IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0540/040/001
Case No: 2070442

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

sanofi-aventis Ireland Limited

Citywest Business Campus, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Semi-Daonil 2.5mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **05/02/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Semi-Daonil 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Glibenclamide 2.5 mg

Excipients: contains Lactose Monohydrate 39.5mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, flat, round tablets, 6mm in diameter, ‘LB’ above and ‘G’ below a breakline on one side and plain on the other side.

The score line allows the tablets to be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Daonil is a sulphonylurea hypoglycaemic agent indicated for the oral treatment of patients with non-insulin dependent diabetes who respond inadequately to dietary measures alone.

4.2 Posology and method of administration

General Instructions

The dosage of glibenclamide must be the lowest possible dose which is effective.

The usual total daily dosage is 2.5 to 15 mg daily with a usual initial dose of 5 mg daily. Weekly adjustments can be made to increase the dosage to the optimal level. Doses of 10 mg or less may be taken as a single dose immediately before after breakfast, but should the daily dose exceed 10 mg, the remainder should be taken immediately before after the evening meal.

The elderly usually require lower dosage.

Dose Omission

A physician should be consulted in the event that a dose has not been taken at the prescribed time, a meal has been skipped, or an extra dose has been taken. It is very important not to skip meals after the tablets have been taken.

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 patients weight changes
- the patients life-style changes
- other factors arise, which cause an increased susceptibility to hypoglycaemia or hyperglycaemia.

Change over from other oral antidiabetics to Daonil

Change over from other oral antidiabetic agents to Daonil should be done under the supervision of a specialist, and due to the potential summation of effects of both medications, entails a risk of hypoglycaemia. A break from mediation may therefore be required when changing over medications. This should be deicded by the attending physician.

4.3 Contraindications

Daonil should not be used in patients who have or have ever had diabetic ketoacidosis or diabetic coma/precoma or in patients who have insulin-dependent diabetes mellitus, serious impairment of renal, hepatic or adrenocortical function, in patients who are hypersensitive to glibenclamide or any of the excipients, or in circumstances of unusual stress, e.g. surgical operations or during pregnancy, when dietary measures and insulin are essential.

Daonil should not be used in the following groups:

Patients with sulphonylurea or sulphonamide intolerance.
'Brittle' or juvenile diabetes.
Pregnancy
Breast feeding women
Children
In patients treated with bosentan

4.4 Special warnings and precautions for use

Patients with rate hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

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

During treatment with Daonil, glucose levels in blood and urine must be measured regularly.

Adjustment of the dosage of hypoglycaemic agents may be required in patients suffering from intercurrent infections, trauma, shock or anaesthesia.

For major surgery, insulin therapy should be substituted for oral hypoglycaemics.

Hepatic or renal dysfunction may require reduction in dosage.

Patients for whom sulphonylurea therapy is intended should be carefully selected, and limited to those who cannot be controlled on dietary measures alone, do not require insulin, and do not suffer from those disorders, the course of which might be affected by this therapy.

Elderly, debilitated patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycaemic action of glucose lowering drugs.

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.
As is necessary during treatment with any blood-glucose-lowering drug, the patient and the doctor must be aware of the risk of hypoglycaemia. Factors favouring hypoglycaemia include:

- Unwillingness or incapacity of the patient to co-operate.
- Undernourishment, irregular mealtimes or missed meal.
- Imbalance between physical exertion and carbohydrate intake.
- Alterations of diet.
- Impaired renal function.
- Serious liver dysfunction.
- Overdosage with Daonil.
- Uncompensated disorders of endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycaemic (as for example in certain disorders of thyroid function and in anterior pituitary of adrenocortical insufficiency).
- Concurrent administration of certain other medicines.

Those symptoms of hypoglycaemic, which reflect the body's adrenergic counter-regulation 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.

Despite initially successful counter-measures, 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 doctor and, in some circumstances, in-patient hospital care.

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

4.5 Interaction with other medicinal products and other forms of interaction

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 steriods and male sex hormones, chloramphenicol, coumarin derivatives, cyclophosphamide, disopryamide, fenfluramine, fenyramidol, fibrates, fluoxetine, ifosfamide, MAO inhibitors, miconazole, para-aminosalicyclic acid, pentoxifylline, phenylbutazone, azapropazone, oxyphenbutazone, probenecid, quinolones, salicylates, sulfinpyrazone, sulfonamides, sympatholytic agents such as beta-blockers and guanethidine, clarithromycin, tetracyclines, tritoqualine, trosfosfamide.

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 and other sympathamimetic agents, glucogon, laxatives, nicotinic acid, oestrogens and progestogens, phenothiazines, phenytoin, thyroid hormones, rifampicin.

H_2-receptor antagonists, clonadine and resperine 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 resperine, the signs of adrenergic counter-regulation to hypoglycaemic may be reduced or absent.

Glibenclamide may increase cyclosporine plasma concentration and potentially lead to its increased toxicity.

Both acute and chronic alcohol intake may potentiate or weaken the blood glucose lowering action of glibenclamide in an unpredicted fashion.

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

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.

4.6 Pregnancy and lactation

Danoil must not be taken during pregnancy or by breastfeeding women. The patient must change over to insulin during pregnancy. Animal studies showed some teratogenic effects. Patients planning a pregnancy must inform their physician. It is recommended that such patients change over to insulin.

4.7 Effects on ability to drive and use machines

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 affect the ability to drive or operate machinery.

4.8 Undesirable effects

Hypoglycaemia

Hypoglycaemia, sometimes prolonged and even life-threatening, may occur as a result of the blood glucose lowering action of Daonil. Possible symptoms of hypoclycaemia 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.
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.

Eyes

Temporary visual impairment.

Digestive tract

Gastrointestinal symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhoea may occur. In isolated cases, there may be elevation of liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice and hepatitis which can regress after withdrawal of Daonil, although they may lead to life-threatening liver failure. Treatment with sulphonylureas has been associated with occasional disturbances of liver function and cholestatic jaundice.

Blood

Potentially life-threatening changes in the blood picture may occur. They may include – rarely – mild to severe thrombopenia (e.g. presenting as purpura), - isolated cases – haemolytic anaemia, erythrocytopenia, leucopenia, granulocytopenia, agranulocytosis and (e.g. due to myelosuppression) pancytopenia.

Other adverse effects

Occasionally, allergic or pseudoallergic reactions may occur, e.g. in the form of itching rashes. In isolated cases, mild reactions in the form of urticaria may develop into serious and even life-threatening reactions.
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 concentration in the serum may decrease.

4.9 Overdose

Hypoglycaemia may be treated in the conscious patients by the administration of glucose, or three to four lumps of table sugar with water. This may be repeated as necessary.

If the patient is comatose, glucose should be administered as an intravenous infusion and the patient monitored. Bolus glucose injections are not recommended because of the possibility of rebound hypoglycaemia, which may be delayed. Alternatively, glucagon may be administered in a dose of 1 mg subcutaneously or intramuscularly to restore consciousness.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pharmacodynamic effect of glibenclamide is to lower blood glucose levels.
Mechanisms proposed for this effect include:

- stimulation of insulin release from pancreatic beta-cells.
- Increasing insulin binding receptor density in peripheral tissues.

There is increasing evidence that extra pancreatic effects involving potentiation of insulin action may be important.

Plasma glucose levels affect the insulin-releasing response in glibenclamide, (a high glucose level increases the response). The minimum active concentration for effect is considered to be 30-50 nanograms/ml glibenclamide.

5.2 Pharmacokinetic properties

A sulphonylurea hypoglycaemic agent rapidly absorbed and inducing its effect within 3 hours with a duration of up to 15 hours although the T ½ of drug is 5 to 10 hours. The drug is metabolised extensively in the liver and excreted via bile and urine. It is strongly protein-bound.

5.3 Preclinical safety data

None of clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Pregelatinised maize starch
Talc
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/Aluminum blister packs of 100 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Ltd.
Citywest Business Campus
Dublin 24.

8 MARKETING AUTHORISATION NUMBER

PA 540/40/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 1978
Date of last renewal: 11th September 2008

10 DATE OF REVISION OF THE TEXT

February 2010