Saint-Denis, May 11, 2017

(Official logo of the French National Agency for Medicines and Health Products Safety)

[date stamped]

REPUBLIC OF FRANCE

Division Division of medicines used in Cardiology, Rheumatology, Stomatology, Endocrinology, Gynecology, Urology, Pulmonology, ENT and Allergology

Unit Endocrinology, Gynecology, Urology, Pulmonology, ENT and Allergology

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Outgoing mail no.: 2017050900072

SANOFI AVENTIS France
82 AVENUE RASPAIL
94250 GENTILLY
FRANCE

[stamp]
RECEIVED on:
May 12, 2017

ANSM reference to be indicated in all correspondence:
File no. 2016081900044

Dear Sir or Madam,

In your letter dated July 29, 2016 received on July 29, 2016, in accordance with the provisions of Commission Regulation (EC) No. 1234/2008 of November 24, 2008 and the guidelines relative to its application, you submitted two applications for a variation of type:

- ❑ IA_{IN}
- ❑ IA
- ❑ IB
- ☒ II
- ❑ grouped variations

for the marketing authorization for the proprietary medicinal product:

Daonil® 5 mg scored tablets

concerning:

C.I.4: Change(s) in the Summary of Product Characteristics, Labeling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

I am pleased to inform you that your application has been approved. Please find enclosed the decision amending the Marketing Authorization for your proprietary medicinal product.

Furthermore, this decision takes into account the accepted variations listed below having modified the Marketing Authorization annexes.

An appeal against this decision can be lodged before the competent administrative court within 60 days from the date of receipt. Please indicate the ANSM reference in all correspondence.

(French formal ending to correspondence)

[stamp]
Division of medicines used in Cardiology, Rheumatology, Stomatology, Endocrinology, Gynecology, Urology, Pulmonology, ENT and Allergology

(Original French document signed)

Céline DRUET
Deputy Director

Q11ADO0008 v 03

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under Tracking No. SA-PH-RTS12181 on September 18, 2017

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REPUBLIC OF FRANCE

References:

VNL	CIS
6487	6 482 350 9

DECISION

amending the Marketing Authorization for the proprietary medicinal product:

Daonil® 5 mg scored tablets

THE DIRECTOR GENERAL OF THE FRENCH NATIONAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS SAFETY

Considering Commission Regulation (EC) No. 1234/2008 of November 24, 2008 concerning the review of variations to the terms of Marketing Authorizations for medicinal products for human use and veterinary medicinal products, and application guidelines thereof;

Considering the French Public Health Code, Part V, and particularly Articles L.5121-8, L.5121-20, R.5121-21 *et seq.*;

Considering the Marketing Authorization granted on: December 18, 1997, as amended;

Considering the application for a change to the Marketing Authorization submitted by:

sanofi-aventis France

on July 29, 2016;

and concerning:

the following section in the Summary of Product Characteristics:

- ❑ 1. Name of the medicinal product
- ❑ 2. Qualitative and quantitative composition
- ❑ 3. Pharmaceutical form
- ❑ 4.1. Therapeutic indications
- ❑ 4.2. Posology and method of administration
- ❑ 4.3. Contraindications
- ❑ 4.4. Special warnings and precautions for use
- ❑ 4.5. Interaction with other medicinal products and other forms of interaction
- ❑ 4.6. Fertility, pregnancy and lactation
- ❑ 4.7. Effects on ability to drive and use machines
- ☒ 4.8. Undesirable effects
- ❑ 4.9. Overdose
- ❑ 5.1. Pharmacodynamic properties
- ❑ 5.2. Pharmacokinetic properties
- ❑ 5.3. Preclinical safety data

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- ❑ 6.1. List of excipients
- ❑ 6.2. Incompatibilities
- ❑ 6.3. Shelf life
- ❑ 6.4. Special precautions for storage
- ❑ 6.5. Nature and contents of container
- ❑ 6.6. Special precautions for disposal and other handling
- ❑ 7. Marketing authorization holder
- ❑ 8. Marketing authorization number(s)
- ❑ General classification for prescription and supply

the following section(s) in Annex II:

- ❑ A. Manufacturer(s) of the biological active substance(s) and manufacturer(s) responsible for batch release
- ❑ B. Conditions or restrictions regarding supply and use
- ❑ C. Other conditions and requirements of the marketing authorization
- ❑ D. Conditions or restrictions with regard to the safe and effective use of the medicinal product
- ❑ E. Specific obligation to complete post-authorization measures for the marketing authorization "under exceptional circumstances"
- ❑ F. Qualitative and quantitative composition in excipients

as well as the corresponding sections in the package leaflet and labeling.

Considering the notification of the intermediate measure dated October 25, 2016;

Considering the rationale presented by the applicant dated December 6, 2016, in response to the above-mentioned notification;

HAS DECIDED

Article 1

The Marketing Authorization for the proprietary medicinal product **Daonil® 5 mg scored tablets** held by **sanofi-aventis France** is amended.

Article 2

The information appended to this Decision supersedes the corresponding information in the Annexes to the current Marketing Authorization.

Article 3

The concerned party has been notified of this Decision.

Date: **May 11, 2017**
[date stamped]

[stamp]
Division for medicines used in Cardiology, Rheumatology, Stomatology, Endocrinology, Gynecology, Urology, Pulmonology, ENT and Allergology

(Original French document signed)

Céline DRUET
Deputy Director

Q11ADO0008 v 03

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Daonil 5 mg scored tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glibenclamide ..... 5 mg

Excipient with known effect: lactose

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Scored tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This medicinal product is used as an adjunct to appropriate dietary measures for the treatment of non-insulin dependent diabetes, when blood glucose levels cannot be controlled adequately by diet alone.

4.2. Posology and method of administration

Posology

For use in adults only

As for all hypoglycemic agents, the dose should be adjusted to each individual case.

In the event of a transient glycemic imbalance, a short period of treatment with the medicinal product may be sufficient in patients who are usually adequately stabilized by diet.

Subjects aged under 65 years

Initial dose:

The recommended initial dose is 1/2 tablet daily, administered before breakfast.

Dose increments:

Dose adjustment usually takes place in increments of 1/2 a tablet, based on glycemic response, in divided doses before the 2 or 3 main meals. Each dose increment should be separated by at least several days.

Maintenance treatment:

The maximum dosage is 3 tablets daily, divided into 2 or 3 doses before the main meals.

Subjects at risk

Elderly patients aged 65 years and over:

The initial dose and the maintenance doses should be cautiously adjusted to reduce the risk of hypoglycemia. Treatment should be initiated with the smallest available dose and gradually increased if necessary (see Section 4.4).

Other patients at risk:

- In patients who are malnourished or show a considerable deterioration in their general condition, or with irregular calorie intake, and in patients with kidney or liver failure, treatment should be initiated at the lowest dose, and the dose increments scrupulously followed, so as to avoid hypoglycemic reactions (see Section 4.4).

Patients receiving other oral hypoglycemic agents:

- As for all sulfonylureas, this medicinal product may follow on from another antidiabetic treatment without a transition period. When changing over from a sulfonylurea with a longer half-life (such as chlorpropamide) to this medicinal product, patients should be carefully monitored for several weeks in order to avoid the onset of hypoglycemia, due to the possible overlap of therapeutic effects.

Method of administration

Oral use.

4.3. Contraindications

This medicinal product is contraindicated in the following situations:

- hypersensitivity to glibenclamide, to other sulfonylureas or to any of the excipients listed in Section 6.1,
- insulin-dependent diabetes, particularly juvenile onset diabetes, diabetic ketoacidosis and diabetic pre-coma,
- severe kidney or liver failure,
- porphyria,
- treatment with miconazole (see Section 4.5),
- breast-feeding.

4.4. Special warnings and precautions for use

Special warnings

This medicinal product contains lactose. It is not recommended for use in patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption syndrome (rare hereditary diseases).

Cases of acute hemolysis have been reported in patients with G6PD deficiency receiving glibenclamide. Prescription is therefore not recommended in these patients, and use of an alternative treatment is strongly recommended if available. If there is no alternative, the decision must take into account the risk of hemolysis and the potential expected benefit of treatment on a case-by-case basis. If prescription of this medicinal product is necessary, monitoring for the possible onset of hemolysis should be performed.

Hypoglycemia: hypoglycemia may occur with sulfonylureas. The risk appears to be increased with glibenclamide. Some cases of hypoglycemia can be severe and prolonged, therefore requiring hospitalization to bring blood sugar levels back to normal over several days.

In addition, clinical signs of adrenergic counter-regulation may be observed, such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias.

The clinical picture of a severe hypoglycemic attack may resemble that of a stroke.

Symptoms generally subside after intake of carbohydrates (sugar) or when hypoglycemia has been corrected.

Careful selection of patients, the dosages used, together with adequate patient information are necessary in order to avoid episodes of hypoglycemia.

Risk factors for hypoglycemia:

- **patient refusal or inability to cooperate** (particularly elderly patients);
- **malnutrition, deterioration in general condition, irregular carbohydrate intake, insufficient calorie intake.** This treatment should only be prescribed if the patient is likely to take regular meals (especially breakfast).

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- **imbalance between physical exercise and carbohydrate intake;**
- **kidney and liver failure:** Glibenclamide pharmacokinetics and/or pharmacodynamics may be altered in patients with kidney or liver failure. If hypoglycemia occurs in these patients, as it is likely to be severe and prolonged, appropriate management should be initiated.
- **non-compensated endocrine disorders affecting carbohydrate metabolism or counter-regulation of hypoglycemia: adrenal insufficiency or hypopituitarism;**
- **elderly patients:** Age 65 years and over has been identified as a risk factor for hypoglycemia in patients treated with sulfonylureas. Hypoglycemia may be difficult to recognize in the elderly.
- **ingestion of alcohol;**
- **drug combinations liable to enhance the hypoglycemic effect of glibenclamide (see Section 4.5):** Hypoglycemia may be difficult to recognize in patients on beta-blocking agents. Hypoglycemia is more likely to occur during administration of a combination of hypoglycemic agents.

In these situations, the initial dose and the maintenance doses should be cautiously adjusted to reduce the risk of hypoglycemia (see Section 4.2).

Glycemic imbalance: glycemic control in a patient receiving antidiabetic treatment may be compromised in the event of fever, trauma, infection or surgical procedures. In this case, it may be necessary to discontinue treatment and administer insulin.

The efficacy of all oral hypoglycemic agents, including glibenclamide, in reducing blood glucose to the desired level, decreases in the long term for certain patients, which may be due to increasing severity of diabetes, or a decline in response to treatment. This is known as secondary failure and should be distinguished from primary failure in which case the medicinal product proves ineffective when prescribed as first-line treatment for a given patient. Adequate dose adjustment and dietary measures should be considered before a patient's treatment is classed as a secondary failure.

Laboratory tests: blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin levels may be helpful.

Glibenclamide and cardiovascular mortality: Epidemiological studies suggest that glibenclamide use is associated with an increased risk of cardiovascular mortality compared to treatment with metformin or gliclazide. This risk was observed in particular in patients with coronary heart disease.

Patient information:

The risks, symptoms and treatment of hypoglycemia together with the predisposing conditions, should be explained to patients and their families. Primary and secondary treatment failure should also be explained (see "Glycemic imbalance" above).

Patients should be informed of the potential risks and benefits of this treatment and other types of treatment. They should be made aware of the importance of following their diet and a regular exercise program, and of regularly monitoring of urine and/or blood glucose levels.

4.5. Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

1) The following medicinal product may enhance the hypoglycemic effect:

+ Miconazole (systemic use, oral gel): increase in the hypoglycemic effect with possible onset of hypoglycemic symptoms, or even coma.

Inadvisable combinations

1) The following medicinal products may enhance the hypoglycemic effect:

+ Phenylbutazone:

All forms of phenylbutazone, including topical forms: increase in the hypoglycemic effect of sulfonylureas due to a reduction in their hepatic metabolism. Preferably use another anti-inflammatory drug less likely to interact, or warn the patient and advise increased self-monitoring of blood glucose levels: if necessary, adjust the dose during and after treatment with the anti-inflammatory drug.

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+ Alcohol: Antabuse effect (heat, flushing, vomiting, tachycardia). Increase in the hypoglycemic effect (inhibition of compensatory reactions), which may facilitate the onset of hypoglycemic coma.

Patients should not consume alcoholic beverages or medicinal products containing alcohol.

2) The following medicinal product may increase blood glucose levels:

+ Danazol: diabetogenic effect of danazol.

If the combination cannot be avoided, warn the patient and advise increased self-monitoring of blood and urine glucose levels. If necessary, adjust the dose of the antidiabetic drug during and after treatment with danazol.

Combinations requiring precautions for use

1) The following medicinal products may enhance the hypoglycemic effect:

+ Beta blockers (except for esmolol): all beta blockers can mask certain symptoms of hypoglycemia: palpitations and tachycardia. Most non-cardioselective beta blockers increase the incidence and severity of hypoglycemia.

Warn the patient and advise increased self-monitoring of blood glucose levels, particularly at the start of treatment.

+ Fluconazole: Increase in the half-life of the sulfonylurea with possible onset of hypoglycemic symptoms.

Warn the patient, advise increased self-monitoring of blood glucose levels, and, if necessary, adjust the sulfonylurea dose during treatment with fluconazole.

+ ACE inhibitors: The use of ACE inhibitors may lead to an increase in the hypoglycemic effect in diabetic patients treated with sulfonylureas.

Hypoglycemic attack appears to be exceptional. It is thought that improved glucose tolerance could result in reduced insulin requirements.

Advise increased self-monitoring of blood glucose levels.

+ Clarithromycin, erythromycin: risk of hypoglycemia due to increased absorption and plasma concentrations of the antidiabetic drug.

Warn the patient, advise increased self-monitoring of blood glucose levels, and if necessary, adjust sulfonylurea dose during treatment with clarithromycin (or erythromycin).

2) The following medicinal products may increase blood glucose levels:

+ Chlorpromazine (neuroleptics): at high doses (over 100 mg chlorpromazine daily), elevated blood glucose levels (decreased insulin release).

Warn the patient and advise increased self-monitoring of blood glucose levels. If necessary, adjust the dose of the antidiabetic drug during and after treatment with the neuroleptic.

+ Glucocorticosteroids (except hydrocortisone as replacement therapy)

(Systemic and topical use: intra-articular, cutaneous and enema) and tetracosactide: Elevated blood glucose levels, sometimes with ketoacidosis (reduced carbohydrate tolerance due to corticosteroid therapy).

Warn the patient and advise increased self-monitoring of blood glucose levels, particularly at the start of treatment. If necessary, adjust the dose of the antidiabetic drug during and after treatment with corticosteroids.

+ Beta-2-adrenergic agonists (ritodrine, salbutamol, terbutaline): (IV use)

Elevation of blood glucose due to beta-2 stimulants. Increase monitoring of blood and urine parameters. Possibly switch to insulin.

3) Other interactions:

+ Bosentan:

Risk of decreased efficacy of glibenclamide as a result of reduced plasma concentrations, due to the inducer effect of bosentan. Furthermore, cases of hepatotoxicity have been reported with this combination.

Monitoring of blood glucose levels, treatment adjustment where necessary, and monitoring of liver function tests.

+ Somatostatin analogs:

Risk of hypoglycemia or hyperglycemia: reduction or increase in sulfonylurea requirements, for instance, decreased endogenous glucagon secretion.

Advise increased self-monitoring of blood glucose levels and, if necessary, adjust sulfonylurea dose during treatment with octreotide or lanreotide.

+ Colesevelam:

Concomitant administration of colesevelam and glibenclamide led to a 32% and 47% reduction in glibenclamide AUC0-inf and Cmax, respectively.

No interaction was observed when colesevelam was administered four hours after glibenclamide.

Therefore, glibenclamide should be taken at least 4 hours before colesevelam.

4.6. Fertility, pregnancy and lactation

Pregnancy

Risk related to diabetes

Uncontrolled diabetes (gestational or permanent) is associated with a higher incidence of congenital malformations and perinatal mortality. Around the time of conception, optimum control of diabetes should be achieved in order to reduce the teratogenic risk.

Risk related to glibenclamide

Sulfonylureas are teratogenic in animals at high doses.

Sufficient relevant clinical data are not currently available to evaluate any potential teratogenic or fetotoxic effect of glibenclamide when administered during pregnancy.

Management

Stabilizing diabetes enables pregnancy to follow a normal course in this patient population. Insulin therapy is obligatory, regardless of diabetes type (I or II), or whether it is gestational or permanent.

In permanent diabetes, oral treatment should be changed over to insulin as soon as pregnancy is considered or if pregnancy is discovered in women exposed to this medicinal product: in this case, it is not necessarily warranted to advise termination of the pregnancy but caution must be exercised and specific prenatal monitoring performed.

Monitoring of blood glucose levels in the neonate is recommended.

Lactation

Due to the lack of data on excretion in breast milk and given the risk of neonatal hypoglycemia, breast-feeding is contraindicated during treatment with this medicinal product.

Fertility

Not applicable.

4.7. Effects on ability to drive and use machines

Patients should be made aware of the symptoms of hypoglycemia and should exercise caution when driving or using machines.

4.8. Undesirable effects

Adverse effect frequencies are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1 000, <1/100), rare (≥1/10 000, <1/1 000), very rare (<1/10 000), frequency not known (cannot be estimated from the available data).

Metabolism and nutrition disorders

- Very common: hypoglycemia (see Sections 4.4 and 4.9). Cases of hypoglycemia may be prolonged and severe, and are not always easy to correct.
- Frequency not known: isolated cases of hyponatremia.

Skin and subcutaneous tissue disorders

- Common: mucocutaneous rash.
- Frequency not known: pruritus, maculopapular rash, bullous reactions, erythema polymorphe, exfoliative dermatitis, a few cases of photosensitivity have been reported.

Immune system disorders

- Frequency not known: hypersensitivity reactions, allergic or pseudo-allergic reactions.
- Frequency not known: isolated cases of urticaria-type reactions that may progress to life-threatening reactions with bronchospasm, dyspnea, hypotension or even shock.

Gastrointestinal disorders

- Common: nausea, diarrhea.
- Uncommon: epigastric discomfort.

Hepatobiliary disorders

- Frequency not known: hepatic disorders: elevated liver enzymes have been observed with the possible onset of cytolytic or cholestatic hepatitis requiring discontinuation of treatment. These disorders may progress to life-threatening liver failure.

Blood and lymphatic system disorders

Hematological disorders generally reversible on treatment discontinuation:

- Frequency not known: hypereosinophilia, leukopenia, moderate or severe thrombocytopenia, possibly manifesting as purpura, agranulocytosis, hemolytic anemia, aplastic anemia and pancytopenia.

Investigations

- Common: like all sulfonylureas, glibenclamide may cause weight gain.
- Frequency not known: mild to moderate occasional elevations of uremia and creatinine.

Eye disorders

- Frequency not known: transient visual disturbances, such as blurred vision or accommodation disorders, particularly at the start of treatment, with or without changes in blood glucose levels.

General disorders

- Frequency not known: antabuse effect if alcohol is consumed during meals.
  Clinical symptoms of porphyria (hepatic or cutaneous) in patients with porphyria (see Section 4.3).
- Frequency not known: in exceptional cases, potentially life-threatening cutaneous or visceral allergic vasculitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. This makes it possible to continuously monitor the benefit/risk ratio of the drug. Healthcare professionals are asked to report any suspected adverse reactions via the French national reporting system, i.e. the French National Agency for Medicines and Health Products Safety (ANSM) and the Regional Pharmacovigilance Centers network - website: www.ansm.sante.fr.

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4.9. Overdose

Sulfonylurea overdose may cause hypoglycemia.

Moderate symptoms of hypoglycemia, not involving loss of consciousness or neurological signs, must imperatively be corrected by carbohydrate intake, dose adjustment and/or changes in eating habits. Close monitoring must be continued until the physician is certain the patient is no longer in danger.

Severe hypoglycemic reactions, with coma, seizures or other neurological disorders are possible and constitute a medical emergency requiring immediate treatment as soon as the cause is diagnosed or suspected, before immediate hospitalization of the patient.

If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of a concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more diluted (10%) glucose solution at a rate that makes it possible to maintain blood glucose above 100 mg/dl. Patients should be closely monitored for at least 48 hours and, based on the patient's condition at that time, the physician should decide whether additional monitoring is necessary.

Glucagon must not be used as it may cause recurrent hypoglycemia due to secondary insulin hypersecretion.

Plasma clearance of glibenclamide may be prolonged in patients with liver disease. Dialysis is not beneficial to patients as glibenclamide is extensively bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: BLOOD GLUCOSE LOWERING DRUGS EXCLUDING INSULINS - SULFONYLUREAS, ATC code: A10BB01 (A: Alimentary tract and metabolism).

Glibenclamide, a second-generation sulfonylurea with a short half-life, appears to cause an acute reduction in blood glucose levels by stimulating insulin release by the pancreas; this effect is dependent on the presence of active beta cells in the pancreatic islets.

Stimulation of insulin secretion by glibenclamide in response to a meal is of major importance. Administration of glibenclamide in diabetic patients enhances postprandial insulinotropic response. Enhancement of postprandial insulin and C-peptide secretion responses continues after at least 6 months of treatment.

5.2. Pharmacokinetic properties

Glibenclamide is extensively absorbed (92%) following oral administration. Peak plasma concentrations are reached in 2 to 6 hours. Food intake does not alter the rate or level of absorption.

Glibenclamide extensively binds to plasma albumin (99%), which can explain certain drug interactions.

Glibenclamide is completely metabolized by the liver into 3 inactive metabolites eliminated via the biliary route (60%) and via the renal route (40%); complete elimination is achieved in 45 to 72 hours.

The elimination half-life is 4 to 11 hours.

Hepatocellular insufficiency reduces glibenclamide metabolism and thus considerably slows elimination.

Biliary excretion of the metabolites increases in the event of kidney failure, in proportion to the severity of the renal disorder.

Renal failure does not affect elimination as long as creatinine clearance remains above 30 ml/min.

5.3. Preclinical safety data

Not applicable.

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6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, maize starch, pregelatinized maize starch, talc, magnesium stearate, colloidal anhydrous silica.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Store at a temperature not exceeding 25°C.

6.5. Nature and contents of container

Blisters (PVC/Aluminum).

6.6. Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORIZATION HOLDER

SANOFI AVENTIS FRANCE
82 Avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORIZATION NUMBER(S)

- 302 810-5: 20 scored tablets in (PVC/Aluminum) blisters
- 302 809-7: 100 scored tablets in (PVC/Aluminum) blisters
- 372 006-0: 180 scored tablets in (PVC/Aluminum) blisters

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

[To be filled in by the Marketing Authorization Holder]

10. DATE OF REVISION OF THE TEXT

[To be filled in by the Marketing Authorization Holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I.

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ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

A.1. Name and address of the manufacturer(s) of the biological active substance(s)

Not applicable.

A.2. Name and address of the manufacturers responsible for batch release

FAMAR L'AIGLE
Route de Crulai – Z.I. N° 1
61300 L'Aigle
France

or

Sanofi Winthrop Industrie
56, Route de Choisy au Bac
60205 Compiègne
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

List I.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

Not applicable.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORIZATION MEASURES FOR THE MARKETING AUTHORIZATION "UNDER EXCEPTIONAL CIRCUMSTANCES"

Not applicable.

F. QUALITATIVE AND QUANTITATIVE COMPOSITION IN EXCIPIENTS

Lactose monohydrate..... 79.0 mg

Maize starch..... 65.5 mg

Pregelatinized maize starch..... 5.0 mg

Talc..... 3.0 mg

Colloidal anhydrous silica ..... 2.0 mg

Magnesium stearate..... 0.5 mg

For one scored tablet

ANNEX IIIA

LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

NATURE/TYPE OUTER PACKAGING OR IMMEDIATE PACKAGING

Box.

1. NAME OF THE MEDICINAL PRODUCT

Daonil 5 mg scored tablets

glibenclamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Glibenclamide ..... 5 mg

3. LIST OF EXCIPIENTS

Excipient(s) with known effect: lactose

See the package leaflet for more information.

4. PHARMACEUTICAL FORM AND CONTENTS

Scored tablets in boxes of 20, 100 or 180.

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP {MM/AAAA}

9. SPECIAL STORAGE CONDITIONS

Store at a temperature not exceeding 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTEMATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable.

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder

sanofi-aventis France
82 Avenue Raspail
94250 Gentilly
France

Operating Company

sanofi-aventis France
82 Avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORIZATION NUMBERS

Marketing Authorization No.:

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR PRESCRIPTION AND SUPPLY

List I.

15. INSTRUCTIONS ON USE

Not applicable.

16. INFORMATION IN BRAILLE

In compliance with current regulations.

PICTOGRAM TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

The pictogram must comply with French Order dated August 8, 2008 in application of Article R.5121139 of the Public Health Code related to the display of a pictogram on the outer packaging of certain medicines and medicinal products.

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MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

NATURE/TYPE BLISTERS / STRIPS

Blisters (PVC/Aluminum).

1. NAME OF THE MEDICINAL PRODUCT

Daonil 5 mg scored tablets

glibenclamide

2. NAME OF THE MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder

SANOFI AVENTIS FRANCE

Operating Company

SANOFI AVENTIS FRANCE

3. EXPIRY DATE

EXP {MM/AAAA}

4. BATCH NUMBER

Batch {number}

5. OTHER

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

NATURE/TYPE SMALL IMMEDIATE PACKAGING UNITS

Not applicable.

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Not applicable.

2. METHOD OF ADMINISTRATION

Not applicable.

3. EXPIRY DATE

Not applicable.

4. BATCH NUMBER

Not applicable.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Not applicable.

6. OTHER

Not applicable.

ANNEX IIIB

PACKAGE LEAFLET: INFORMATION FOR THE USER

Name of the medicinal product

Daonil 5 mg scored tablets

Glibenclamide

Boxed text

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet:

1. What **Daonil 5 mg scored tablets** are and what they are used for
2. What you need to know before you take **Daonil 5 mg scored tablets**
3. How to take **Daonil 5 mg scored tablets**
4. Possible side effects
5. How to store **Daonil 5 mg scored tablets**
6. Contents of the pack and other information.

1. WHAT Daonil 5 mg scored tablets ARE AND WHAT THEY ARE USED FOR

Pharmacotherapeutic group:

Daonil 5 mg scored tablets are an oral antidiabetic belonging to a group of medicines called sulfonylureas (medicines that decrease blood sugar levels, or glycemia).

Therapeutic indications:

It is used to treat non-insulin-dependent diabetes (also called type 2 diabetes, which does not require insulin) when dietary measures alone have not been enough to control your blood sugar.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE Daonil 5 mg scored tablets

If your doctor has told you that you are intolerant to certain sugars, consult him/her before taking this medicine.

Do not take Daonil 5 mg scored tablets if you:

- are allergic (hypersensitive) to the active substance (glibenclamide), or any of the other ingredients of Daonil 5 mg scored tablets listed in Section 6,
- are allergic (hypersensitive) to medicines in the same group as Daonil 5 mg scored tablets or related substances (sulfonylureas or sulfonamides),
- have diabetes requiring treatment with insulin,
- have diabetes complications such as ketoacidosis or consciousness disorders (pre-coma),
- have severe liver or kidney disease,
- are already taking miconazole (see "Other medicines and Daonil 5 mg scored tablets"),
- have a hereditary blood disease called porphyria,
- are breast-feeding.

Unless otherwise indicated by your doctor, you should not take Daonil 5 mg scored tablets with phenylbutazone or danazol (see "Other medicines and Daonil 5 mg scored tablets").

If you are unsure of anything, ask your doctor or pharmacist for advice.

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Warnings and precautions

Before you take Daonil 5 mg scored tablets, tell your doctor if you or a family member have G6PD (glucose-6-phosphate dehydrogenase) deficiency (hereditary disease of the red blood cells), as there is a risk of hemolysis (destruction of red blood cells) if you take Daonil 5 mg scored tablets.

Hypoglycemia: (abnormal decrease in blood sugar levels).

The various signs of hypoglycemia include headache, ravenous hunger, nausea, shakiness, sweating, pallor, tiredness, sleepiness, feeling of faintness, dizziness, visual and speech disturbances, behavioral disorders (aggressiveness, depression, confusion), sleep disturbances, impaired concentration, impaired alertness and reactions, and heart problems.

During your treatment, you may experience hypoglycemia. If this occurs, you may need to be hospitalized to have your blood sugar levels restored to normal. After an episode of hypoglycemia, your doctor will monitor you carefully for at least 24 hours.

Your doctor will explain to you and your family how to avoid episodes of hypoglycemia, how to recognize the first symptoms and how to treat them. The doctor will also describe to you the circumstances in which you might become resistant to this treatment. Other medicines could then be prescribed as replacement treatment.

In order to avoid episodes of hypoglycemia, you should take the following information into account:

- It is important to eat regular meals, including breakfast, due to the increased risk of hypoglycemia if you forget a meal, do not eat enough, or have a diet that is not well balanced in carbohydrates;
- Age, kidney or liver failure and some adrenal or pituitary problems can increase the risk of hypoglycemia;
- Patients aged 65 years and over are especially sensitive to the blood sugar-lowering action of glibenclamide and therefore have a higher risk of hypoglycemia. In elderly patients, low glucose levels may be difficult to identify. The initial dose and maintenance dose of glibenclamide must be carefully determined by your doctor to avoid any hypoglycemic reactions.
- Hypoglycemia is more likely to occur if your diet is too strict or unbalanced, after prolonged or intense exercise, if you drink alcohol, or if you are also taking other blood sugar-lowering medicines (see “Other medicines and Daonil 5 mg scored tablets”).

Blood sugar imbalance

- Your doctor may stop your Daonil 5 mg scored tablets and prescribe insulin if you:
  - are due to undergo surgery,
  - have had an injury,
  - have a fever or an infection.
- Your doctor may also change this treatment if your blood sugar is not satisfactorily controlled.

Glibenclamide and cardiovascular mortality

Epidemiological studies suggest that glibenclamide use is associated with an increased risk of cardiovascular mortality compared to treatment with metformin or gliclazide. This risk was observed in particular in patients with coronary heart disease.

Laboratory tests

Your urine and blood sugar levels should be tested regularly.

Other medicines and Daonil 5 mg scored tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Be sure to tell your doctor, in particular, if you are taking any of the following medicines:

- medicines that may increase hypoglycemia:
  - miconazole, fluconazole,
  - phenylbutazone,
  - beta-blockers (except esmolol), converting enzyme inhibitors,
  - clarithromycin, erythromycin,

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- medicines containing alcohol.

- medicines that may cause hyperglycemia (abnormal increase in blood sugar) due to reduced efficacy of Daonil 5 mg scored tablets:
  - danazol,
  - chlorpromazine,
  - glucocorticosteroids (except hydrocortisone),
  - salbutamol, terbutaline,
  - ritodrine.

- other possible interactions:
  - bosentan: risk of increase in certain liver enzymes,
  - somatostatin analogues: risk of hyperglycemia or hypoglycemia,
  - colesevelam: Daonil 5 mg scored tablets should be taken at least 4 hours before colesevelam.

Daonil 5 mg scored tablets with food and drink

An antabuse effect (feeling hot, redness, vomiting, increased heart rate) may occur if you consume alcohol.

Pregnancy and breast-feeding

Pregnancy

If you are pregnant, your diabetes must be treated with insulin.

If you discover that you are pregnant while you are taking Daonil 5 mg scored tablets, your treatment must be stopped.

Consult your doctor as soon as possible and he or she will adjust your treatment.

Breast-feeding

Daonil 5 mg scored tablets should not be taken at any time during the breast-feeding period.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Athletes

Not applicable.

Driving and using machines

During your treatment, episodes of hypoglycemia may occur. The symptoms of hypoglycemia and its effects on alertness can make it dangerous to drive or operate machinery.

Daonil 5 mg scored tablets contain lactose

This medicine contains a type of sugar (lactose) that is broken down into galactose and glucose. It is not recommended for use in patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption syndrome (rare hereditary diseases).

3. HOW TO TAKE Daonil 5 mg scored tablets

Dosage and method of administration

Always use the dose prescribed by your doctor. If you are unsure of anything, ask your doctor or pharmacist.

The usual dosage is ½ to 3 tablets per day.

The tablets are scored, which means that you can break them into two equal halves.

Swallow the tablets with about half a glass of water immediately before a meal (oral use).

If you take more Daonil 5 mg scored tablets than you should:

Contact your doctor or the emergency services immediately.

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If you experience symptoms of hypoglycemia such as weakness, sweating, hunger pangs, shakiness, sleepiness, dizziness, headache or visual disturbances, eat or drink something sweet.

If you forget to take Daonil 5 mg scored tablets:

Take a tablet at the next meal. **Do not take a double dose.**

If you stop taking Daonil 5 mg scored tablets:

Not applicable.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Daonil 5 mg scored tablets can cause side effects, although not everybody gets them.

Side effect frequencies are defined using the following convention: very common (may affect more than 1 patient in 10), common (may affect up to 1 patient in 100), uncommon (may affect up to 1 patient in 100), rare (may affect up to 1 patient in 1 000), very rare (may affect up to 1 patient in 10 000), frequency not known (cannot be estimated from the available data).

Very common side effects:

- hypoglycemia, which can be severe (see "Warnings and precautions" and "If you take more Daonil 5 mg scored tablets than you should"),

Common side effects:

- skin reactions: rash with spots or patches,
- nausea, diarrhea,
- weight gain,

Uncommon side effects:

- stomach discomfort.

Side effects of unknown frequency:

- temporary visual disturbances such as blurred vision,
- skin reactions: hives, itching, development of blisters on the skin (bullous reactions), rash with spots and sometimes blisters on the skin, which may also affect the mouth (erythema polymorphe), rash with spots causing itching and skin peeling (exfoliative dermatitis), exaggerated skin reaction after exposure to the sun or UV rays,
- allergic reactions that can be serious: difficulty breathing (bronchospasm, dyspnea), decrease in blood pressure, or even sudden malaise with a severe drop in blood pressure (shock),
- liver problems: increase in liver enzymes, jaundice, hepatitis that could progress to serious liver impairment and be life-threatening,
- liver or skin symptoms if you have a hereditary disease called porphyria,
- abnormal laboratory values from a blood test:
    - increased number of certain white blood cells (eosinophils), reduced number of other white blood cells (leukopenia and, more rarely, agranulocytosis), reduced number of platelets (thrombocytopenia) that can result in red spots on the skin (purpura), reduced number of red blood cells (hemolytic anemia),
    - decrease in the number of all blood cells (pancytopenia), decrease in the production of blood cells (bone marrow aplasia),
    - reduced levels of sodium in the blood,
    - increased levels of urea and creatinine in the blood,
- antabuse effect (feeling hot, redness, vomiting, and increased heart rate on drinking alcohol),
- in exceptional cases, inflammation of the small blood vessels (allergic vasculitis) that could be life-threatening.

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Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system i.e.: the French National Agency for Medicines and Health Products Safety (ANSM) and the regional network of Pharmacovigilance Centers, at: www.ansm.sante.fr

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE DAONIL 5 mg scored tablets

Keep this medicine out of the sight and reach of children.

Do not use Daonil 5 mg scored tablets after the expiry date which is stated on the box.

Do not store above 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Daonil 5 mg scored tablets contain

- The active substance is:

Glibenclamide .....5 mg

For one scored tablet.

- The other ingredients are: lactose monohydrate, maize starch, pregelatinized maize starch, talc, colloidal anhydrous silica, magnesium stearate.

What Daonil 5 mg scored tablets look like and contents of the pack

This medicine is available as scored tablets (tablets that can be split into two equal halves). One box can contain 20, 100 or 180 tablets.

Not all pack sizes may be marketed.

Marketing authorization holder

SANOFI AVENTIS FRANCE
82 Avenue Raspail
94250 Gentilly
France

Marketing authorization operator

SANOFI AVENTIS FRANCE
82 Avenue Raspail
94250 Gentilly
France

Manufacturer

FAMAR L'AIGLE
Route de Crulai – Z.I. N° 1
61300 L'Aigle
France

or

Sanofi Winthrop Industrie
56, Route de Choisy au Bac
60205 Compiègne
France

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Names of the medicinal product in the Member States of the European Economic Area

Not applicable.

This leaflet was last revised in {month YYYY}.

Other

Detailed information on this medicine is available on the ANSM website (France).

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