

**GLUCOPHAGE SR 1000MG PROLONGED-RELEASE TABLETS
PL 11648/0067**

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**GLUCOPHAGE SR 1000MG PROLONGED-RELEASE TABLETS
PL 11648/0067**

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Merck Serono Limited a Marketing Authorisation (licence) for the medicinal product Glucophage SR 1000mg Prolonged Release Tablets (PL 11648/0067) on 16th September 2008. This is a prescription-only medicine for the treatment of diabetes in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate control of sugar in the blood. This product contains the active ingredient metformin hydrochloride.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Glucophage SR 1000mg Prolonged Release Tablets (PL 11648/0067) outweigh the risks; hence a Marketing Authorisation has been granted.

**GLUCOPHAGE SR 1000MG PROLONGED-RELEASE TABLETS
PL 11648/0067**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Merck Serono Limited a Marketing Authorisation for the medicinal product Glucophage SR 1000mg Prolonged Release Tablets (PL 11648/0067) on 16th September 2008. The product is a prescription-only medicine.

The application was submitted as an abridged hybrid national application, according to Article 10.3 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Glucophage 500mg Film-Coated Tablets (PL 03759/0012), licensed to Lipha Pharmaceuticals on 21st September 1982 and hence has been marketed in the EEA for at least 10 years.

The biguanide metformin hydrochloride is an oral antihyperglycaemic agent used in the management of diet-failed non-insulin dependent diabetes mellitus (NIDDM). It is especially used in overweight patients or in those for whom attempts to achieve acceptable control with sulfonylurea therapy and physical activity have failed. Since metformin does not promote weight gain or hypoglycaemia, it is considered as first-line pharmacotherapy in obese patients with NIDDM inadequately controlled by non-pharmacological measures. Metformin appears similarly effective in the pharmacological management of NIDDM in non-obese patients.

Metformin acts by reducing elevated blood glucose levels, predominantly by improving hepatic and peripheral tissues sensitivity to insulin without affecting secretion of this hormone.

Glucophage SR 1000mg Prolonged Release Tablets (PL 11648/0067) is indicated for the treatment of type 2 diabetes mellitus. The proposed indications for this product are the same as for the innovator product.

PHARMACEUTICAL ASSESSMENT

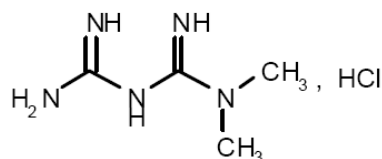
DRUG SUBSTANCE

Metformin hydrochloride

INN/Ph.Eur name: Metformin hydrochloride

Chemical name: 1-(diaminomethylidene)-3,3-dimethyl-guanidine

Structural formula:



Molecular formula: C₄H₁₁ClN₅

Molecular weight: 165.63

Physical form: White crystalline appearance

Solubility: Freely soluble in water. It is slightly soluble in alcohol and practically insoluble in acetone and in methylene chloride.

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a certificate of suitability for the active substance manufacturer.

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 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, when stored at appropriate storage instructions.

DRUG PRODUCT**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely sodium carboxymethylcellulose, hypromellose and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contains material of animal or human origin. There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to those 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. Satisfactory process validation data have been provided on three commercial scale batches.

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

All strengths of tablet are packaged in polyvinylchloride/polyvinylidenechloride/aluminium blister strips in pack sizes of 14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 180 or 600 tablets.

Stability

Stability studies were performed on three commercial batches of the finished product and in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies were within specified limits. These data support a shelf-life of 3 years, with no specific storage conditions, which is satisfactory. The company commits that the first three commercial batches of the 1000mg tablets will be placed on on-going stability studies.

This is satisfactory.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.3 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

1 INTRODUCTION

This is a national application for a line extension of an existing modified release form of metformin (Glucophage SR). The current MAH (Merck Serono Limited) seek a further strength of 1000mg strength. Metformin (Gluophage) has been in use for a number of years and the 500 mg modified release formulation was authorised in September 2003 (PL 11648/0054). The 750mg modified release formulation was authorised in early 2008.

The original application was based on clinical data including single dose, steady state and fed state studies and clinical studies demonstrating effectiveness of 500mg modified release formulation in comparison to the immediate release preparations.

1.1 TYPE OF APPLICATION AND REGULATORY BACKGROUND

The current application is for a further strength of the modified release preparation based on the same clinical studies but in addition demonstration of bioequivalence between the Glucophage 1000mg SR (1 tablet) and Glucophage 500mg SR (2 tablets) as well as between 500mg SR and the newly formulated 750 mg SR preparations. The applicant has submitted the following studies;

1. A bioequivalence study between Glucophage 1000mg SR (1 tablet) and Glucophage SR 500mg (2 tablets) after single oral administrations in healthy volunteers in the fasted and fed state.
2. The original studies of 500mg modified release formulation
 - CV 138-021, 028, 031 in healthy volunteers
 - CV 138-035 in ty-2 diabetic subjects.
 - CV 18-010, 036 and 012 in type- DM
3. A set of BE studies between 500mg SR and 750mg SR (OL, random, active controlled)
 - CV 138-085 ; 2x 750 vs 3x 500mg tablets Fed state, in HV
 - CV 138- 082 : 2x 750 vs 3x 500mg tablets, Fasted state in HV
 - CV 138 -087; comparison of tablets from two manufacturing sites (2 X750mg)
4. A set of arguments regarding the studies applicable to 1000mg SR along with point 5.
5. A satisfactory clinical overview has been provided.

1.2 CLINICAL BACKGROUND

The applicant presents the following argument and reasoning;

The present national application for 'Glucophage XR 750 mg Prolonged Release Tablets' is a line extension, to the previously authorised product 'Glucophage XR 500 mg Prolonged Release tablets' PL 11648/0054. The 500 mg prolonged release tablet is itself a line extension of the immediate-release formulation, 'Glucophage 500 mg Film-coated Tablets' PL 03759/0012. The active ingredient of Glucophage XR 750

mg Prolonged Release Tablets is metformin hydrochloride, a biguanide well-established in the treatment of type 2 diabetes mellitus. Metformin has antihyperglycaemic effects, lowering both basal and postprandial plasma glucose in diabetic patients. It does not stimulate insulin secretion and therefore does not cause hypoglycaemia.

The immediate-release formulation of metformin is recommended to be taken two or three-times a day. The prolonged release formulation was developed to provide a once-daily dosage regimen, thereby offering simplicity of dosing, the potential for improved compliance, and consequently, improved glycaemic control. Intensification of treatment to reach glycaemic targets (HbA1C <7.0%) is a recommendation for good management in the 2005 revised UK Clinical Guidelines for type 2 diabetics endorsed by NICE, Diabetes UK and several Royal Colleges. A further benefit offered with the once-daily formulation is that of improved gastro-intestinal tolerability compared to the immediate release tablet.

Assessor's Comments

The reasoning follows logic and is acceptable. The applicant accepts that 1000mg SR tablets will not be for initiation of therapy but only as a replacement of existing therapy.

1.3 INDICATIONS & POSOLOGY

The indication sought is claimed to be the same as the 500mg SR formulation.

“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. Glucophage XR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.”

Assessor's Comments

The indication sought is identical to the existing formulation and the application is based on the Bioequivalence studies and the posology is identical to the 500mg tablets.

1.4 LEGAL STATUS

The only permissible legal status would be POM and renewable.

2 CLINICAL PHARMACOLOGY

2.1 BIOEQUIVALENCE

A randomised, open-label trial with two parallel two-way-crossover designs has been submitted. The objective of this study was to evaluate the bioequivalence between single doses of the test product (Glucophage XR 1000mg (one tablet); Merck KGaA, Germany) and the reference product (Glucophage XR 500mg (two tablets); Merck Santé, France) in healthy subjects in fed and fasted state.

Healthy male volunteers aged between 18 and 55 years entered the study.

Each subject received two single doses (Glucophage XR 1000mg, Glucophage XR 500mg) on two treatment days, separated by a wash out period of at least a week. Blood samples were collected at frequent intervals for up to 32 hours post-dose.

Bioequivalence between Glucophage XR 1000mg and Glucophage XR 500mg was evaluated based on the PK parameters C_{max} and $AUC_{0-\infty}$ of metformin hydrochloride in plasma (results are shown in the table below). Analysis of variance (ANOVA) has been performed on these primary variables. The model included effects for sequence, treatment and period. Based upon the residual (within-subject) variation, 90% confidence intervals for the ratio of geometric means (Test/Reference) were calculated. Within each group bioequivalence was concluded if the confidence intervals for the two ratios were included in the range 0.80 to 1.25. For t_{max} the Hodges-Lehmann estimates for the pair-wise treatment differences and the corresponding 95% confidence intervals were calculated.

A summary of all main pharmacokinetic parameters for Group 1 (fasted condition) and for Group 2 (fed condition) are shown below.

**Pharmacokinetic Parameters of Metformin in Plasma
(Geometric mean, Range, Arithmetic Mean and CV %)**

Treatment	C_{max} (ng/mL)	t_{max} * (h)	AUC_{0-t} (ng•h/mL)	$AUC_{0-\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	CL/f (L/h)	V_z / f (L/h)	MRT (h)
Group 1 (Fasted), n = 28								
A	962 (457-1850)	4.0 (1-5)	6433 (3021-12442)	6660 (3135-12593)	7.22 (2.26-13.5)	150.2 (79.4-319)	1565 (459-5542)	8.11 (4.74-11.9)
	1034 38.6	25.4	6814 34.2	7024 32.9	7.75 36.2	158.8 35.7	1876 62.1	8.25 18.8
B	1023 (502-1580)	4.0 (2-5)	6681 (3615-10697)	6914 (3700-10997)	7.52 (2.37-16.3)	144.6 (90.9-270)	1569 (799-4224)	7.96 (4.48-11.7)
	1057 25.3	23.9	6887 24.1	7116 23.5	8.05 37.3	149.4 27.7	1729 47.8	8.12 20.4
Group 2 (Fed), n = 20								
A	1214 (664-1660)	5.0 (4-10)	11649 (7070-16867)	11785 (7196-17066)	4.64 (3.78-7.31)	84.9 (58.6-139)	568 (339-1097)	8.77 (6.75-10.7)
	1235 18.1	26.8	11992 24.3	12130 24.3	4.71 19.0	87.4 25.4	602 36.6	8.83 12.2
B	1203 (602-1570)	5.0 (4-10)	11531 (7563-17054)	11669 (7761-17267)	4.61 (3.39-6.78)	85.7 (57.9-129)	571 (360-1053)	8.66 (6.70-10.3)
	1224 17.1	30.5	11808 22.1	11948 22.1	4.68 18.2	87.8 22.9	599 33.9	8.72 12.0

Treatment A: Glucophage® XR 1000 mg (test), Treatment B: Glucophage® XR 500 mg (reference)

Geometric mean (* median for t_{max}), range (min-max), arithmetic mean and CV (%) are listed

There were no relevant differences for any of the derived pharmacokinetic parameters when Glucophage XR 500mg was compared with Glucophage XR 1000mg either upon fasted administration (group 1) or after intake of food (group 2).

**Assessment of Bioequivalence by Intra-Individual Comparison
of Glucophage XR 1000 mg Versus Glucophage XR 500 mg –
Group 1 (Fasted)**

PK Parameter	Unit	Treatment A		Treatment B		GMR A/B [%]	90% CI [%]
		N	gMean	N	gMean		
AUC _{0-∞}	(ng•h/mL)	28	6659.76	28	6913.64	96.328	87.047; 106.599
AUC _{0-t}	(ng•h/mL)	28	6433.44	28	6681.26	96.291	86.607; 107.058
C _{max}	(ng/mL)	28	962.4	28	1023.1	94.073	83.383; 106.134

Treatment A: Glucophage[®] XR 1000 mg (test), Treatment B: Glucophage[®] XR 500 mg (reference)

GMR A/B = Geometric mean ratio of Treatment A versus B

The statistical analysis of the ANOVA model for AUC_{0-t}, AUC_{0-∞} and C_{max} of metformin hydrochloride in the plasma indicates bioequivalence between a single 1000mg dose of metformin hydrochloride administered as either one tablet of Glucophage XR 1000mg or two tablets of Glucophage XR 500mg in the fasted state (Group 1). The geometric mean ratios of AUC_{0-t}, AUC_{0-∞} and C_{max} are slightly below the 100% value and respective 90% CIs, which all include the 100% value, are within the pre-defined limits of bioequivalence of [80%;125%].

**Assessment of Bioequivalence by Intra-Individual Comparison
of Glucophage XR 1000 mg Versus Glucophage XR 500 mg –
Group 2 (Fed)**

PK Parameter	Unit	Treatment A		Treatment B		GMR A/B [%]	90% CI [%]
		N	gMean	N	gMean		
AUC _{0-∞}	(ng•h/mL)	20	11785.04	20	11668.98	100.995	94.717; 107.689
AUC _{0-t}	(ng•h/mL)	20	11649.45	20	11531.42	101.024	94.707; 107.761
C _{max}	(ng/mL)	20	1214.1	20	1203.1	100.911	96.631; 105.380

Treatment A: Glucophage[®] XR 1000 mg (test), Treatment B: Glucophage[®] XR 500 mg (reference)

GMR A/B = Geometric mean ratio of Treatment A versus B

Similarly, bioequivalence is also shown between a single 1000mg dose of metformin hydrochloride administered as either one tablet of Glucophage XR 1000mg or two tablets of Glucophage XR 500mg after intake of food (Group 2). The geometric mean ratios for AUC_{0-t}, AUC_{0-∞} and C_{max} are all around 101% and the pre-defined limits of bioequivalence encloses all the 90% CIs.

Relative bioavailability was also assessed by statistical analysis of treatment differences of t_{max} between Glucophage XR 1000mg and Glucophage XR 500mg and these results are summarised below.

Assessment of relative bioavailability by intra-individual comparison of t_{max} between Glucophage XR 1000 mg and Glucophage XR 500 mg

PK Parameter	Unit	N	Median of Difference A - B [h]	95% CI [h]
Group 1 - 'Fasted'				
t_{max}	h	28	0	-0.5; 0
Group 2 - 'Fed'				
t_{max}	h	20	0.5	-0.5; 1

Treatment A: Glucophage® XR 1000 mg (test), Treatment B: Glucophage® XR 500 mg (reference)

Median of Difference A - B = Median of pairwise average treatment differences between Treatment A and B according to Hodges-Lehmann estimation

Analysis of pair wise treatment differences of t_{max} reveal no differences between Glucophage XR 1000mg and Glucophage XR 500mg when administered as a dose of 1000mg.

In conclusion, the use of single dose bioequivalence data in support of the line extension for the Glucophage SR 1000mg formulation is considered justified.

The following supporting information was also included:

Table 2.7.1.1 Summary of bioavailability studies

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No) Type	Pharmacokinetic parameters:										Study Report Location		
					C_{max} (ng/mL)		AUC(INF) (ng·h/mL)		AUC(0-T) (ng·h/mL)		T_{max} (h)		$T_{1/2}$ (h)				
					Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean	Median (Min, Max)	Mean (S.D.)	Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean			
CV138085	1. BE of 2x 750 mg Glucophage SR tablets vs. 3x 500 mg Glucophage SR tablets in fed subjects. 2. Safety of Glucophage SR and Glucophage SR formulations administered with food.	Open-label, randomized, single-dose, two-treatment, two-period, crossover.	500mg, Prolonged-release tablet, oral [500 mg] 750 mg, Prolonged-release tablet, oral [750 mg]	23 Healthy volunteers - fed	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	Mod 5, sec 5.3.1
					1104 (16) 1105	1193 (17) 1197	14622 (15) 14651	14607 (16) 14642	14219 (14) 14245	14209 (16) 14243	5.0 (3.0, 12.0)	5.0 (4.0, 12.0)	4.6 (0.76)	4.8 (0.84)			
CV138082	1. BE of 2x 750 mg Glucophage SR tablets vs. 3x 500 mg Glucophage SR tablets in fasting subjects. 2. Safety of Glucophage SR and Glucophage SR formulations.	Open-label, randomized, single-dose, two-treatment, three period, optimally-designed replicate crossover. (ABB or BAA)	500mg, Prolonged-release tablet, oral [500 mg] 750 mg, Prolonged-release tablet, oral [750 mg]	20 Healthy volunteers - fasting	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	Mod 5, sec 5.3.1
					1321 (31) 1315	1400 (32) 1392	9063 (30) 9087	9293 (26) 9254	8293 (32) 8343	8552 (28) 8429	3.0 (1.0, 5.0)	3.0 (2.0, 5.0)	9.5 (4.8)	9.7 (6.0)			
CV138087	1. BE of Glucophage SR 750 mg tablets manufactured in Humacao, Puerto Rico, vs. Glucophage SR 750 mg tablets manufactured in Evansville. 2. Safety of Glucophage SR 750 mg tablets.	Open-label, randomized, two-period, two-treatment, crossover.	750 mg, Prolonged-release tablet, oral - Evansville [Ev.] 750 mg, Prolonged-release tablet, oral - Humacao [Hu.]	23 Healthy volunteers - fasting	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	Mod 5, sec 5.3.1
					835 (39) 834	798 (34) 798	6264 (34) 6266	5861 (32) 5860	5738 (36) 5738	5500 (34) 5500	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	8.9 (7.5)	7.8 (3.9)			

2.1.1 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 (23 and 20 completed respectively). 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 are fairly closely matched except of the content of each tablet.

The study 138 -087 compared tablets manufactured at two different sites and the results albeit with wider 90% CI suggest that the tablets manufactured at the two sites fulfil the criteria for Bioequivalence as defined by the CHMP guidance note (CPMP/EWP/QWP/1401/98).

2.1.2 Assessor's Conclusion

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.

2.2 PHARMACODYNAMICS

The pharmacodynamics of Metformin (Glucophage) are well established using the immediate release and the 500mg SR formulations. The kinetics of the 100mg SR tablets have are similar (dose per dose) to 500mg SR formulations. It is therefore possible to conclude that 1000mg SR could be a replacement for 500mg SR tablets at equivalent dose (dose per dose). The PD of 1000mg tablets have not been tested in the clinical setting directly although in one study a starting dose of 1000mg was utilised. However it is unclear if these were metformin naïve patients or those who were already had some exposure to metformin but had shown an inadequate response. Therefore, further extrapolations of the PD effect would not be based on evidence.

Hence based on the current dataset, 1000mg SR would be useful primarily as a replacement for the 500mg tablets at specified dose and posology and the SPC should remain identical.

3 CLINICAL EFFICACY & SAFETY;

The application was based on bioequivalence studies and those clinical studies submitted with the original 500mg application. Therefore the 1000mg SR tablet could be accepted as a replacement for does per dose equivalent to the 500mg strength where appropriate.

The applicant has not provided any data to suggest that the safety / efficacy profile of 1000mg is similar to any other formulation (strength). Hence the risk:benefit of 750 SR tablets when administered at doses different to those achieved by any combination of 500mg SR tablets has not been established. Any claims for reduced GI side effects or increased efficacy of 750 over 500 SR [or any other formulation of metformin (glucophage)] is not established in the absence of specific clinical data.

4 EXPERT REPORTS

The expert reports include an update to the original report submitted with the 500mg SR application and these are acceptable. A further justification for not conducting

steady state studies with the new formulation was sought and obtained. This is acceptable.

5 PRODUCT LITERATURE

5.1 SPC

The SPC is identical to the existing modified release SPC (500mg strength) as this is a replacement (generic equivalent) dose per dose. The SPC and PIL are in line with the suggestions to state only 500mg as the starting dose but the higher strength 1000mg is a replacement dose per dose.

5.2 PATIENT INFORMATION LEAFLET

The PIL is satisfactory.

5.3 LABEL

The labels are satisfactory.

6 OVERALL CONCLUSION

6.1 RISK BENEFIT

The 1000mg SR formulation has been shown to be bioequivalent (fed and fasted single dose studies) with the 500mg SR formulation. It is therefore acceptable as replacement at this dose. Single 1000mg dose administration has not been tested independently and hence the risk:benefit of this as a starting dose is not demonstrated.

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

Further justification for the absence of the steady state was requested and provide by the applicant which is considered acceptable.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Glucophage SR 1000mg Prolonged-Release Tablets 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 an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Glucophage SR 1000mg Prolonged-Release Tablets and originator products Glucophage SR 500mg Prolonged Release Tablets (Merck Serono Ltd). These products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPC, PIL, technical leaflet, and labelling are satisfactory and consistent with that for the innovator product.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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.

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with metformin hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**GLUCOPHAGE SR 1000MG PROLONGED-RELEASE TABLETS
PL 11648/0067**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 28 th September 2007.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 29 th October 2007.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 8 th April 2008 and 16 th June 2008.
4	The applicant responded to the MHRA's requests, providing further information on 20 th May 2008 and 9 th July 2008 for the quality sections.
5	The application was determined on 16 th September 2008.

**GLUCOPHAGE SR 1000MG PROLONGED-RELEASE TABLETS
PL 11648/0067**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

GLUCOPHAGE SR 1000MG PROLONGED-RELEASE TABLETS

PL 11648/0067

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Glucophage SR 1000 mg prolonged release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged release tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablet

White to off-white capsule-shaped, biconvex tablet, debossed on one side with 'SR1000

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. Glucophage 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:

- Glucophage SR 1000 mg should be taken once daily with the evening meal at a maximum recommended dose of 2 tablets per day.
- Glucophage SR 1000 mg is intended as a maintenance therapy for patients currently treated with either 1000 mg or 2000 mg of metformin hydrochloride. On switch, the daily dose of Glucophage SR should be equivalent to the current daily dose of metformin hydrochloride.
- In patients treated with metformin hydrochloride at a dose above 2000 mg daily, switching to Glucophage SR is not recommended.
- **For patients new to metformin hydrochloride**, the usual starting dose of Glucophage SR is 500 mg once daily given with the evening meal. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increment in dose may improve gastrointestinal tolerability.
- If glycaemic control is not achieved on once daily dosing of Glucophage SR at a maximum dose of 2000 mg a day, then a twice daily dosing schedule should be considered with both doses being given with food, at the time of the morning and evening meals. If glycaemic control is still not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum dose of 3000 mg daily.
- In the event of transfer from another oral antidiabetic agent, titration should begin with Glucophage SR 500 mg before switching to Glucophage SR 1000 mg as indicated above.

Combination with insulin:

Metformin hydrochloride and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of Glucophage SR is 500 mg once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, switch to Glucophage SR 1000 mg should be considered.

Elderly:

Due to the potential for decreased renal function in elderly subjects, the metformin hydrochloride 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, Glucophage 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 section 4.4).
- 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 USELactic 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 hydrochloride 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 hydrochloride 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 a non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast agent:

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin hydrochloride should be discontinued prior to, or at the time of the test and not reinstated 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 hydrochloride 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 hydrochloride should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.4).

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 foetal 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 hydrochloride but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal 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 hydrochloride, taking into account the importance of the compound to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Glucophage 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 hydrochloride 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 Glucophage SR was similar in nature and severity to that reported in patients treated with Glucophage immediate release.

The following undesirable effects may occur with metformin hydrochloride.

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.

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.

Skin and subcutaneous tissue disorders

very rare: Skin reactions such as erythema, pruritus, urticaria

Metabolism and nutrition disorders

very rare:

Lactic acidosis (see section 4.4)

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin hydrochloride. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Hepatobiliary disorders:

Not known: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin hydrochloride discontinuation.

4.9 OVERDOSE

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUT).

In humans, independently of its action on glycaemia, immediate release metformin hydrochloride 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 hydrochloride 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 hydrochloride as first-line therapy after diet failure. Analysis of the results for overweight patients treated with metformin hydrochloride after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years ($p=0.01$)

For metformin hydrochloride 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 hydrochloride 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 in the fed state of one tablet of Glucophage SR 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Glucophage SR 1000 mg was shown to be bioequivalent to Glucophage SR 500 mg at a 1000 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 hydrochloride prolonged release tablets is similar to that observed after administration of 1000 mg of metformin hydrochloride immediate release tablets b.i.d.

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

When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and T_{max} is slightly prolonged by about 1 hour).

Mean metformin hydrochloride absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000 mg of metformin hydrochloride 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 (V_d) 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

Carmellose sodium

Hypromellose

Magnesium stearate

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/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

Merck Serono Ltd
Bedfont Cross
Stanwell Road
Feltham
Middlesex
TW14 8NX, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 11648/0067

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/09/2008



10 DATE OF REVISION OF THE TEXT

16/09/2008

GLUCOPHAGE SR 1000MG PROLONGED-RELEASE TABLETS

PL 11648/0067

PATIENT INFORMATION LEAFLET

 	
<p>500 mg Prolonged release tablets 750 mg Prolonged release tablets 1000 mg Prolonged release tablets metformin hydrochloride</p>	
<p><i>This medicine is intended for adult patients only</i> Read all of this leaflet carefully before you start taking this medicine. <i>Keep this leaflet. You may need to read it again.</i> <i>If you have any further questions, ask your doctor or pharmacist.</i> <i>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.</i> <i>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.</i></p>	
<p>In this leaflet:</p> <ol style="list-style-type: none"> 1. What Glucophage SR is and what it is used for 2. Before you take Glucophage SR 3. How to take Glucophage SR 4. Possible side effects 5. How to store Glucophage SR 6. Further information 	<ul style="list-style-type: none"> • 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. <p>Take special care with Glucophage SR.</p> <p>After you have started taking your medicine:</p> <p>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).</p> <p>If you start 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 there is too much acid in the blood (see also under '4. Possible side effects').</p> <p>You may see some remains of the tablets in your stools. Do not worry- this is normal for this type of tablet.</p> <p>If you need to have an X-ray examination involving the injection of a dye, tell the doctor that you take Glucophage SR as you may need to stop taking it for a few days afterwards.</p> <p>Tell your doctor if you are going to have an operation under general anaesthetic, as you may need to stop taking Glucophage SR for a couple of days before and after the procedure.</p> <p>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.</p> <p>Do not stop taking this medicine without speaking to your doctor.</p> <p>Taking Glucophage SR with other medicines:</p> <p>Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.</p> <p>If you are taking any of the following medicines, your blood sugar levels may need to be checked more often and your dose adjusted:</p> <ul style="list-style-type: none"> • 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, captopril. <p>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').</p>
<p>1. WHAT GLUCOPHAGE SR IS AND WHAT IT IS USED FOR</p> <p>Glucophage 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. Glucophage 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. Glucophage SR makes the body more sensitive to insulin and helps return to normal the way your body uses glucose. Glucophage 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.</p>	
<p>2. BEFORE YOU TAKE GLUCOPHAGE SR</p> <p>Do not take Glucophage SR if:</p> <ul style="list-style-type: none"> • 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. 	

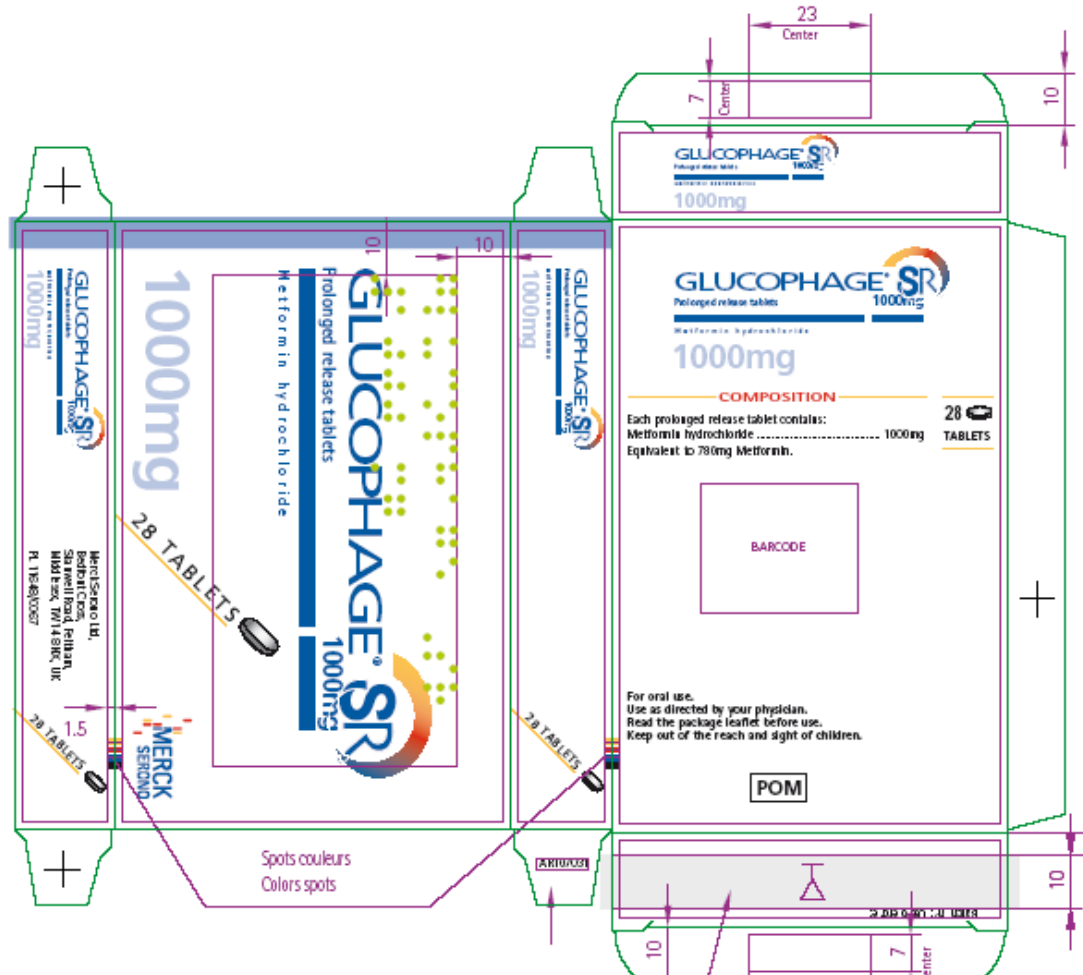
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<p>Taking Glucophage SR with food and drink: You should take Glucophage SR with or immediately after food.</p> <p>Pregnancy and breast-feeding Do not take Glucophage SR if you are pregnant or breast feeding. Ask your doctor or pharmacist for advice before taking any medicine.</p> <p>Driving and using machines Glucophage 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 Glucophage SR taken with other antidiabetic medicines can cause hypos, so in this case you should take extra care when driving or operating machinery.</p> <p>3. HOW TO TAKE GLUCOPHAGE SR Your doctor may prescribe Glucophage SR for you to take on its own, or in combination with other oral antidiabetic medicines or insulin. Always take Glucophage 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. Usually you will start treatment with 500 milligrams Glucophage SR daily. After you have been taking Glucophage SR for about 2 weeks, your doctor may measure your blood sugar and adjust the dose. The maximum daily dose is 2000 milligrams of Glucophage SR. Normally, you should take the tablets once a day, with your evening meal. In some cases, your doctor may recommend that you take the tablets twice a day. Always take the tablets with food. If you take more Glucophage SR than you should If you take extra tablets by mistake you need not worry, but if you have unusual 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 Glucophage SR Take it as soon as you remember with some food. Do not take a double dose to make up for a forgotten dose.</p> <p>4. POSSIBLE SIDE EFFECTS Like all medicines, Glucophage 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.</p>	<p>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.</p> <p>5. HOW TO STORE GLUCOPHAGE SR Keep Glucophage 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.</p> <p>6. FURTHER INFORMATION What the tablets contain Each prolonged release tablet contains 500, 750 or 1000 milligrams of the active ingredient metformin hydrochloride. The other ingredients are magnesium stearate, carmellose sodium and hypromellose. The 500 milligram tablet also contains microcrystalline cellulose. What Glucophage SR looks like and contents of the pack The 500 milligram tablets are white to off-white and capsule-shaped with '500' on one side. The 750 milligram tablets are white to off-white and capsule-shaped with '750' on one side and 'Merck' on the other side. The 1000 milligrams tablets are white to off-white and capsule-shaped with 'SR 1000' on one side. Glucophage SR is supplied in packs of 28 and 56 prolonged release tablets. Glucophage SR 500 mg Prolonged Release Tablets are manufactured for Merck Serono Ltd, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX, UK by Merck Santé s.a.s., Centre de Production de Semoy, 2 rue du Pressoir Vert, 45400 Semoy, France. Glucophage SR 750 mg and Glucophage SR 1000 mg Prolonged Release Tablets are manufactured for Merck Serono Ltd, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX, UK by Merck KGaA, Frankfurter Strasse 250, Darmstadt, D-63293 Germany.</p> <p>This leaflet was last revised in July 2008.</p> <p>Useful tips</p> <ul style="list-style-type: none"> • 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 <p>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</p>
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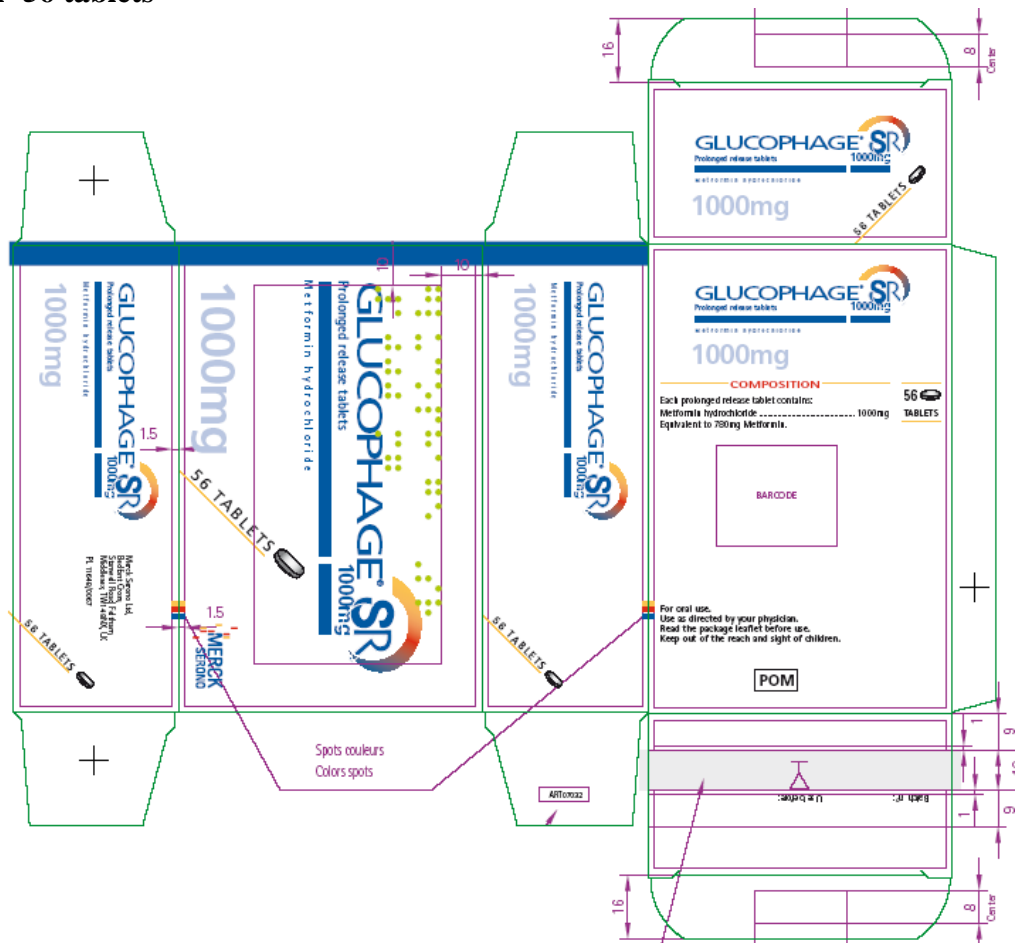
GLUCOPHAGE SR 1000MG PROLONGED-RELEASE TABLETS PL 11648/0067

LABELLING

Carton- 28 tablets



Carton- 56 tablets



Blister foil

