with a sulfonylurea or in dual therapy with insulin may be at risk for dose-related hypoglycaemia, and a reduction in the dose of the sulfonylurea or insulin may be necessary. .

**Bladder cancer:**
Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR = 2.64 (95% CI 1.11–6.31, P = 0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Epidemiological studies have also suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone although not all studies identified a statistically significant increased risk. Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.
Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment . (see boxed warning).

**Fractures:**
An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomised, controlled, double blind clinical trials in over 8100 pioglitazone and 7400 comparator treated patients, on treatment for up to 3.5 years.
Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%). The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100

patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.
In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women. The risk of fractures should be considered in the long term care of patients treated with pioglitazone .

**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***

**Monitoring of liver function:**

. There have been rare reports of hepatocellular dysfunction during post-marketing experience (see section ADVERSE REACTIONS). It is recommended, therefore, that patients treated with pioglitazone undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with pioglitazone in all patients. Therapy with pioglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5× upper limit of normal) or with any other evidence of liver disease. Following initiation of therapy with pioglitazone, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3× upper limit of normal during pioglitazone therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3× the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, the medicinal product should be discontinued

Weight gain

In clinical trials with pioglitazone there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure, therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Haematology

There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with pioglitazone, consistent with haemodilution. Similar changes were seen in metformin (haemoglobin 3–4% and haematocrit 3.6–4.1% relative reductions) and to a lesser extent sulfonylurea and insulin (haemoglobin 1–2% and haematocrit 1–3.2% relative reductions) treated patients in comparative controlled trials with pioglitazone.

Eye disorders

Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between pioglitazone and macular oedema, but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Elderly
Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure. In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.

Others
As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should be aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, the treatment should be discontinued (see section PREGNANCY).

Pioglitazone should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin).Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered (see section INTERACTION).

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AMARYL MP contains lactose monohydrate and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

**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**
. Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC of pioglitazone. Since there is a potential for an increase in dose-related adverse events, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered. (See WARNINGS AND PRECAUTIONS)

**CYP2C8 Inducers**
A. Coadministration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC of pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered (See WARNINGS AND PRECAUTIONS)

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Co-administration of pioglitazone with sulfonylureas does not appear to affect the pharmacokinetics of the sulfonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. In vitro studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolized by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers, and HMGCoA reductase inhibitors are not to be expected

**PREGNANCY**
There are no adequate human data to determine the safety of pioglitazone during pregnancy. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear

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.

FERTILITY
In animal fertility studies there was no effect on copulation, impregnation or fertility index.

**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***

Tabulated list of adverse reactions

Adverse reactions reported in excess (> 0.5%) of placebo and as more than an isolated case in patients receiving pioglitazone in double-blind studies are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing incidence followed by decreasing seriousness.

| Adverse reaction | Frequency of adverse reactions of pioglitazone by treatment regimen | | | | |
|---|---|---|---|---|---|
| | Monotherapy | Combination | | | |
| | | with metformin | with sulfonylurea | with metformin and sulfonylurea | with insulin |
| Infections and infestations | | | | | |
| upper respiratory tract infection | common | common | common | common | common |
| bronchitis | | | | | common |
| sinusitis | uncommon | uncommon | uncommon | uncommon | uncommon |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | | | | |
| bladder cancer | uncommon | uncommon | uncommon | uncommon | uncommon |
| **Blood and lymphatic system disorders** | | | | | |
| anaemia | | common | | | |
| **Immune system disorders** | | | | | |
| hypersensitivity and allergic reactions[1] | not known | not known | not known | not known | not known |
| **Metabolism and nutrition disorders** | | | | | |
| hypo-glycaemia | | | uncommon | very common | common |
| appetite increased | | | uncommon | | |
| **Nervous system disorders** | | | | | |
| hypo-aesthesia | common | common | common | common | common |
| headache | | common | uncommon | | |
| dizziness | | | common | | |
| insomnia | uncommon | uncommon | uncommon | uncommon | uncommon |
| **Eye disorders** | | | | | |
| visual disturbance[2] | common | common | uncommon | | |
| macular oedema | not known | not known | not known | not known | not known |
| **Ear and labyrinth disorders** | | | | | |
| vertigo | | | uncommon | | |
| **Cardiac disorders** | | | | | |
| heart failure[3] | | | | | common |
| **Respiratory, thoracic and mediastinal disorders** | | | | | |
| dyspnea | | | | | Common |

| Adverse reaction | Frequency of adverse reactions of pioglitazone by treatment regimen | | | | |
|---|---|---|---|---|---|
| | Monotherapy | Combination | | | |
| | | with metformin | with sulfonylurea | with metformin and sulfonylurea | with insulin |
| **Gastrointestinal disorders** | | | | | |
| flatulence | | uncommon | common | | |
| **Skin and subcutaneous tissue disorders** | | | | | |
| sweating | | | uncommon | | |
| fracture bone[4] | common | common | common | common | common |
| arthralgia | | common | | common | common |
| back pain | | | | | Common |
| **Renal and urinary disorders** | | | | | |
| haematuria | | common | | | |
| glycosuria | | | uncommon | | |
| proteinuria | | | uncommon | | |
| **Reproductive system and breast disorders** | | | | | |
| erectile dysfunction | | common | | | |
| **General disorders and administration site conditions** | | | | | |
| oedema[5] | | | | | very common |
| fatigue | | | uncommon | | |
| **Investigations** | | | | | |
| weight increased[6] | common | common | common | common | common |
| blood creatine phospho-kinase increased | | | | common | |
| increased lactic dehydro-genase | | | uncommon | | |
| alanine aminotransferase increased[7] | not known | not known | not known | not known | not known |

Description of selected adverse reactions

1 Postmarketing reports of hypersensitivity reactions in patients treated with pioglitazone have been reported. These reactions include anaphylaxis, angioedema, and urticaria.

2 Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic treatments.

3 In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulfonylurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo, when added to therapy that included insulin. However, this did not lead to an increase in mortality in this study. In this study in patients receiving pioglitazone and insulin, a higher percentage of patients with heart failure was observed in patients aged ≥65 years compared with those less than 65 years (9.7% compared to 4.0%). In patients on insulin

with no pioglitazone the incidence of heart failure was 8.2% in those ≥65 years compared to 4.0% in patients less than 65 years. Heart failure has been reported with marketing use of pioglitazone, and more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

4 A pooled analysis was conducted of adverse reactions of bone fractures from randomised, comparator controlled, double blind clinical trials in over 8100 patients in the pioglitazone-treated groups and 7400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%). In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). Post- marketing, bone fractures have been reported in both male and female patients (see section 5).

5 Oedema was reported in 6–9% of patients treated with pioglitazone over one year in controlled clinical trials. The oedema rates for comparator groups (sulfonylurea, metformin) were 2–5%. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

6 In active comparator controlled trials mean weight increase with pioglitazone given as monotherapy was 2–3 kg over one year. This is similar to that seen in a sulfonylurea active comparator group. In combination trials pioglitazone added to metformin resulted in mean weight increase over one year of 1.5 kg and added to a sulfonylurea of 2.8 kg. In comparator groups addition of sulfonylurea to metformin resulted in a mean weight gain of 1.3 kg and addition of metformin to a sulfonylurea a mean weight loss of 1.0 kg.

7 In clinical trials with pioglitazone the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulfonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases fatal outcome has been reported, causal relationship has not been established.

**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:***

## SIGNS AND SYMPTOMS
In clinical studies, patients have taken pioglitazone at higher than the recommended highest dose of 45 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms. Hypoglycaemia may occur in combination with sulfonylureas or insulin.

## MANAGEMENT
Symptomatic and general supportive measures should be taken in case of overdose.

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

**MANUFACTURED BY:**
Sanofi India Limited
121, Verna Industrial Estate, Verna, Goa- 403722, India

**Updated: November 2022**

**Reference:**
CCDS version 11 dated October 2017 for Glimepiride plus Metformin Fixed Dose Combination and Pioglitazone CCDS V1 dated 29 July 2021