NAME OF THE MEDICINAL PRODUCT

GLUCOVANCE 1000 mg/5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1000 mg metformin hydrochloride, equivalent to 780 mg metformin, and 5 mg glibenclamide

Excipient: lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white oval-shaped, biconvex film-coated tablet with '1000' engraved on one side and '5' engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of type 2 diabetes in adults, as replacement for previous combination therapy with metformin and glibenclamide in patients whose glycaemia is stable and well-controlled.

4.2 Posology and method of administration

Oral route.

For use in adults only.

General:

As for all hypoglycaemic agents, the dosage should be adapted according to the individual metabolic response (glycaemia, HbA1c).

Initiation of treatment:

Treatment should be initiated with a dose of the combination product equivalent to previous individual doses of metformin and glibenclamide; the dose being gradually increased depending on results on glycaemic parameters.
**Dose titration:**

The dosage should be adjusted every 2 weeks or longer, by increments of 1 tablet of metformin hydrochloride/glibenclamide 500 mg/2.5 mg, depending on glycaemia results.

A gradual increase in the dosage may aid gastrointestinal tolerance and prevent the onset of hypoglycaemia.

For patients already treated with a combination of metformin and glibenclamide, two tablets of metformin hydrochloride/glibenclamide 500 mg/2.5 mg can be replaced by one tablet of Glucovance 1000 mg/5 mg.

**Maximum daily recommended dose:**

The maximum daily recommended dose is 3 tablets of Glucovance 1000 mg/5 mg.

**Dosage regimen:**

The dosage regimen depends on the individual posology:

- Once a day, in the morning at breakfast, for a dosage of 1 tablet/day,
- Twice a day, morning and evening, for a dosage of 2 tablets/day,
- Three times a day, morning, noon and evening, for a dosage of 3 tablets/day.

The tablets should be taken with meals. The dosage regimen should be adjusted according to the individual eating habits. However, any intake must be followed by a meal with a sufficiently high carbohydrate content to prevent the onset of hypoglycaemic episodes.

**Combination with insulin therapy:**

No clinical data are available on the concomitant use of this product with insulin therapy.

**Elderly subjects:**

The dosage of Glucovance should be adjusted depending on renal function parameters (start with 1 tablet of Glucovance 500 mg/2.5 mg); regular checks on the renal function are necessary (see section 4.4).

**Paediatric patients:**

Glucovance is not recommended for use in children (see section 5.1).

**4.3 Contraindications**

This medicinal product must never be used in case of:

- hypersensitivity to metformin hydrochloride, glibenclamide or other sulphonylurea(s) and sulphonamide(s) or to any of the excipients;
- type 1 diabetes (insulin-dependent diabetes), ketoacidosis, diabetic pre-coma;
- renal failure or renal dysfunction (creatinine clearance < 60 ml/min);
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast materials (see section 4.4 and section 4.5);
• acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock;
• hepatic insufficiency, acute alcohol intoxication, alcoholism;
• porphyria;
• lactation;
• in association with miconazole (see section 4.5).

4.4 Special warnings and precautions for use

Lactic acidosis

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

Diagnosis:

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia. Lactic acidosis is characterised by acidic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, this medicinal product should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Hypoglycaemia

As it contains a sulphonylurea, Glucovance exposes the patient to a risk of onset of hypoglycaemic episodes. After treatment initiation, a progressive dose titration may prevent the onset of hypoglycaemia. This treatment should only be prescribed if the patient adheres to a regular meal schedule (including breakfast). It is important that carbohydrate intake is regular since the risk of hypoglycaemia is increased by a late meal, insufficient or unbalanced carbohydrate intakes. Hypoglycaemia is more likely to occur in case of energy-restricted diet, after intensive or prolonged exercise, when alcohol intake or during the administration of a combination of hypoglycaemic agents.

Diagnosis:

The symptoms of hypoglycaemia are: headache, hunger, nausea, vomiting, extreme tiredness, sleep disorder, restlessness, aggression, impaired concentration and reactions, depression, confusion, speech impediment, visual disturbances, trembling, paralysis and paraesthesia, dizziness, delirium, convulsions, somnolence, unconsciousness, superficial breathing and bradycardia. Due to a counterregulation caused by the hypoglycaemia sweating, fear, tachycardia, hypertension, palpitations, angina and arrhythmia can occur. These latter symptoms can be absent when the hypoglycaemia is developed slowly, in case of autonomic neuropathy or when the patients take beta-blocking agents, clonidine, reserpine, guanethidine or sympathomimetics.
**Management of hypoglycaemia:**

Moderate hypoglycaemic symptoms without loss of consciousness or neurological manifestations should be corrected by the immediate intake of sugar. An adjustment to the dosage and/or changes to meal patterns should be ensured. Severe hypoglycaemic reactions with coma, seizures or other neurological signs are also possible and constitute a medical emergency requiring immediate treatment with intravenous glucose once the cause is diagnosed or suspected, prior to prompt hospitalisation of the patient.

The careful selection of patients and dosage and adequate instructions for the patient are important to reduce the risk of hypoglycaemic episodes. If the patient encounters repeated episodes of hypoglycaemia, which are either severe or associated with unawareness of the situation, antidiabetic treatment options other than Glucovance should be taken into consideration.

Factors favouring hypoglycaemia:

- concomitant administration of alcohol, especially combined with fasting,
- refusal or (more particularly in elderly patients) inability of the patient to co-operate,
- malnutrition, irregular meals, missed meals, fasting or changes to diet,
- poor balance between physical exercise and carbohydrate intake,
- renal failure,
- severe liver failure,
- overdose of Glucovance,
- certain endocrine disturbances: thyroid insufficiency, pituitary and adrenal gland insufficiency,
- concomitant administration of certain other drugs (see section 4.5).

**Renal and hepatic failure:**

The pharmacokinetics and/or pharmacodynamics of Glucovance may be modified in patients with hepatic failure or severe renal failure. If hypoglycaemia occurs in such patients, it may be prolonged, and appropriate treatment must be initiated.

**Patient information:**

The risks of hypoglycaemia, its symptoms and its treatment, as well as its predisposing conditions, must be explained to the patient and his or her family. Similarly, the risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps accompanied by digestive disorders, abdominal pain and severe asthenia, dyspnoea attributed to acidose, hypothermia and coma.

In particular, the patient should be informed of the importance of adhering to a diet, following a programme of regular physical exercise and making regular checks on glycaemia.

**Blood sugar imbalance**

In case of surgery or any other cause of diabetic decompensation, temporary insulin therapy should be envisaged instead of this treatment.

The symptoms of hyperglycaemia are: increased urinating, raging thirst and a dry skin.

**Kidney function**

As metformin is excreted by the kidney, it is recommended that creatinine clearance and/or serum creatinine levels be determined before initiating treatment and regularly thereafter:
at least annually in patients with normal renal function,
at least two to four times a year in patients with serum creatinine levels at the upper limit of
normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be
exercised in situations where renal function may become impaired, for example when initiating
antihypertensive therapy or diuretic therapy, and when starting therapy with a non-steroidal anti-
-inflammatory drug (NSAID).

**Administration of iodinated contrast materials**

The intravascular administration of iodinated contrast materials in radiological studies can lead to
renal failure. Depending on the renal function, Glucovance must be discontinued 48 hours before the
test or at the time of the test and may not be re-instituted until 48 hours afterwards, and only after renal
function has been re-evaluated and found to be normal (see section 4.3 and section 4.5).

**Concomitant use of glibenclamide with other medicinal products**

The concomitant use of glibenclamide with alcohol, phenylbutazone or danazol is not recommended
(see section 4.5).

**Surgery**

Because Glucovance contains metformin hydrochloride, Glucovance must be discontinued 48 hours
before elective surgery under general, spinal or peridural anaesthesia and may not be re-instituted
earlier than 48 hours following surgery or resumption of oral nutrition and only after renal function
has been re-evaluated and found to be normal.

**Other precautions**

All patients should continue their diet, with a regular distribution of carbohydrate intake during the
day. Overweight patients should continue their energy-restricted diet,

Regular physical exercise is as necessary as taking Glucovance.
The usual laboratory tests for diabetes monitoring (glycaemia, HbA1c) should be performed regularly,

Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to haemolytic
anaemia. Since glibenclamide belongs to the chemical class of sulphonylurea drugs, caution is
recommended when using Glucovance in patients with G6PD-deficiency and a non-sulphonylurea
alternative may be considered.

Because this medicinal product contains lactose, it is contraindicated in case of congenital
galactosemia, glucose and galactose malabsorption syndrome or in case of lactase deficiency.
4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combination

Related to glibenclamide

*Miconazole (systemic route, oromucosal gel):* Increase in the hypoglycaemic effect with possible onset of hypoglycaemic manifestations, or even coma (see section 4.3).

Combinations not recommended

Related to sulphonlurea(s)

*Alcohol:*
Antabuse effect (intolerance to alcohol), notably for chlorpropamide, glibenclamide, glipizide, tolbutamide.
Increase of the hypoglycaemic reaction (inhibition of compensation reactions), which may facilitate the onset of a hypoglycaemic coma (see section 4.4). Avoid consumption of alcohol and alcohol-containing medications.

*Phenylbutazone (systemic route):*
Increase in the hypoglycaemic effect of sulphonlurea(s) (displacement of sulphonlurea(s) from protein-binding sites and/or decrease in their elimination). Preferably use another anti-inflammatory agent exhibiting fewer interactions, or else warn the patient and step up self-monitoring; if necessary, adjust the dosage during treatment with the anti-inflammatory agent and after its withdrawal.

Related to all antidiabetic agents

*Danazol:*
If the combination cannot be avoided, warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment during treatment with danazol and after its withdrawal.

Related to metformin

*Alcohol:*
Increased risk of lactic acidosis during acute alcoholic intoxication, particularly in cases of fasting (see section 4.4) or malnutrition and hepatocellular failure. Avoid drinking alcoholic beverages and taking drugs that contain alcohol.

Combinations requiring precautions

Related to all antidiabetic agents

*Chlorpromazine:*
At high dosages (100 mg per day of chlorpromazine), elevation in blood glucose (reduction in release of insulin).
Precaution for use: warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic treatment during treatment with the neuroleptic and after its withdrawal.

*Corticosteroids (glucocorticoids) and tetracosactides (systemic and local routes):*
Elevation in blood glucose, sometimes accompanied by ketosis (decreased carbohydrate tolerance with corticosteroids).
Precaution for use: warn the patient and step up self-monitoring of blood glucose. Possibly adjust the dosage of the antidiabetic during treatment with corticosteroids and after their withdrawal.

\( \beta \)2-agonists:
Elevation in blood glucose due to the \( \beta \)2-agonists.
Precaution for use: warn the patient, step up blood glucose monitoring and possibly transfer to insulin therapy.

Angiotensin converting enzyme inhibitors (e.g. captopril, enalapril):
ACE inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of Glucovance during therapy with an ACE inhibitor and upon its discontinuation.

Related to metformin

Diuretics:
Lactic acidosis due to metformin triggered by any functional renal insufficiency, related to diuretics and more particularly to loop diuretics.

Iodinated contrast materials:
Intravascular administration of iodinated contrast materials may lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Depending on the renal function, Glucovance must be discontinued 48 hours before the test or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Related to glibenclamide

Beta-blockers:
All beta-blockers mask some of the symptoms of hypoglycaemia; palpitations and tachycardia; Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia.
Warn the patient and step up blood glucose self-monitoring, especially at the start of treatment.

Fluconazole:
Increase in the half-life of sulphonylurea with possible onset of hypoglycaemic manifestations.
Warn the patient and step up blood glucose self-monitoring, and possibly adjust the dosage of the antidiabetic treatment during treatment with fluconazole and after its withdrawal.

Bosentan:
Risk of decreased hypoglycaemic effect of glibenclamide because bosentan reduces the plasma concentration of glibenclamide. An increased risk of liver enzyme elevations was reported in patients receiving glibenclamide concomitantly with bosentan.
Warn the patient, set-up monitoring of glycaemia and liver enzymes and adjust the dosage of the antidiabetic treatment if necessary.

Other interaction: combination to be taken into account:

Related to glibenclamide

Desmopressin:
Reduction in antidiuretic activity.

4.6 Pregnancy and lactation

Pregnancy
No preclinical and clinical data on exposed pregnancies are available for Glucovance.
Risk related to diabetes

When uncontrolled, diabetes (gestational or permanent) gives rise to an increase in congenital abnormalities and perinatal mortality. Diabetes must be controlled as far as possible during the period of conception in order to reduce the risk of congenital abnormalities.

Risk related to metformin (see section 5.3)

Studies in animals have shown no evidence of teratogenic activity. In the absence of a teratogenic effect in animals, foetal malformation in humans is not to be expected since to date, substances known to cause malformation in humans have proved to be teratogenic in well-conducted animal studies in two species.

Clinical studies involving a few small series have not shown evidence of foetal malformation directly related to metformin.

Risk related to glibenclamide (see section 5.3)

Studies in animals have shown no evidence of teratogenic activity. In the absence of a teratogenic effect in animals, foetal malformation in humans is not to be expected since to date, substances known to cause malformation in humans have proved to be teratogenic in well-conducted animal studies in two species.

In clinical practice, there are currently no relevant data on which to base an evaluation of potential malformation or fetotoxicity due to glibenclamide when administered during pregnancy.

Management

Adequate blood glucose control allows pregnancy to proceed normally in this category of patients. Glucovance must not be used for the treatment of diabetes during pregnancy.

It is imperative that insulin be used to achieve adequate blood glucose control. It is recommended that the patient be transferred from oral antidiabetic therapy to insulin as soon as she plans to become pregnant or if pregnancy is exposed to this medicinal product. Neonatal blood glucose monitoring is recommended.

Lactation

Metformin is excreted in milk in lactating rats. In humans, in the absence of data concerning passage of metformin and glibenclamide into breast milk, and in view of the risk of neonatal hypoglycaemia, this medicinal product is contraindicated in the event of breast-feeding.

4.7 Effects on ability to drive and use machines

Patients should be alerted to the symptoms of hypoglycaemia and should be advised to exercise caution when driving or using machines.

4.8 Undesirable effects

The following undesirable effects may occur under treatment with Glucovance. Frequencies are defined as follows: 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 not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Investigations:
*Uncommon:* Average to moderate elevations in serum urea and creatinine concentrations.
*Very rare:* Hyponatremia.

**Blood and lymphatic system disorders:**
These are reversible upon treatment discontinuation.
*Rare:* Leukopenia, thrombocytopenia.
*Very rare:* Agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia.

**Nervous system disorders:**
*Common:* Taste disturbance.

**Eye disorders:**
Transient visual disturbances may occur at the start of treatment due to a decrease in glycaemia levels.

**Gastrointestinal disorders:**
*Very common:* Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur more frequently during treatment and resolve spontaneously in most cases. To prevent them, it is recommended that Glucovance be taken in 2 or 3 daily doses. A slow increase of the dose may also improve gastrointestinal tolerability.

**Skin and subcutaneous tissue disorders:**
*Rare:* Skin reactions such as pruritus, urticaria, maculopapular rash.
*Very rare:* Cutaneous or visceral allergic angitis, erythema multiforme, exfoliative dermatitis, photosensitization, urticaria evolving to shock.
A cross reactivity to sulphonamide(s) and their derivatives may occur.

**Metabolism and nutrition disorders:**
Hypoglycaemia (see section 4.4).
*Uncommon:* Crises of hepatic porphyria and porphyria cutanea.
*Very rare:* Lactic acidosis (see section 4.4). Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia. Disulfiram-like reaction with alcohol intake.

**Hepatobiliary disorders:**
*Very rare:* Liver function test abnormalities or hepatitis requiring treatment discontinuation.

### 4.9 Overdose

Overdose may precipitate hypoglycaemia due to the presence of the sulphonylurea (see section 4.4).

High overdose or the existence of concomitant risk factors may lead to lactic acidosis due to the presence of metformin (see section 4.4). Lactic acidosis is a medical emergency and must be treated in hospital. The most effective treatment is to remove lactate and metformin by haemodialysis.

The plasma clearance of glibenclamide may be prolonged in patients suffering from liver disease. Since glibenclamide is extensively bound to proteins, it is not eliminated by dialysis.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Biguanides and sulphonamide(s) in combination. ATC code: A10BD02

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

1. by reducing hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
2. in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
3. and by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL-cholesterol and triglyceride levels. In clinical trials conducted so far with combination therapy with metformin and glibenclamide, these favourable effects on lipid metabolism have not been shown.

Glibenclamide is a second generation sulphonylurea with a medium half-life: it causes acute lowering of blood glucose by stimulating the release of insulin by the pancreas, this effect being dependent on the presence of functioning beta cells in the islets of Langerhans.

The stimulation of insulin secretion by glibenclamide in response to a meal is of major importance.

The administration of glibenclamide to diabetics induces an increase in the postprandial insulin-stimulating response. The increased postprandial responses in insulin and C-peptide secretion persist after at least 6 months of treatment.

Metformin and glibenclamide have different mechanisms and sites of action, but their action is complementary. Glibenclamide stimulates the pancreas to secrete insulin, while metformin reduces cell resistance to insulin by acting on peripheral (skeletal muscle) and hepatic sensitivity to insulin.

Results from controlled, double blind clinical trials versus reference products in the treatment of type 2 diabetes inadequately controlled by monotherapy with metformin or glibenclamide combined with diet and exercise, have demonstrated that the combination had an additive effect on glucose regulation.

Paediatric patients:
In a 26-week, active controlled, double-blind, clinical study performed in 167 paediatric patients aged 9 to 16 years with type 2 diabetes not adequately controlled with diet and exercise, with or without an oral antidiabetic treatment, a fixed combination of metformin hydrochloride 250 mg and glibenclamide 1.25 mg was not shown more effective to either metformin hydrochloride or glibenclamide in reducing HbA1c from baseline. Therefore, Glucovance should not be used in paediatric patients.
5.2 Pharmacokinetic properties

Related to the combination

The bioavailability of metformin and glibenclamide in the combination is similar to that noted when one tablet of metformin and one tablet of glibenclamide are taken simultaneously. The bioavailability of metformin in the combination is unaffected by the ingestion of food. The bioavailability of glibenclamide in the combination is unaffected by the ingestion of food, but the absorption speed of glibenclamide is increased by eating.

Related to metformin

Absorption:

After an oral dose of metformin, $T_{\text{max}}$ is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels ($C_{\text{max}}$) did not exceed 4 µg/ml, even at maximum doses.

Distribution:

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution $V_d$ ranged from 63 to 276 l.

Metabolism:

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Related to glibenclamide

Absorption:

Glibenclamide is very readily absorbed (> 95%) following oral administration. The peak plasma concentration is reached in about 4 hours.

Distribution:

Glibenclamide is extensively bound to plasma albumin (99%), which may account for certain drug interactions.
Metabolism:
Glibenclamide is completely metabolised in the liver to two metabolites. Hepatocellular failure decreases glibenclamide metabolism and appreciably slows down its excretion.

Excretion:
Glibenclamide is excreted in the form of metabolites via biliary route (60%) and urine (40%), elimination being complete within 45 to 72 hours. Its terminal elimination half-life is 4 to 11 hours.

Biliary excretion of the metabolites increases in cases of renal insufficiency, according to the severity of renal impairment until a creatinine clearance at 30 ml/min. Thus, glibenclamide elimination is unaffected by renal insufficiency as long as the creatinine clearance remains above 30 ml/min.

Paediatric patients
There were no differences in pharmacokinetics of glibenclamide and metformin between paediatric patients and weight-and gender-matched healthy adults.

5.3 Preclinical safety data
No preclinical studies have been performed on the combination product. Preclinical evaluation of the constituents metformin and glibenclamide revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.

Animal studies on metformin and glibenclamide do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Sodium croscarmelllose
Povidone K30
Magnesium stearate

Film-coating
Opadry II OY-L-28900 white (lactose monohydrate, hypromellose, titanium dioxide (E171), macrogol 4000).

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years
6.4  Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5  Nature and contents of container

30, 60 or 90 tablets in clear blister (PVC/Aluminium).
Not all pack sizes may be marketed.

6.6  Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7.  MARKETING AUTHORIZATION HOLDER

[To be completed nationally]

8.  MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9.  DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]