GETEMIN SR 750 MG PROLONGED RELEASE TABLET

PL 03759/0249

UKPAR

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GETEMIN SR 750 MG PROLONGED RELEASE TABLET

PL 03759/0249

LAY SUMMARY

The MHRA granted Lipha Pharmaceuticals Ltd a Marketing Authorisation (licence) for the medicinal product Getemin SR 750 mg prolonged release tablet (PL 03759/0249). This medicine is available by prescription only and is used for the treatment of Type 2 (non-insulin dependent) diabetes mellitus when diet and exercise changes alone have not been enough to control blood glucose (sugar).

Getemin SR 750 mg prolonged release tablets contain the active ingredient metformin hydrochloride and are used in the treatment of diabetes.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Getemin SR 750 mg prolonged release tablets outweigh the risks, hence a Marketing Authorisation has been granted.

GETEMIN SR 750 MG PROLONGED RELEASE TABLET

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Getemin SR 750 mg prolonged release tablet (PL 03759/0249) to Lipha Pharmaceuticals Ltd on 21 February 2008. This is a prescription-only medicine (POM).

This is an abridged hybrid application for Getemin SR 750 mg prolonged release tablet submitted under Article 10.3 of Directive 2001/83/EC, as amended. The marketing authorisation holder is Lipha Pharmaceuticals Ltd. The applicant claims that Getemin SR 750 mg prolonged release tablet is a line extension from the declared reference product.

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) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
(3) and delay of 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, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

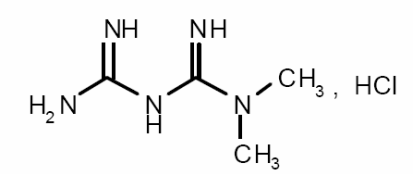
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

INN: Metformin hydrochloride

Structure



Molecular formula: $C_4H_{12}ClN_5$

Relative Molecular Mass = 165.6 g/mol

Metformin hydrochloride is present as white crystals and is freely soluble in water, slightly soluble in alcohol and practically insoluble in acetone and methylene chloride.

A valid Certificate of Suitability has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active metformin hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 5 years.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely magnesium stearate, sodium carboxymethylcellulose, hypromellose, and purified water. All excipients used comply with their respective European Pharmacopoeia monograph.

Satisfactory certificates of analysis have been provided for all excipients.

It was stated that the magnesium stearate was of vegetable origin.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce a product containing metfomin hydrochloride that are tolerable and which could be considered as generic product to the originator product Glucophage SR 500 mg Prolonged release tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

Dissolution and impurity profiles
Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished Product Specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is packaged in to PVC/Aluminium blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with no storage conditions has been set. This is acceptable.

Bioequivalence/Bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Bioequivalence has been demonstrated to the reference product.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion

Data provided in support of pharmaceutical quality aspects of the application comply with regulatory and, where applicable, official standards. These demonstrate that the product can consistently be produced to an acceptable standard and will comply with that standard over the declared shelf-life, when stored as directed. It is recommended that Marketing Authorisation should be granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is an abridged hybrid application for Getemin SR 750 mg prolonged release tablet submitted under Article 10.3 of Directive 2001/83/EC, as amended. The marketing authorisation holder is Lipha Pharmaceuticals Ltd. The application claim that the release profile of the new formulation is similar to that of Glucophage SR 500 mg prolonged release tablets (PL 11648/0054) which are manufactured by Merck Ltd. Glucophage 500 mg film-coated tablets were first authorised in the UK in 21/09/1982 by Lipha Pharmaceuticals Ltd and hence have been marketed in the EEA for at least 10 years.

2. INDICATIONS

Satisfactory. Consistent with originator.

3. DOSE & DOSE SCHEDULE

Satisfactory. Consistent with originator.

4 TOXICOLOGY

No new data.

5. CLINICAL PHARMACOLOGY

Pre-defined bioequivalence acceptance criteria

The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and C_{max}. This is satisfactory. Duration of sampling following dosing and sampling frequency around T_{max} is considered adequate.

The Washout period, Randomisation scheme and method of data analysis are considered acceptable.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

	Fed HV	Fasted HV
C_{max} (ng/mL)	1.083 (1.032- 1.137)	1.058 (0.949- 1.181)
AUC_t (ng.h/mL)	1.00 (0.969 – 1.032)	1.010 (0.911 – 1.121)
AUC_∞ (ng.h/mL)	0.99 (0.967 – 1.033)	1.018 (0.920 – 1.127)

Assessor's Comment

The standard pharmacokinetic parameters suggest that the two formulations dose per dose fall within the conventional definitions of bioequivalence with 90% CI between 80-125% for all. It is interesting to note that the 90% CI are narrower in the fed state although the results are well within the limits.

The study design is adequate although the number of subjects are few. This however was based on statistical power calculations using pilot data and it is not surprising that the estimates were a good fit suggesting that the two formulations do not significantly differ in release and absorption profiles.

Assessor's Conclusion on Bioequivalence
Based on the studies submitted, the two dose formulations (dose per dose) could be considered bioequivalent. This permits substitution for dose per dose but no alterations in posology would be possible based on these studies.

6. EFFICACY
No new data.

7. SAFETY
No new data.

8. EXPERT REPORTS
The expert reports include an update to the original report submitted with the 500mg SR application and these are acceptable.

9. PATIENT INFORMATION LEAFLET (PIL)
Satisfactory.

10. LABELLING
Satisfactory.

11. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
Satisfactory. Fully consistent with originator.

12. DISCUSSION
The 750mg SR formulation has been shown to be bioequivalent (fed and fasted single dose studies) with the 500mg SR formulation (dose per dose at 1500mg). It is therefore acceptable as replacement at this dose.

The formulation would be approvable only as a replacement at the specified dose with the SPC that is identical to the existing formulation.

13. MEDICAL CONCLUSION
Marketing authorisation is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Getemin SR 750 mg prolonged release tablet are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Based on the submitted bioequivalence study Getemin SR 750 mg prolonged release tablet are considered bioequivalent with Glucophage SR Tablets 500mg when administered at the same dose.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and Labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data support the new strength product within the existing approved posology for Glucophage prolonged release tablets. The risk benefit is, therefore, considered to be positive.

GETEMIN SR 750 MG PROLONGED RELEASE TABLET

PL 03759/0249

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 6th February 2006
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 9th February 2006
3	Following assessment of the applications the MHRA requested further information relating to the quality dossier on 27th September 2006 and 7th March 2007
4	The applicant responded to the MHRA's requests, providing further information to the quality section on 27th February 2007 and 30th March 2007
5	The application was determined on 21st February 2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Getemin SR 750 mg prolonged release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet
White capsule-shaped, biconvex tablet, debossed on one side with '750' and on the other side with 'Merck'.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Getemin SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Monotherapy and combination with other oral antidiabetic agents:
Getemin SR 750 mg is intended for patients who are already treated with metformin tablets (prolonged or immediate release).
The dose of Getemin SR 750 mg should be equivalent to the daily dose of metformin tablets (prolonged or immediate release), up to a maximum dose of 1500 mg given with the evening meal.
After 10 to 15 days, it is recommended to check that the dose of Getemin SR 750 mg is adequate on the basis of blood glucose measurements.
Combination with insulin:
For patients already treated with metformin and insulin in combination therapy, the dose of Getemin SR 750 mg should be equivalent to the daily dose of metformin tablets, up to a maximum of 1500 mg given with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements.
Elderly: Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).
Children: In the absence of available data, Getemin SR should not be used in children.

4.3 CONTRAINDICATIONS

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic 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 agents (see 4.4 Special warnings and precautions for use).
- 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
- Lactation (see section 4.6)

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, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

Diagnosis:

Lactic acidosis is characterised by acidotic 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, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9).

Renal function:

As metformin is excreted by the kidney, creatinine clearance (this can be estimated using the Cockcroft-Gault formula) and/or serum creatinine levels should 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 creatinine clearance at the 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 an NSAID.

Administration of iodinated contrast agent:

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, 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.

Surgery:
Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not be usually resumed earlier than 48 hours afterwards.
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.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulphonylureas.
- The tablet shells may be present in the faeces. Patients should be advised that this is normal.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Inadvisable combinations
Alcohol
Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition,
- hepatic insufficiency.

Avoid consumption of alcohol and alcohol-containing medications.
Iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin should be discontinued prior to, 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 (see 4.4 Special warnings and precautions for use).
Associations requiring precautions for use
Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic medicinal product during therapy with the other medicinal product and upon its discontinuation.
ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic medicinal product during therapy with the other medicinal product and upon its discontinuation.

4.6 PREGNANCY AND LACTATION

Pregnancy
To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or fœtal development, parturition or postnatal development (see also section 5.3)
When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Lactation
Metformin is excreted into milk in lactating rats. Similar data is not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Getemin SR monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.
However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (sulphonylureas, insulin, repaglinide).

4.8 UNDESIRABLE EFFECTS

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Getemin SR was similar in nature and severity to that reported in patients treated with metformin immediate release.
The following undesirable effects may occur with metformin.
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 and isolated reports.
Metabolism and nutrition disorders
very rare: Decrease of vitamin B12 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.
very rare: Lactic acidosis (see 4.4. Special warnings and precautions for use).
Nervous system disorders
Common: Taste disturbance
Gastrointestinal disorders
very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.
Hepatobiliary disorders:
Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.
Skin and subcutaneous tissue disorders
very rare: Skin reactions such as erythema, pruritus, urticaria

4.9 OVERDOSE

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ORAL ANTI-DIABETICS

(A10BA02: Gastrointestinal tract and metabolism)

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) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
(3) and delay of 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, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Clinical efficacy :

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetic patients treated with immediate release metformin as first-line therapy after diet failure. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/ 1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/ 1000 patient-years), p=0.0034.
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/ 1000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1000 patient-years versus diet alone 20.6 events/ 1000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/ 1000 patient-years (p=0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years (p=0.01)

For metformin used as second-line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following a single oral administration of 1500 mg of Getemin SR 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Getemin SR 750 mg was shown to be bioequivalent to Glucophage SR 500 mg at a 1500 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

The bioequivalent product shows the following properties:

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of metformin prolonged release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets b.i.d.

Intrasubject variability of C_{max} and AUC of metformin prolonged release tablets is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected).

Metformin absorption from the prolonged release formulation is not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000 mg of metformin prolonged release tablets.

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 (Vd) ranged between 63-276 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.

5.3 PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Magnesium stearate

Carmellose sodium
Hypromellose

6.2 INCOMPATIBILITIES
None

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
14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 180 or 600 tablets in blister strips composed of aluminium foil + PVC or PVC/PVDC (60 g/m² or 90g/m²).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Lipha Pharmaceuticals Ltd
Harrier House
High Street
West Drayton
Middlesex
UB7 7QG
United Kingdom

8 MARKETING AUTHORISATION NUMBER
PL 03759/0249

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/02/2008

10 DATE OF REVISION OF THE TEXT
21/02/2008

PATIENT INFORMATION LEAFLET

GETEMIN SR

750milligrams Prolonged release tablets
metformin hydrochloride

MERCK

This medicine is intended for **adult** patients only

Read all of this leaflet carefully before you start taking this medicine.
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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT GETEMIN SR IS AND WHAT IT IS USED FOR

Getemin SR prolonged release tablets contain the active ingredient metformin hydrochloride and belong to a group of medicines called biguanides, used in the treatment of diabetes.

Getemin SR is used for the treatment of Type 2 (non-insulin dependent) diabetes mellitus when diet and exercise changes alone have not been enough to control blood glucose (sugar). Insulin is a hormone that enables body tissues to take glucose from the blood and to use it for energy or for storage for future use. People with Type 2 diabetes do not make enough insulin in their pancreas or their body does not respond properly to the insulin it does make. This causes a build-up of glucose in the blood which can cause a number of serious long-term problems so it is important that you continue to take your medicine, even though you may not have any obvious symptoms. Getemin SR makes the body more sensitive to insulin and helps return to normal the way your body uses glucose.

Getemin SR Prolonged Release Tablets are specially made to release the drug slowly in your body and therefore are different to many other types of tablet containing metformin.

2. BEFORE YOU TAKE GETEMIN SR

Do not take Getemin SR if:
- you are allergic to metformin or to any of the other ingredients which are listed later on in the leaflet (see under '6. Further information'),
- you have ketosis (this is a symptom of uncontrolled diabetes in which substances called 'ketone bodies' accumulate in the blood – you may notice that your breath has an unusual, fruity odour),

- you have long-term kidney or liver problems,
- you have had serious complications with your diabetes or other serious conditions which resulted in rapid weight loss, nausea, vomiting or dehydration,
- you have a severe infection or have recently suffered a severe injury,
- you need to have an X-ray examination involving the injection of a dye into the bloodstream,
- you have been treated for heart problems or have recently had a heart attack or have severe circulatory problems or breathing difficulties,
- you are a heavy drinker of alcohol,
- you are under 18 years of age.

Take special care with Getemin SR
After you have started taking your medicine:
If you have diabetes you should have your blood or urine tested for sugar regularly. You should return to your doctor at least once a year to check the function of your kidneys (more often if you are elderly or if you have kidney problems).

If you start to lose weight unexpectedly or suffer severe nausea or vomiting, uncontrolled rapid breathing or abdominal pains, stop taking the medicine and tell your doctor straight away. This can be a sign of a rare, but serious, complication with your diabetes called 'lactic acidosis' which means that there is too much acid in the blood (see under '4. Possible side effects').

You may see some remains of the tablets in your stools. Do not worry- this is normal for this type of tablet.

If you need to have an X-ray examination involving the injection of a dye, tell the doctor that you take Getemin SR as you may need to stop taking it for a few days afterwards. Tell your doctor if you are going to have an operation under general anaesthetic, as you may need to stop taking Getemin SR for a couple of days before and after the procedure.

You should continue to follow any dietary advice that your doctor has given you and you should make sure that you eat carbohydrates regularly throughout the day.

Do not stop taking this medicine without speaking to your doctor.

Taking Getemin SR with other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

If you are taking any of the following medicines, your blood sugar levels may need to be checked more often and your dose adjusted:

- Steroids such as prednisolone, mometasone, beclometasone
- Beta-2-agonists such as salbutamol used for asthma
- Diuretics (water tablets) such as bendroflumethiazide
- ACE inhibitors such as lisinopril, enalapril

You should avoid drinking alcohol and using alcohol-containing medicines as this will increase the risk of lactic acidosis (see under '4. Possible side effects').

Taking Getemin SR with food and drink
You should take Getemin SR with or immediately after food.

Pregnancy and breast feeding
Do not take Getemin SR if you are pregnant or breast feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Getemin SR taken on its own does not cause 'hypos' (symptoms of low blood sugar or hypoglycaemia, such as faintness, confusion and increased sweating) and therefore should not affect your ability to drive or use machinery. You should be aware, however, that Getemin SR taken with other antidiabetic medicines can cause hypos, so in this case you should take extra care when driving or operating machinery.

3. HOW TO TAKE GETEMIN SR
Your doctor may prescribe Getemin SR for you to take on its own, or in combination with other oral antidiabetic medicines or insulin.
Always take Getemin SR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow the tablets whole with a glass of water, do not chew.

Getemin SR is intended for patients already being treated with metformin hydrochloride tablets. You will receive Getemin SR at an equivalent dose to your previous metformin hydrochloride dose. The maximum daily dose is two tablets of Getemin SR 750 milligrams.

Normally, you should take the tablets once a day, with your evening meal.

If you take more Getemin SR than you should
If you take extra tablets by mistake you need not worry, but if you have unsual symptoms, contact your doctor. If the overdose is large, lactic acidosis is more likely and this is a medical emergency requiring treatment in hospital (see also under '4. Possible side effects).

If you forget to take Getemin SR
Take it as soon as you remember with some food. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Getemin SR can cause side effects, although not everybody gets them. Possible side effects are listed by frequency as follows:
Very common (affects more than 1 person in 10):
- Diarrhoea, nausea, vomiting, stomach ache or loss of appetite. If you get these, do not stop taking the tablets as these symptoms will normally go away in about 2 weeks. It helps if you take the tablets with or immediately after a meal.

Common (affects less than 1 person in 10, but more than 1 person in 100):
- Taste disturbance.

Very rare (affects less than 1 person in 10,000):
- Decreased vitamin B12 levels,
- Lactic acidosis (too much acid in the blood). If you lose weight unexpectedly, feel sick with stomach pains and have rapid uncontrolled breathing you should stop taking the medicine and tell your doctor straight away.

- Skin rashes including redness, itching and hives,
- Abnormal liver function tests and hepatitis (inflammation of the liver) which may result in jaundice. If you develop yellowing of the eyes and/or skin contact your doctor immediately.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE GETEMIN SR

Keep Getemin SR tablets out of the reach and sight of children.

Do not use them after the expiry date that is printed on the pack after "Use before:". The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What the tablets contain

Each prolonged release tablet contains 750 milligrams of the active ingredient metformin hydrochloride. The other ingredients are magnesium stearate, carmellose sodium and hypromellose.

What Getemin SR looks like and contents of the pack

The tablets are white and capsule-shaped with '750' on one side and 'Merck' on the other side.

Getemin SR is supplied in packs of 28 and 56 prolonged release tablets.

Getemin SR 750 mg Prolonged Release Tablets are manufactured for Lipha Pharmaceuticals Ltd, Harrier House, High Street, West Drayton, Middlesex, UB7 7QG, UK by Merck KGaA, Frankfurter Strasse 250, Darmstadt, D-63293, Germany.

This leaflet was last revised in February 2008.

Useful tips

- If you smoke, try to stop,
- Take regular exercise,
- Drink as little alcohol as possible,
- Look after your feet. Ask about this at the surgery or hospital,
- Carry a card, bracelet or disk saying you are diabetic,
- Visit your diabetic clinic regularly.

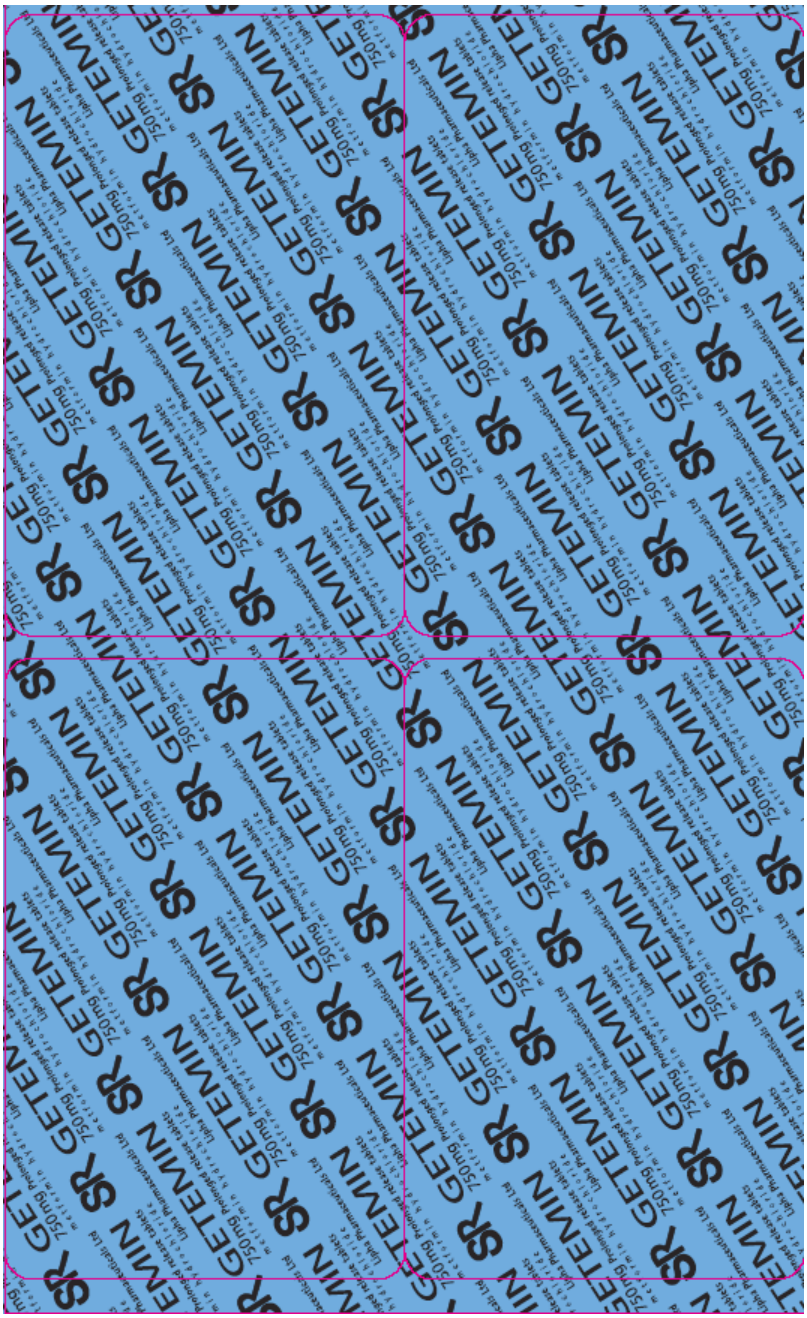
If you want more information about diabetes contact:

Diabetes UK Central Office
Macleod House
10 Parkway
London NW1 7AA

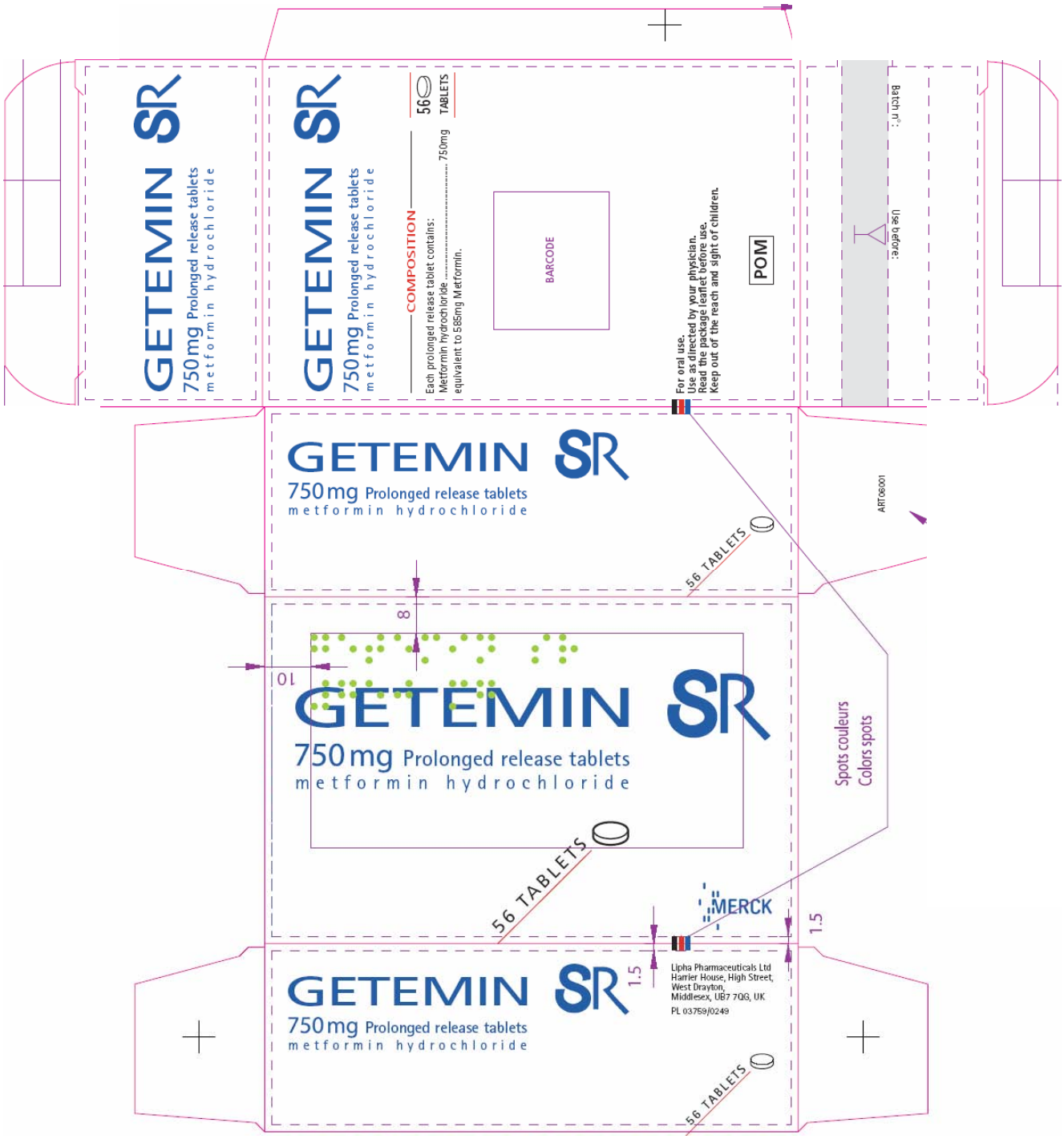
Tel: 020 7424 1000
www.diabetesuk.co.uk

LABELLING

Blister:



Carton:


GETEMIN SR
750mg Prolonged release tablets
metformin hydrochloride
COMPOSITION
Each prolonged release tablet contains:
Metformin hydrochloride 750mg
equivalent to 585mg Metformin.
56 TABLETS
BARCODE
For oral use.
Use as directed by your physician.
Read the package leaflet before use.
Keep out of the reach and sight of children.
POM
Batch n°:
Use before:
ART06001
8
10
Spots couleurs
Colors spots
MERCK
1.5
Lipha Pharmaceuticals Ltd
Harrier House, High Street,
West Drayton,
Middlesex, UB7 7QG, UK
PL 03759/0249