Amaryl® M S.R.
(Glimepiride + Metformin)

This package insert is continually updated; please read carefully before using a new pack! In case of any question, please contact your physician or pharmacist.

**Composition**
- Amaryl M S.R. 1mg Tablet: Each bilayered tablet contains, as active ingredients, 1 mg Glimepiride and 500mg Metformin hydrochloride (as sustained release).
- Amaryl M S.R. 2mg Tablet: Each bilayered tablet contains, as active ingredients, 2 mg Glimepiride and 500mg Metformin hydrochloride (as sustained release).

**Indications**
For Glimepiride and Metformin: As an adjunct to diet and exercise in type 2 diabetes mellitus patients:
- In case that the monotherapy with glimepiride or metformin does not result in adequate glycemic control.
- Replacement of combination therapy of glimepiride and metformin.

**Dosage and administration**
**Dosage:** In principle, the dosage of Amaryl M S.R. is governed by the desired blood glucose level. The dosage of Amaryl M S.R. must be the lowest which is sufficient to achieve the desired metabolic control.
During treatment with Amaryl M S.R., 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 beforehand.
As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, glimepiride requirements may fail as treatment proceeds. To avoid hypoglycaemia timely dose reduction or cessation of Amaryl M S.R. therapy must therefore be considered.
The highest recommended dose per day should be 8 mg of glimepiride and 2000 mg of metformin. Daily doses of glimepiride of more than 6 mg are more effective only in a minority of patients. In order to avoid hypoglycaemia the starting dose of Amaryl M S.R. should not exceed the daily doses of glimepiride or metformin already being taken. When switching from combination therapy of glimepiride plus metformin as separate tablets, Amaryl M S.R. should be administered on the basis of dosage currently being taken.

**Administration:** Amaryl M S.R. should be administered once per day during breakfast or the first main meal. Due to the sustained release formulation, Amaryl M S.R. must be swallowed whole and not crushed or chewed.

**Titration:** The daily dose should be titrated in increments of 1 tablet only.
corresponding to the lowest strength (in case various strengths are available).

**Duration of treatment:** Treatment with Amaryl M S.R. is normally a long-term therapy.

**Special Populations**

**Children:** Data are insufficient to recommend pediatric use of Amaryl N S.R.

**Contraindications**

**For Glimepiride**
- In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, or any of the excipients of Amaryl M S.R.
- 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.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (e.g., serum creatinine levels > 135 micromol/L in males and > 110 micromol/L in females).
- **Acute conditions with the potential to alter renal function such as**
  - Dehydration
  - Severe infection
  - Shock
  - Intravascular administration of iodinated contrast agents
- **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.

**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:** Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

**Diagnosis:** Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalized immediately.
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.
- undernutrition, irregular meal times 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.
- overdose 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.
- 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 adrenocortical counter regulation 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

Renal function: As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and preferably thereafter:
- at least annually in patients with normal renal function,
- at least two to four times a year in patients with serum creatinine levels at the limit of normal and in elderly subjects.

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: As the intravenous administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not re instituted until...
48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

**Surgery:** Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.

**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 CYP 2C9. 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; fenofibrate; fluoxetine; guanethidine; ifosfamide; MAO inhibitors; miconazole; fluconazole; para-aminosalicylic acid; pentoxifylline (high dose parenteral); phenylbutazone; azapropazone; oxypenbutazone; probenecid; quinolones; salicylates; sulfapyrazine; clarithromycin; sulfonamide antibiotics; tetracyclines; tricyclics; 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.

**For Metformin**

**Inadvisable combinations**

**Alcohol:** Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:
- fasting or malnutrition,
- hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.

**Iodinated contrast agents:** Intravenous administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.
acidosis. Metformin should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

**Associations requiring precautions for use:**
Glucorticoids (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.

**Pregnancy**
*For Glimepiride*
Glimepiride 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.

*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 glucose levels.

**Lactation**
*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-feeding.

*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.

**Driving a vehicle or performing other hazardous tasks**
*For Glimepiride*
Alertness and reactions may be impaired due to hypo- or hyperglycaemia, 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).

**Adverse effects**
Please tell your physician or pharmacist if you experience any adverse effect with the use of Amaryl M S.R.
For Glibenclamide 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 characteristics as the use of each compound separately.

For Glibenclamide

- Metabolism and nutrition disorders: As a result of the blood-glucose-lowering action of glibenclamide, 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, lachrymation, 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 epigastrum, 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 glibenclamide.

- Blood and lymphatic system disorders: Changes in the blood picture may occur: Rarely, thrombocytopenia and, in isolated cases, leucopenia, anaemia, leucopenia, granulocytopenia, agranulocytosis or pancytopenia may develop.

- General disorders: Occasionally, allergic or pseudoallergic reactions may occur, e.g., in the form of itching, urticaria or rash. 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.

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 (p<0.01).
- Lactic acidosis (0.03 cases/1000 patient-years) is very rare

Based on experience with Amaryl and on what is known of other sulfonylureas, the following adverse effects must be considered:

**Overdose**

*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.

**Storage:** Store below 30°C.

**Expiry Date:** Do not use later than the date of expiry printed on carton & blisters.

**Keep medicines out of the reach of children.**

**Presentations**

Amaryl M S.R. 1mg Tablets: Pack of 3 x 10 Tablets.

Amaryl M S.R. 2mg Tablets: Pack of 3 x 10 Tablets.

**Manufactured by**

sanofi-aventis Pakistan limited
Plot No. 23, Sector 22, Korangi Industrial Area, Karachi.

515538-01
شرکت:
سائفل ایومن آرتس آمریکا

توضیحات:
این اینفوگرافیک به ویژه بر روی پوست و لعاب کوريسپورانس‌های (لیپوپرومیک) تولید کرده است. آماده‌ترین و خوب‌ترین لیپومسکوری تولید کننده‌ی این داروی در میان داروهای جهان گزارش شده‌است.

اگر مصرف کننده‌ی مصرف این داروی را بروز رسانی نمی‌کند، می‌تواند تاکید داشته باشد که جراحی سلول‌های اورژانسی (لیپوماسکوری) ممکن است برای جلوگیری از تولید ظاهر کردن این داروی در موردین استفاده‌ای خاصی را ارائه دهد.

طلاییت: به ویژه در کنار داروهای مصرفی برای این دارو، مصرف کننده‌ی این داروی را به ویژه در مواردی که به دلیل شرایط بدی داشته باشد، مصرف کننده‌ی این داروی را به ویژه در مواردی که به دلیل عامل‌های پزشکی داروها مصرف کننده‌ی این داروی را به ویژه در مواردی که به دلیل عامل‌های پزشکی داروها یا جراحی سلول‌های اورژانسی (لیپوماسکوری) ممکن است برای جلوگیری از تولید ظاهر کردن این داروی در موردین استفاده‌ای خاصی را ارائه دهد.

غیره: این داروی را به ویژه در کنار داروهای مصرفی برای این دارو، مصرف کننده‌ی این داروی را به ویژه در مواردی که به دلیل عامل‌های پزشکی داروها مصرف

105mm
ملاحظات

محاسبہ کی مقدار کی ہے۔ ایک ایک بڑی کمیونکیشن کا ماحول دیکھنے کی لئی یہ ماحول کی ہے۔

جامعہ کے لیے:

- اشاریہ کی کمیونکیشن نے ماحول کی کمیونکیشن کا ماحول کی ہے۔
- اشاریہ کی کمیونکیشن کا ماحول کی ہے۔

ملاحظات:

- اشاریہ کی کمیونکیشن کا ماحول کی ہے۔
- اشاریہ کی کمیونکیشن کا ماحول کی ہے۔

(Diabetic Pre-Coma)

(دیاپاکیسی پیک کرا)

(دیاپاکیسی پیک کرا)

(دیاپاکیسی پیک کرا)
مختصرات:

G6PD: انکیپٹینس کا ایک افراد میں ایک خطرناک سیل کا ایک اندازہ ہے جسے G6PD بیماری کہا جاتا ہے۔

G6PD بیماری کی بہت سے افراد میں ہے، لیکن اس کا اثر عام طور پر بہت سخت نہیں ہوتا۔