0001/02

Dear patient,
Please read the following Patient Information Leaflet carefully, as it contains important information about what you should bear in mind when using this drug. If you have any questions, please consult your doctor or pharmacist.

Patient Information Leaflet

SIOFOR® 850

Active substance: metformin hydrochloride

Composition
1 film-coated tablet contains:
Pharmacologically active substance:
Metformin hydrochloride 850 mg
Other constituents:
Colloidal anhydrous silica, povidone, magnesium stearate, cellulose acetate phthalate, diethyl phthalate, macrogol 4000.

Dosage form and contents
Siofor® 850 is available in packages of 30 film-coated tablets (N1) and 120 film-coated tablets (N2).

Substance or indication group
Biguanide derivative, oral antidiabetic.

Pharmaceutical entrepreneur and manufacturer
BERLIN-CHEMIE AG
Glienicker Weg 125 D-12489 Berlin
Telephone: (030) 6707 – 0 Telefax: (030) 6707 – 2120

Uses
Non-insulin-dependent diabetes (type 2 diabetes mellitus), particularly in obesity, if it is not possible to adjust the metabolism satisfactorily through appropriate diet and exercise alone.

Siofor® 850 can also been combined with sulphonylureas (other special tablets for diabetes, type 2 diabetes mellitus) if the contra-indications are observed.

Contra-indications
When must you not take Siofor® 850?
Siofor® 850 must not be taken if the following risks exist:
- impairment to kidney function;
- impairment to liver function;
- derangement of the sugar metabolism (excretion of acetone in the urine, precoma, diabetic coma);
- severe functional impairment of the heart or circulation (cardiovascular functional impairment), including peripheral arterial blood flow disturbances (arterial occlusive diseases);
- lung disease with impairment to lung function (respiratory insufficiency);
- a lack of oxygen in the body tissues (hypoxic states, e.g. due to anaemia, gangrene, collapse, shock);
- distinct diabetic retina disease (diabetic retinopathy above stage I);
- protein-degenerating (catabolic) states, for example tumour disease;
- severe chronic or severe acute infections;
- alcoholism;
- known allergy to metformin hydrochloride or the other constituents contained in Siofor® 850.

Siofor® 850 must be withdrawn:
- before planned major surgical procedures (operations under general anaesthetic);
- before X-ray examinations with intravenous administration of contrast media (see precautions);
- in slimming diets (reduction diet) with food consumption of less than 1000 kcal or 4200 kJ/day;
- in planned or existing pregnancy and during the breast-feeding period.

In these cases, the doctor will institute a different blood sugar-lowering therapy (e.g. insulin).

Siofor® 850 is not indicated in the presence of:
- insulin-dependent diabetes (type 1 diabetes mellitus);
- non-insulin-dependent diabetes (type 2 diabetes mellitus) in which the therapy with sulphonylureas has become inadequate after initially adequate metabolic adjustment (complete secondary failure of sulphonylurea therapy in type 2 diabetes mellitus).

When must you only take Siofor® 850 after consulting your doctor?
Age over 65 years

In advanced age, a certain risk exists for therapy with Siofor® 850. Patients over the age of 65 more frequently display impairments to organ functions and/or have accompanying diseases – conditions which can increase the risk of over-acidification of the blood with lactic acid (lactic acidosis) under treatment with metformin. The doctor treating you will check whether your state of health allows the use of Siofor® 850.

What must you bear in mind in pregnancy and the breast-feeding period?
Insufficient experience exists of use during pregnancy. There is evidence of increased perinatal mortality of exposed children, but this is possibly attributable to inadequate control of the underlying disease by metformin hydrochloride in pregnancy. Insulin should be regarded as the preferred medication during pregnancy.
No experience exists on the breast-feeding period. It is not known whether metformin or metabolites are excreted into the breast-milk. If use in the breast-feeding period is necessary, weaning off should take place.

What must be taken into consideration with children and the elderly?
Siofor® 850 must not be taken in insulin-dependent diabetes (type 1 diabetes mellitus). No experience exists on therapy of the very rare non-insulin-dependent diabetes in young adults (the so-called MODY diabetes) with Siofor® 850.
As the kidney function declines in people of advanced age, and the risk of over-acidification of the blood with lactic acid exists in the case of impairment to kidney function, the kidney function should be investigated regularly in these patients (determination of the serum creatine value and of creatinine clearance if necessary), and treatment may only be continued if normal kidney function has been verified. It may be necessary to reduce the dose in elderly patients.

Precautions for use and warnings
Which precautions must be borne in mind?
As the risk of accumulation of metformin hydrochloride in the body, and therefore the risk of over-acidification of the blood with lactic acid, is determined above all by the kidney function, verified normal kidney function is a prerequisite for a therapy with Siofor® 850.
Before the beginning of therapy and at six-monthly intervals (possibly earlier, e.g. in the case of interim infections), kidney function values (serum creatinine) and, if necessary, creatinine clearance must be determined in elderly patients for example.

Liver function values must also be monitored before the beginning of therapy and during treatment, as the breakdown of lactic acid may be impaired in the case of disturbances to liver function.

It is not possible to rule out a disturbance to vitamin B_{12} metabolism in isolated cases. Blood count monitoring should therefore be conducted annually.

It must be established whether the above contra-indications have occurred.

If you are scheduled to have an X-ray examination with administration of contrast media into a blood vessel, treatment with Siofor® 850 must be interrupted 2 days before the examination due to the risk of acute kidney failure, and not recommenced until 2 days after the examination.
Treatment with Siofor® 850 must also be interrupted for these times in the case of operations under general anaesthetic.

In exceptional cases, in combined treatment with sulphonylurea preparations or on combined use with other drugs (see interactions), there may be an undesirably pronounced lowering of the blood sugar (hypoglycaemia). The signs of this may be: sudden sweating, trembling, palpitations, nervousness, intense hunger, tingling in the mouth region, paleness, headache, drowsiness, sleep disturbances, anxiety, unsteady movements, irritability, depressive mood. In advancing low blood sugar, you may become unconscious. You can rectify mild low blood sugar by immediately taking glucose, sugar or food containing sugar. If you are unable to rectify the low blood sugar immediately, a doctor must be called urgently.

The consumption of alcohol entails a risk for low blood sugar and dangerous over-acidification of the blood with lactic acid occurring. You should therefore avoid alcohol during therapy with Siofor® 850.

If pregnancy occurs under treatment with Siofor® 850 or you plan a pregnancy, then a doctor must be sought immediately, so that they can carry out a transfer of your diabetes therapy.

What must you bear in mind with road traffic or when working with machines or without a secure foothold?
Siofor® 850 itself does not generally lead to the ability to drive being impaired. Low blood sugar (hypoglycaemia), which impairs the ability to take part actively in road traffic, is also generally unlikely. In a combination treatment with sulphonylureas or other medicines with a blood sugar-lowering effect, the ability to drive and to operate machines may be impaired by possible low blood sugar (hypoglycaemia).

Interactions with other drugs
Which other drugs influence the effect of Siofor® 850?
During a long-term treatment with Siofor® 850, the beginning and the ending of an additional therapy with medicines can interfere with the blood sugar adjustment.

An intensification of the blood sugar-lowering effect is possible on simultaneous use of drugs such as:
- insulin, oral antidiabetics (e.g. sulphonylureas, acarbose);

- oxytetracycline (antibiotic);
- ACE inhibitors (for high blood pressure);
- fibrates (for high blood fats);
- cyclophosphamide or derivatives (for tumour growth), meaning that, unlike with the action of Siofor® 850 alone, low blood sugar (hypoglycaemia) is possible. (For signs of low blood sugar and measures in low blood sugar, see precautions).

Beta-receptor blockers and antisympathotonics (for high blood pressure) such as clonidine, reserpine and guanethidine can also lower the blood sugar if taken permanently; however, it is their characteristic of masking the signs of low blood sugar (hypoglycaemia) that is significant.

Substances that delay the excretion of metformin hydrochloride, for example cimetidine (for stomach diseases), increase the risk of over-acidification of the blood with lactic acid.

The blood sugar-lowering effect of Siofor® 850 can be reduced by the simultaneous use of drugs such as:
- glucocorticoids;
- oestrogen-progestogen combinations ("the pill", or drugs for hormone therapy during the menopause);
- epinephrine and other sympathomimetics;
- glucagon;
- thyroid hormones;
- thiazide and loop diuretics (for high blood pressure or removing water);
- diazoxide;
- phenothiazides (tranquillisers or sleeping tablets);
- nicotinic acid derivatives.

Substances that reduce the uptake of Siofor® 850, for example guar and cholestyramine, lead to a reduction in the effect of Siofor® 850.

How does Siofor® 850 influence the effect of other drugs?

During a treatment with Siofor® 850, the excretion of phenprocoumon and possibly other coumarins (drugs for inhibiting blood clotting) is accelerated. If Siofor® 850 is started or withdrawn during an existing coumarin therapy, close monitoring of blood clotting must be conducted.

Please bear in mind that this information can also apply to drugs used until recently.

Which stimulants, food and drink should you avoid?

Both regular and occasional drinking of alcohol poses a risk for low blood sugar and a dangerous over-acidification of the blood with lactic acid occurring. You should therefore not drink alcohol during therapy with Siofor® 850.

Dosage instructions, method and length of use

The following information applies unless your doctor has prescribed Siofor® 850 otherwise. Please keep to the instructions for use, as Siofor® 850 is otherwise unable to work properly!

How much Siofor® 850 should you take and how often?

The adjustment of the diabetic to Siofor® 850 must only be carried out by the doctor and must be adapted to dietary adjustment. Therapy should be tapered in, beginning with 1 Siofor® 850 film-coated tablet daily (equivalent to 0.85 g metformin hydrochloride daily).

If adjustment of the metabolism is inadequate, the dose is increased, under the direction of the doctor, stepwise at intervals of a few days to about two weeks to the therapeutically required dose.

The required daily doses are between 1 to 3 Siofor® 850 film-coated tablets daily (equivalent to 0.85 to a maximum 2.55 g metformin hydrochloride daily). In general, the daily doses of 2 Siofor® 850 film-coated tablets daily (equivalent to 1.7 g metformin hydrochloride daily) are adequate.

Daily doses of over 3 Siofor® 850 film-coated tablets daily (equivalent to over 2.55 g metformin hydrochloride daily) do not generally achieve a further increase in effect.

How and when should you take Siofor® 850?

Swallow the film-coated tablets whole with liquid (e.g. a glass of water) with meals. If your necessary daily dose is 2 or more film-coated tablets, divide the tablets over 2 or 3 single doses with main meals. Dividing the daily dose is less important for a good adjustment of blood sugar levels than for better tolerability.

As the requirement for Siofor® 850 can fall when blood sugar adjustment improves, the necessity for prescription should be reviewed regularly by your doctor, for example by lowering the dose, or, in the case of lower daily doses, by an attempt at withdrawal. This particularly applies in elderly patients to reduce the risk of over-acidification of the blood with lactic acid.

If the effect of Siofor® 850 alone is not sufficient to normalise the blood sugar, Siofor® 850 can be combined with sulphonylureas.

How long should you take Siofor® 850?

If it is not possible to adjust the metabolism adequately with other measures such as weight loss, exercise and appropriate diet, non-insulin-dependent diabetes (type 2 diabetes mellitus) must be treated permanently with a medicine. The doctor treating you will decide as to the length of treatment with Siofor® 850.

Overdose and other incorrect use

What must be done if Siofor® 850 has been taken in excessive quantities (intentional or accidental overdose)?

An intoxication with Siofor® 850 does not lead to low blood sugar (hypoglycaemia), but entails the risk of over-acidification of the blood with lactic acid. If over-acidification of the blood with lactic acid is suspected, or there is evidence in the medical history of a metformin overdose, for example in suicidal intent, emergency admission to a hospital is necessary.

The signs of over-acidification of the blood with lactic acid beginning can resemble the direct side effects of metformin in the gastro-intestinal tract: nausea, vomiting, diarrhoea and abdominal pain. The full-blown picture with muscle pain, excessive increase in breathing (hyperventilation), clouding of consciousness and coma may develop within hours. Completely developed over-acidification of the blood with lactic acid caused by metformin leads to death in 50 % of cases.

Counter-measures

Immediate emergency admission to a hospital!

Washing the blood by means of an artificial kidney (haemodialysis) is the most effective measure for removing lactic acid and metformin. The circulation must be stabilised, the over-acidification (acidosis) compensated for, and the lack of oxygen in the blood and body tissue (hypoxia) must be rectified.

What must you bear in mind if you have taken too little Siofor® 850 or have forgotten to use it?

If you have forgotten to take Siofor® 850, continue to take Siofor® 850 as prescribed by the doctor, without making up for the forgotten administration through an increased dose.

What must you bear in mind if you interrupt or prematurely end treatment?

If you discontinue treatment without being directed to do so by a doctor, you must expect that blood sugar levels will rise uncontrollably and that the late complications of diabetes, such as eye, kidney and vessel damage will occur in the long term.

Side effects

Which side effects can occur on use of Siofor® 850?

Gastro-intestinal complaints such as nausea, vomiting, abdominal pain, flatulence, weight loss, diarrhoea and metallic taste occur at the beginning of therapy in 5 –20 % of those treated. Interruption of therapy is generally not necessary, as the complaints usually recede, even if the dosage is unchanged. Any diarrhoea that might persist stops after withdrawal of therapy. The frequency and severity of the gastro-intestinal complaints can be reduced by a slow dose increase and taking Siofor® 850 with meals.

Headache, dizziness and tiredness occur occasionally.

In rare cases, there may be allergic reactions of the skin.

One case of inflammation of the vessels and pneumonia under therapy with metformin was reported.

Due to a reduction in the uptake of vitamin B_{12} and folic acid there may in isolated cases be a lowering in the number of red blood cells (megaloblastic anaemia). Annual monitoring of the blood count is therefore required during therapy with Siofor® 850. In the case of a disturbance, the blood count change can be rectified by an additional B_{12} administration.

In very rare cases, over-acidification of the blood with lactic acid, which can assume life-threatening proportions (e.g. coma), may occur under treatment with Siofor® 850.

The causes of over-acidification of the blood may, besides overdose, be the existence or occurrence of contra-indications (see "Contraindications"). The contra-indications must therefore be strictly observed.

The signs of over-acidification of the blood with lactic acid beginning can resemble the side effects of metformin in the gastro-intestinal tract: nausea, vomiting, diarrhoea and abdominal pain. The full-blown picture with muscle pain and cramps, an excessive increase in breathing, as well as clouding of consciousness and coma, can develop within hours.

Therefore, if these symptoms occur under therapy with Siofor® 850, tablet-taking should be interrupted and a doctor sought or notified immediately, so that counter-measures (possibly emergency admission to a hospital) can be instituted.

If you observe that you have side effects not listed in this package insert, please inform your doctor or pharmacist.

Which counter-measures should be taken in the case of side effects?

Please inform your doctor immediately. Only the doctor can decide whether you should continue taking the drug prescribed.

If over-acidification of the blood with lactic acid is suspected, the immediate assistance of a doctor should be sought (see "Overdose and other incorrect use").

Notes and information on the shelf life of the drug

The expiry date is printed on the folding box and the push-through package. Do not use this drug after this date!

Last revised

March 2001

This drug is on the market in accordance with legal transitional provisions. Investigation by the authorities of the pharmaceutical quality, efficacy and safety has not yet been completed.

Keep drugs out of the reach of children!

Marketing Authorization Holder:
BERLIN-CHEMIE AG - Berlin - Germany
Further informations are available on request:

./644 / V 022635/01