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

Abridged Prescribing Information

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

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.

COMPOSITION
Amaryl® MP 1mg/2mg : Each uncoated bilayered tablet contains Metformin Hydrochloride IP 500 mg (in sustained release form) + Glimepiride IP 1mg/2mg + Pioglitazone Hydrochloride IP equivalent to Pioglitazone 15 mg.

THERAPEUTIC 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 in adults should not exceed 3 tablets. Tablet should not be crushed or chewed and should be taken as a whole with water. **Pediatrics**: Safety and effectiveness has not been established. **Females of reproductive potential:** Discuss the potential of unintended pregnancy with premenopausal females. **Renal Impairment:** GFR should be assessed before initiation of treatment and at least annually thereafter. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses.

SAFETY RELATED INFORMATION
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 in severe impairment of liver function and in dialysis patients.
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 (dehydration, severe infection or shock), acute or chronic disease which may cause tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock), hepatic insufficiency, acute alcohol intoxication, alcoholism, lactation.
For Pioglitazone: In patients with established New York Heart Association (NYHA) Class III or IV heart failure, 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:*** Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. Metformin should be temporarily discontinued in case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake). Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy. Metformin should be discontinued prior to, or at the time of the imaging procedure, surgery under general, spinal or epidural anaesthesia and

not restarted until 48 hours after re-evaluation of renal function and found stable. ***For Pioglitazone:*** Can cause dose – related fluid retention. Fluid retention may lead to or exacerbate heart failure. Not recommended in patients with symptomatic heart failure. When used with insulin or insulin secretagogues lower dose of insulin or insulin secretagogue is needed to reduce risk of hypoglycemia. Should not be used in patients with active bladder cancer or with history of bladder cancer and those with uninvestigated haematuria. The risk of fracture should be considered especially in female patients.

Precautions: ***For Glimepiride***: In the initial weeks of treatment, the risk of hypoglycaemia may be increased and necessitates careful monitoring. Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia.

For Metformin**:** Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism. Long-term treatment with metformin has been associated with a decrease in vitamin B12 serum levels.

For Pioglitazone hydrochloride**:** There have been postmarketing reports of fatal and non fatal hepatic failure in patients taking pioglitazone. Pioglitazone should be used with caution in patients with oedema. Macular edema has been reported in post-marketing experience in diabetic patients. Patients with diabetes should have regular eye exams by an ophthalmologist. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Amaryl MP.

Pregnancy & Lactation:

Amaryl® MP must not be taken during pregnancy and lactation to prevent possible harm to the child. Change over to insulin is recommended.

Adverse Reactions:

Hypoglycaemia, eye disorders, gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, change in the blood picture may occur. Metallic taste is common. Hepatobiliary disorders, congestive heart failure, oedema, fractures may occur, Upper respiratory tract infection, headache, sinusitis, myalgia and pharyngitis are most common.

For full prescribing information please write to: Sanofi India Ltd., Sanofi House, CT Survey No 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai 400072

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Source: CCDS Version 11 dated October 2017 for Glimepiride plus Metformin Fixed Dose Combination and Actoplus leaflet dated December 2017