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

This package insert is continually updated: Please read carefully before using a new pack

Glibenclamide Tablets I.P
DAONIL® / SEMI-DAONIL®

Description
Active Ingredient
Glibenclamide

Therapeutic or Pharmacological Class
Antidiabetic. Sulfonylurea.

Pharmaceutical Form
Uncoated tablet.

Composition
DAONIL®
Each uncoated tablet contains Glibenclamide I.P. 5.0 mg.

SEMI-DAONIL®
Each uncoated tablet contains Glibenclamide I.P. 2.5 mg.

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®/ Semi-Daonil® decreases (partial secondary failure) it can be given together with insulin. Daonil®/Semi-Daonil® can also be combined with other, non-betacytotropic oral antidiabetics.

DOSAGE AND METHOD OF ADMINISTRATION
Dosage
In principle, the dosage of Daonil®/ Semi-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®/ Semi-Daonil® must be initiated and monitored by a physician. The patient must take Daonil®/ Semi-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 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®/ Semi-Daonil® has been taken, a physician must be notified immediately.

Initial dose and dose titration
Usual initial dose: ½ to 1 tablet Daonil® 5 mg or 1 to 2 tablets Semi-Daonil® 2.5 mg, respectively, 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 section 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® 5 mg or 1 tablet Semi-Daonil® 2.5 mg, respectively, 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® 5 mg or 1 to 4 tablets Semi-Daonil® 2.5 mg, respectively. A single dose of 2 tablets Daonil® 5 mg or 4 tablets Semi-Daonil® 2.5 mg, respectively, 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® 5 mg or 2 to 4 tablets Semi-Daonil® 2.5 mg, respectively. Exceeding a total daily dose of 3 tablets Daonil® 5 mg or 6 tablets Semi-Daonil® 2.5 mg, respectively, is not recommended, because higher daily doses of up to 4 tablets Daonil® 5 mg or 8 tablets Semi-Daonil® 2.5 mg, respectively, 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®/ Semi-Daonil® is sufficient. It is recommended that daily doses of up to 2 tablets Daonil® 5 mg or 4 tablets Semi-Daonil®2.5 mg, respectively, 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 (MODY)
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 hypoglycemia, timely dose reduction or cessation of Daonil®/ Semi-Daonil® therapy must therefore be considered.

Correction of dosage must also be considered, whenever:
- the patient's weight changes,
- the patient's life-style changes,
-other factors arise, which cause an increased susceptibility to hypoglycaemia or hyperglycaemia (see section WARNINGS and PRECAUTIONS).

Duration of treatment
Treatment with Daonil®/ Semi-Daonil® is normally a long-term therapy.
Changeover from other oral antidiabetics to Daonil®/ Semi-Daonil®

There is no exact dosage relationship between Daonil®/Semi-Daonil® and other oral antidiabetics. When substituting Daonil®/Semi-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® 5mg or 1 to 2 tablets Semi-Daonil® 2.5 mg, respectively. This applies even in cases where 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 supplied by sanofi-aventis in different pharmaceutical formulations in other countries. The patient is asked to consult a physician before changing over to any other formulation.

Administration
Daonil®/ Semi-Daonil® tablets must be swallowed without chewing with sufficient amounts of liquid, e.g. with roughly half to one glass.

CONTRAINDICATIONS
Daonil®/Semi-Daonil® must not be used:

- in patients with insulin-dependent (type 1) diabetes mellitus (for example diabetics with a history of ketoacidosis).
- in treatment of diabetic ketoacidosis.
- in treatment of diabetic precoma or coma.
- in patients with serious renal dysfunction.
- in patients with serious hepatic dysfunction.
- in patients hypersensitive to glibenclamide.
- in patients hypersensitive to any of the excipients of Daonil®/ Semi-Daonil® tablets
- in pregnant women
- in breast feeding women
- in patients treated with bosentan (see section INTERACTIONS).

WARNINGS

Epidemiological studies suggest that the administration of glibenclamide is associated with an increased risk of cardiovascular mortality, when compared to treatment with metformin or gliclazide. This risk was especially observed in patients with diagnosed coronary diseases.

Clinical signs of hyperglycaemia are: increased urinary frequency, intense thirst, dryness of the mouth, and dry skin. 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 sulfonamide derivatives may develop an allergic reaction to glibenclamide as well.

PRECAUTIONS
To achieve the goal of treatment with Daonil®/ Semi-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®/Semi-Daonil®. During treatment with Daonil®/ Semi-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®/ Semi-Daonil® and about its interaction with dietary measures and physical exercise; the importance of adequate cooperation 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 or (more commonly in older patients) incapacity of the patient to cooperate.
• undernourishment, irregular mealtimes, or missed meals.
• imbalance between physical exertion and carbohydrate intake.
• alterations of diet.
• impaired renal function.
• serious liver dysfunction.
• overdosage with Daonil®/Semi-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 section INTERACTIONS).
• treatment with Daonil®/ Semi-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 such risk factors for hypoglycaemia are present, it may be necessary to adjust the dosage of Daonil®/ Semi-Daonil® or the entire therapy. This also applies whenever illness occurs during therapy or the patient's life-style changes.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly. The initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.[1]

Those symptoms of hypoglycaemia which reflect the body's adrenergic counter regulation (see section ADVERSE REACTIONS) 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 drugs.

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 a 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.

Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia. Since glibenclamide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a nonsulfonylurea alternative should be considered.

INTERACTIONS

Food

No information currently deemed necessary.

Drug interactions

Not recommended associations

Bosentan: An increased incidence of elevated liver enzymes was observed in patients receiving glibenclamide concomitantly with bosentan.

Both glibenclamide and bosentan inhibit the bile salt export pump, leading to intracellular accumulation of cytotoxic bile salts. Therefore this combination should not be used (see section WARNINGS).

Precautions for Use

No information currently deemed necessary.

Take into account

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

Glibenclamide is mainly metabolized by CYP 2C9 and to a lesser extent by CYP 3A4. This should be taken into account when glibenclamide is coadministered with inducers or inhibitors of CYP 2C9[2]

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

Insulin and other oral antidiabetics, ACE inhibitors, anabolic steroids and male sex hormones, chloramphenicol, coumarin derivatives, cyclophosphamide, disopyramide, fenfluramine, fenyramidol, fibrates, fluoxetine, ifosfamide, MAO inhibitors, miconazole, para-aminosalicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulfonamides, sympatholytic agents such as beta-blockers and guanethidine, clarithromycin, tetracyclines, tritoqualine, trofosfamide.

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

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, thyroid hormones, rifampicin.

H_2-receptor antagonists, 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 glibenclamide in an unpredictable fashion.

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

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

Colesevelam binds to glibenclamide and reduces glibenclamide absorption from the gastro-intestinal 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[3].

ABSENCE OF PHARMACOKINETIC DRUG INTERACTION
No information currently deemed necessary

PREGNANCY
Daonil®/ Semi-Daonil® must not be taken during pregnancy. 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, Daonil®/ Semi-Daonil® must not be taken by breast-feeding women. If necessary the patient must change over to insulin, or must stop breast-feeding.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
Alertness and reactions may be impaired by hypo- or hyperglycaemic episodes, especially when beginning or after altering treatment, or when Daonil®/ Semi-Daonil® is not taken regularly. This may, for example, affect the ability to drive or operate machinery.

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).

Metabolism and nutrition disorders
Hypoglycaemia(very common frequency), sometimes prolonged and even life-threatening, may occur as a result of the blood-glucose-lowering action of Daonil®/ Semi-Daonil®. This happens when there is imbalance between Daonil®/ Semi-Daonil® dosage, carbohydrate intake (diet), physical exercise and other factors influencing metabolism.

Possible symptoms of hypoglycaemia include headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, 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 (very common frequency) may resemble that of a stroke.

The symptoms of hypoglycaemia nearly always subside when hypoglycaemia is corrected.

In isolated cases, **sodium concentration in the serum may decrease (**not known frequency)**..**

Eye disorders
Especially at the start of treatment, there may be temporary visual impairment **(**not known frequency**)** 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
Gastrointestinal symptoms such as nausea **(**common frequency), vomiting **(**not known frequency), sensations of pressure or fullness in the epigastrium **(**uncommon frequency), abdominal pain **(**common frequency) and diarrhea **(**common frequency) may occur. However, despite continued treatment, these often subside and usually do not necessitate discontinuing Daonil®/ Semi-Daonil®.

Hepatobiliary disorders
There may be hepatitis**(**not known frequency), elevation of liver enzyme levels **(**not known frequency)and/or cholestasis **(**not known frequency) and jaundice **(**not known frequency) which may progress to life-threatening liver failure **(**not known frequency) but can regress after withdrawal of Daonil®/ Semi-Daonil®.

Blood and lymphatic system disorders
Potentially life-threatening changes in the blood picture may occur. They may include mild to severe thrombopenia (e.g. presenting as purpura) (not known frequency) and haemolytic anaemia (not known frequency), erythrocytopenia (not known frequency), leucopenia (not known frequency), granulocytopenia (not known frequency), agranulocytosis (not known frequency), and (e.g. due to myelosuppression) pancytopenia (not known frequency). In principle, these reactions are reversible once Daonil®/Semi-Daonil® has been withdrawn.

Immune system disorders
Hypersensitivity reactions, allergic or pseudoallergic reactions **(**not known frequency) may occur;they may be directed against glibenclamide itself, but may alternatively be triggered by excipients. Allergy to sulfonamide derivatives may also be responsible for an allergic reaction to glibenclamide. **Mild reactions in the form of urticaria** (not known frequency) **may develop into serious and even life-threatening reactions** with **dyspnoea** and **fall in blood pressure**, sometimes progressing to **shock (**not known frequency). In the event of **urticaria, a physician must therefore be notified immediately.**

Skin and subcutaneous disorders
Itching (not known frequency**), rashes (**common frequency**), bullous reactions (**not known frequency**), erythema multiforme (6 (**not known frequency))**,, dermatitis exfoliative (**not known frequency**)** have been observed**.**

Hypersensitivity of the skin to light (not known frequency) may occur.
Allergic vasculitis **(**not known frequency**)** may arise and, in some circumstances, may be life-threatening.
Investigations
Glibenclamide, like all sulfonylureas, can cause **weight gain** (commonfrequency).

OVERDOSE

Signs and Symptoms:
Acute overdose 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®/ Semi-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 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®/ Semi-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.

PHARMACODYNAMICS

Mode of action
Both in healthy people and in patients with non-insulin dependent (type 2) diabetes mellitus, glibenclamide lowers blood glucose concentration by stimulating insulin release from the beta-cells of the pancreas. This effect operates in interaction with glucose (improvement in the responsiveness of beta-cells to the physiological glucose stimulus). Glibenclamide is also reported as having extrapancreatic effects: it reduces hepatic glucose production and enhances insulin binding and insulin sensitivity in peripheral tissues.

Pharmacodynamic characteristics

After a single morning dose the blood-glucose-lowering effect remains detectable for approx. 24 hours. During long-term therapy the hypoglycaemic effect of glibenclamide persists, while insulin levels return to the normal range. Glibenclamide has a mild diuretic action and increases free water clearance.

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