

DATA SHEET

DAONIL

NAME OF MEDICINE

glibenclamide 5 mg tablet

PRESENTATION

Each tablet of Daonil is white, biplane, oblong, with a score-line on both sides. LDI is engraved each side of the score-line and inverted. The other side is plain.

USES

ACTIONS

Glibenclamide appears to lower the blood glucose acutely in healthy individuals and patients with type 2) diabetes by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells. It acts in concert with glucose (improved sensitivity of beta cells to physiological glucose stimulus) and leads to an insulin secretion in the rhythm of meals. Other mechanisms of the hypoglycaemic action associated with short term therapy appear to include reduction of basal hepatic glucose production and enhancement of peripheral insulin action at post-receptor (probably intracellular) sites.

With chronic administration of glibenclamide in patients with type 2 diabetes, the improvement in glucose tolerance persists despite a gradual decline in glucose- or meal-stimulated secretion of insulin towards pretreatment levels. Extrapancreatic effects appear to contribute substantially to the hypoglycaemic action of the drug during long term administration. The effects appear to include enhanced peripheral sensitivity to insulin and reduction of basal hepatic glucose production. There is evidence that glibenclamide enhances the peripheral action of insulin at post-receptor (probably intracellular) sites and increases insulin binding and/or the number of insulin receptors.

Glibenclamide also exerts a direct inhibitory effect on glucagon-producing alpha cells of the pancreas and increases the release of somatostatin. However, these two pancreatic extra-beta cell actions may play only a minor clinical role.

In addition to its blood glucose lowering effect, glibenclamide has a mild diuretic action and increases free water clearance.

PHARMACOKINETICS

ABSORPTION, METABOLISM AND EXCRETION

Glibenclamide is nearly completely absorbed ($84 \pm 9\%$) after oral administration and is extensively bound (99%) to serum proteins. The peak serum concentration is reached in 2-6 hours after taking a 5 mg tablet of Daonil and falls within 24 hours to less than 5% of the peak value. The area under the serum concentration time curve (AUC) increases in proportion to increasing doses. Food apparently does not affect the rate or extent of absorption of glibenclamide.

Multiple-dose studies with glibenclamide in diabetic patients demonstrate drug level concentration-time curves similar to single-dose studies, indicating no build-up of drug in tissue depots. In non-fasting diabetic patients, the hypoglycaemic action of a single morning dose of glibenclamide persists for 24 hours.

Serum concentrations of glibenclamide appear to decline in a biphasic manner. The elimination half-life of glibenclamide after intravenous dosage is approximately 2 hours, and 2 to 5 hours after oral administration. Some reports indicate a longer half-life of 8 to 10 hours in patients with diabetes.

Glibenclamide is completely metabolised in the liver. The drug is metabolised at the cyclohexyl ring principally to a 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites contribute some hypoglycaemic action; they are weakly active (0.25% and 2.5%, respectively, as glibenclamide) in rabbits.

Glibenclamide is excreted as metabolites in the bile and urine, approximately 50% by each route. In patients with renal insufficiency, depending on the degree of the renal excretion disorder, there is increased elimination of metabolites via the bile. This dual excretory pathway is qualitatively different from that of other sulphonylureas, which are excreted primarily in the urine.

INDICATIONS

Non insulin dependent (type 2 diabetes mellitus), whenever blood glucose levels cannot be controlled adequately by diet, physical exercise, and weight reduction alone.

When the efficacy of Daonil decreases (partial secondary failure) it can be given together with insulin.

Daonil can also be combined with other, non-betacytotropic oral antidiabetics.

DOSAGE AND ADMINISTRATION

In principle, the dosage of Daonil is governed by the desired blood glucose level. The dosage of glibenclamide must be the lowest possible dose which is effective.

Treatment with Daonil must be initiated and monitored by a physician. The patient must take Daonil at the times and in the doses prescribed by the physician.

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 in the event that a dose cannot be taken at the prescribed time must be discussed and agreed between physician and patient beforehand.

If it is discovered that too high a dose or an extra dose of Daonil has been taken, a physician must be notified immediately.

INITIAL DOSE AND DOSE TITRATION

Usual initial dose: ½ to 1 tablet Daonil once daily.

It is recommended that treatment be started with the smallest possible dose. This applies in particular to patients who are prone to hypoglycaemia (see Warnings and Precautions) or who weigh less than 50 kg.

If necessary, the daily dose can be raised. It is recommended that the dose be increased gradually, i.e. in increments of no more than ½ tablet Daonil and at intervals of one to two weeks, and that the increase be guided by regular blood glucose monitoring.

DOSE RANGE IN PATIENTS WITH WELL-CONTROLLED DIABETES; MAXIMUM DOSES

Usual single dose: ½ to 2 tablets Daonil. A single dose of 2 tablets Daonil must not be exceeded. Larger daily doses must be divided into at least two separate single doses.

Usual daily dose: 1 to 2 tablets Daonil. Exceeding a total daily dose of 3 tablets Daonil is not recommended, because higher daily doses of up to 4 tablets Daonil are more effective only in exceptional cases.

DISTRIBUTION OF DOSES

Timing and distribution of doses are to be decided by the physician, taking into consideration the patient's current life-style.

Normally a single daily dose of Daonil is sufficient.

It is recommended that daily doses of up to 2 tablets Daonil be taken before a substantial breakfast or before the first main meal, and any remaining portions of the total daily dose before the evening meal.

It is very important not to skip meals after the tablets have been taken.

DOSAGE IN YOUNG ADULTS WITH TYPE 2 DIABETES MELLITUS

Dosage is basically the same as for older adults.

SECONDARY DOSAGE ADJUSTMENT

As an improvement in control of diabetes is, in itself, associated with higher insulin sensitivity, glibenclamide requirements may fall as treatment proceeds. To avoid hypoglycaemia, timely dose reduction or cessation of Daonil therapy must therefore be considered.

Correction of dosage must also be considered, whenever

- the patient's weight changes
- the patient's lifestyle changes
- other factors arise, which cause an increased susceptibility to hypoglycaemia or hyperglycaemia (see Warnings and Precautions)

DURATION OF TREATMENT

Treatment with Daonil is normally a long-term therapy.

CHANGEOVER FROM OTHER ORAL ANTIDIABETICS TO DAONIL

There is no exact dosage relationship between Daonil and other oral antidiabetics. When substituting Daonil for other oral antidiabetics, it is recommended that the procedure be the same as for initial dosage, starting with daily doses of ½ to 1 tablet Daonil. This applies even in cases when the patient is being switched from the maximum dose of another oral antidiabetic.

Consideration must be given to the potency and duration of action of the previous antidiabetic agent. A break from medication may be required to avoid any summation of effects entailing a risk of hypoglycaemia.

Note: Glibenclamide is provided in different pharmaceutical formulations in other countries. The patient is asked to consult a physician before changing over to any other formulation.

ADMINISTRATION

Daonil tablets must be swallowed whole with sufficient amounts of liquid, e.g. with roughly half to one glass.

CONTRAINDICATIONS

Daonil must not be used for

- patients with type 1 (insulin-dependent) diabetes mellitus (for example diabetics with a history of ketoacidosis)
- treatment of diabetic ketoacidosis
- treatment of diabetic precoma or coma
- patients with serious renal dysfunction
- patients with serious hepatic dysfunction
- patients hypersensitive to glibenclamide
- patients hypersensitive to any of the excipients
- pregnant women
- breastfeeding woman
- patients treated with bosentan (see Interactions)

To achieve the goal of treatment with Daonil - optimal control of blood glucose - adherence to correct diet, regular and sufficient physical exercise and, if necessary, reduction of body weight are just as necessary as regular ingestion of Daonil.

WARNINGS AND PRECAUTIONS

HYPOGLYCAEMIC REACTIONS

Patients and responsible family members should be made aware of the clinical signs and symptoms of hyperglycaemia and hypoglycaemia and the prompt action required in the event of such occurrences

Symptoms of hyperglycaemia include increased urinary frequency, intense thirst, dryness of the mouth and dry skin.

Possible symptoms of hypoglycaemia include intense hunger, nausea, vomiting, sweating, tremor, pareses, sensory disturbances, restlessness, irritability, aggressiveness, depression, confusion, speech disorders, aphasia, visual disturbances, impaired concentration, impaired alertness and reactions, headaches, dizziness, disturbed sleep, helplessness, loss of self-control, delirium, transient neurological disorders such as cerebral convulsion, lassitude, sleepiness, somnolence, 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 of hypoglycaemia nearly always subside when hypoglycaemia is corrected.

During treatment with Daonil, 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.

Monitoring of glucose levels in blood and urine also serves to detect failure of therapy - either primary or secondary.

In accordance with current guidelines (e.g. European NIDDM consensus), the monitoring of certain other parameters is also recommended.

When starting treatment, the patient must be informed about the effects and risks of Daonil and about its interaction with dietary measures and physical exercise; the importance of adequate co-operation must also be stressed.

As is necessary during treatment with any blood-glucose-lowering drug, the patient and the physician must be aware of the risk of hypoglycaemia.

Factors favouring hypoglycaemia include:

- unwillingness of (more commonly in older patients) incapacity of the patient to co-operate
- undernutrition, irregular mealtimes, or missed meals
- alterations of diet or unaccustomed physical exertion
- consumption of alcohol, especially in combination with skipped meals
- impaired renal function
- serious liver dysfunction
- overdosage with Daonil.
- 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 adrenocortical insufficiency)
- concurrent administration of certain other medicines (see Interactions)
- treatment with Daonil in the absence of any indication

The patient must inform the physician about such factors and about hypoglycaemic episodes since they may indicate the need for particularly careful monitoring.

If necessary, the dosage of Daonil or the entire therapy must be modified. This also applies whenever illness occurs during therapy or the patient's lifestyle changes.

Those symptoms of hypoglycaemia which reflect the body's adrenergic counter-regulation (see Adverse Effects) may be milder or absent where hypoglycaemia develops gradually, where there is autonomic neuropathy or where the patient is receiving concurrent treatment with beta-blockers, clonidine, reserpine, guanethidine, or other sympatholytic medicines.

Hypoglycaemia can, almost always, be promptly controlled by immediate intake of carbohydrates (glucose or sugar, e.g. in the form of sugar lumps, sugar-sweetened fruit juice or tea). For this purpose, patients must carry in minimum of 20 grams of glucose with them at all times. They may require the assistance of other persons to avoid complications.

Artificial sweeteners are ineffective in controlling hypoglycaemia.

Despite initially successful countermeasures, hypoglycaemia may recur. Patients must, therefore, remain under close observation.

Severe hypoglycaemia, or a protracted episode, which can only be temporarily controlled by usual amounts of sugar, further requires immediate treatment and follow-up by a physician and, in some circumstances, in-patient hospital care.

If treated by different physicians (e.g. hospital stay, after an accident, illness while on holiday), the patients must inform them of their diabetic condition and previous treatment.

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.

Persons allergic to other sulphonamide derivatives may develop an allergic reaction to glibenclamide as well.

Daonil must not be used beyond the expiry date.

Medicines must be kept out of the reach of children.

HAEMOLYTIC ANAEMIA

Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulphonylurea agents can lead to haemolytic anaemia. Since glibenclamide belongs to the class of sulphonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

PREGNANCY (CATEGORY C)

Daonil must not be taken during pregnancy. The patient must change over to insulin during pregnancy. The sulphonylureas may enter the foetal circulation and cause neonatal hypoglycaemia. In animal studies, embryotoxicity and/or birth defects have been demonstrated.

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

Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing

malformations. These effects may be reversible. Relevant texts should be consulted for further details.

LACTATION

It is not known whether glibenclamide is excreted in milk or whether it has a harmful effect on the newborn. To prevent possible ingestion with the breast milk, Daonil must not be taken by breastfeeding women. If necessary the patient must change over to insulin, or must stop breastfeeding

EFFECTS ON ABILITY TO DRIVE AND TO OPERATE MACHINERY

Alertness and reactions may be impaired by hypo- or hyperglycaemic episodes, especially when beginning or after altering treatment, or when Daonil is not taken regularly. This may, for example, affect the ability to drive or operate machinery.

INTERACTIONS

An increased incidence of elevated liver enzymes was observed in patients receiving glibenclamide concomitantly with bosentan. Both bosentan and glibenclamide inhibit the bile salt export pump, leading to intracellular accumulation of cytotoxic bile salts. Therefore, this combination should not be used (see Contraindications).

Glibenclamide is mainly metabolized by CYP2C9 and to a lesser extent by CYP3A4. This should be taken into account when glibenclamide is coadministered with inducers or inhibitors of CYP2C9.

Patients who take or discontinue taking, certain other medicines while undergoing treatment with Daonil may experience changes in blood glucose control.

Potential of the blood-glucose-lowering, effect and, thus, in some instances hypoglycaemia may occur when taking other medicines, including:

insulin, other oral antidiabetics, ACE inhibitors, alcohol, aminosalicic acid, anabolic steroids and male sex hormones, azapropazone, beta-receptor blockers, bezafibrate, biguanides, chloramphenicol, clarithromycin, clifibrate, clonidine, co-trimoxazole, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, gemfibrozil, guanethidine, heparin, ifosfamide, MAO inhibitors, miconazole, oxypentifylline (parenteral, in high doses), oxyphenbutazone, para-aminosalicylic acid, phenylbutazone, phenylramidol, phosphamides, probenecid, quinolone antibiotics, ranitidine, reserpine, salicylates, sulphinpyrazone, certain long-acting sulphonamides, tetracycline compounds, tritoqualine and trofosfamide.

Highly protein-bound drugs which may also potentiate the hypoglycaemic action of Daonil due to glibenclamide displacement from plasma proteins, include oral anticoagulants, hydantoins, salicylates and other non-steroidal anti-inflammatory agents.

Weakening of the blood-glucose-lowering effect and, thus, raised blood glucose levels may occur when taking other medicines, including:

acetazolamide, adrenaline (epinephrine) and other sympathomimetic agents, alcohol, barbiturates, calcium channel blockers, cimetidine, clonidine, corticosteroids, diazoxide, diuretics, glucagon, isoniazid, large doses of laxatives, nicotinic acid (in high doses), oestrogens, progestogens, phenothiazine derivatives, phenytoin, ranitidine, rifampicin, ritodrine and thyroid hormones.

H₂-receptor antagonists, clonidine, and reserpine may lead to either potentiation or weakening of the blood glucose-lowering effect.

Under the influence of sympatholytic medicines such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent. The symptoms of hypoglycaemia may also be milder or absent where hypoglycaemia develops gradually or where there is autonomic neuropathy.

In very rare cases, an intolerance to alcohol may occur. Both acute and chronic alcohol intake, or excessive alcohol ingestion by people who drink occasionally, may attenuate the hypoglycaemic effect of glibenclamide or dangerously potentiate it by delaying its metabolic inactivation. Disulfiram-like reactions have occurred very rarely following the concomitant use of alcohol and glibenclamide.

Glibenclamide may increase cyclosporin plasma concentration and potentially lead to its increased toxicity. Monitoring and dosage adjustment of cyclosporin are therefore recommended when both drugs are co-administered.

Glibenclamide may either potentiate or weaken the effect of coumarin derivatives.

Colesevelam binds to glibenclamide and reduces glibenclamide absorption from the gastrointestinal tract. No interaction was observed when glibenclamide was taken at least 4 hours before colesevelam. Therefore glibenclamide should be administered at least 4 hours prior to colesevelam.

ADVERSE EFFECTS

HYPOGLYCAEMIA

Hypoglycaemia, sometimes prolonged and even life-threatening, may occur as a result of the blood-glucose-lowering action of Daonil. This happens when there is imbalance between Daonil dosage, carbohydrate intake (diet), physical exercise and other factors influencing metabolism (see Warning and Precautions).

EYES

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.

DIGESTIVE TRACT

Adverse gastrointestinal effects such as nausea, vomiting, epigastric fullness or sensation of pressure, abdominal pain, anorexia, heartburn, dyspepsia and diarrhoea are the most common adverse reactions to glibenclamide, occurring in about 1-2% of patients. Glibenclamide-induced adverse gastrointestinal effects appear to be dose related, may subside following a reduction in dosage and usually do not necessitate discontinuing Daonil. Pancreatitis has been reported rarely.

HEPATIC REACTIONS

Increased liver enzymes (AST, ALT), abnormal liver function, cholestasis, cholestatic hepatitis, granulomatous hepatitis and bilirubinaemia has been reported with sulphonylureas.

In isolated cases, there may be hepatitis, elevation of liver enzyme levels and/or cholestasis and jaundice, which may lead to life-threatening liver failure but can regress after withdrawal of glibenclamide.

HAEMATOLOGIC REACTIONS

Anaemia, leukopaenia, thrombocytopaenia, thrombocytopaenic purpura, agranulocytosis, pancytopaenia, eosinophilia, haemolytic anaemia, aplastic anaemia, bone marrow aplasia, eosinophilia and coagulation disorders have been reported with sulphonylureas. Potentially life-threatening changes in the blood picture may occur. They may include, rarely, mild to severe thrombopaenia (e.g. presenting as purpura) and, in isolated cases, haemolytic anaemia, erythrocytopaenia, leucopaenia, granulocytopaenia, agranulocytosis, and (for example, due to myelosuppression) pancytopaenia. In principle, these reactions are reversible once glibenclamide has been withdrawn.

DERMATOLOGIC REACTIONS

Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching or rashes. Allergic skin reactions e.g. pruritus, erythema, urticaria, erythematous and maculo-papular and bullous skin eruptions or psoriasiform drug eruptions occur in 1.5% of treated patients. These may be transient and may disappear despite continued use of glibenclamide; if skin reactions persist, the drug should be discontinued. In isolated cases, mild reactions in the form of urticaria may develop into serious and event life-threatening reactions with dyspnoea and fall in blood pressure, sometimes progressing to shock. In the event of urticaria, a physician must therefore be notified immediately.

A hypersensitivity reaction may be directed against glibenclamide itself, but may alternatively be triggered by excipients. Allergy to sulphonamide derivatives may also be responsible for an allergic reaction to glibenclamide.

In isolated cases, allergic vasculitis may arise and, in some circumstances, may be life-threatening. In isolated cases, hypersensitivity of the skin to light may occur, and sodium concentrations in the serum may decrease. Porphyria cutanea tarda and pellagra-like changes have been reported with sulphonylureas.

IN THE EVENT OF AN ADVERSE EFFECT, THE PATIENT MUST CONSULT A PHYSICIAN.

OVERDOSAGE

SIGNS AND SYMPTOMS

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

MANAGEMENT

As soon as an overdose of Daonil 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 and its clinical signs 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 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 Daonil 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.

PHARMACEUTICAL PRECAUTIONS

Store below 25°C.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Each pack of Daonil contains 100 x 5 mg tablets

FURTHER INFORMATION

Excipients: lactose, maize starch, talc, colloidal silica, magnesium stearate

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