Public Assessment Report

UK PAR

Glucient SR 1000 mg prolonged-release tablets (metformin hydrochloride)

UK Licence No: PL 24837/0060

Consilient Health Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Glucient SR 1000 mg prolonged-release tablet (metformin hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Glucient SR 1000 mg prolonged-release tablets (PL 24837/0060). It explains how the application for Glucient SR 1000 mg prolonged-release tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Glucient SR 1000 mg prolonged-release tablets.

For practical information about using Glucient SR 1000 mg prolonged-release tablet, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as 'Glucient SR' in this report.

What is Glucient SR and what is it used for?

Glucient SR is a generic medicine. This means that Glucient SR is similar to 'reference medicines already authorised in the UK called Glucophage 500 mg film-coated tablets (PL 11648/0085; Merck Serono Limited, UK) and Glucophage SR 1000 mg prolonged release tablets (PL 11648/0067; Merck Serono Limited).

Glucient 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).

How does Glucient SR work?

Glucient SR contains the active ingredient metformin hydrochloride, which belongs to a group of medicines called biguanides. This medicine works by reducing the amount of sugar produced in the liver and increases the sensitivity of muscle cells to insulin. This enables the cells to remove sugar from the blood more effectively.

Glucient SR prolonged release tablets are specially made to release the drug slowly in the body and therefore are different to many other types of tablet containing metformin.

How is Glucient SR used?

Glucient SR is available as prolonged- release tablets and are taken by mouth. Glucient SR should be swallowed whole; the tablet(s) should not be chewed. The tablet(s) should always be taken with food.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Glucient SR can only be obtained with a prescription.

What benefits of Glucient SR have been shown in studies?

As Glucient SR is a generic medicine, studies in patients have been limited to tests to determine that Glucient SR is bioequivalent to the reference medicine, Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the Marketing Authorisation Holder (Consilient Health Limited) has provided data from the published literature on metformin.

What are the possible side effects of Glucient SR?

Because Glucient SR is a generic medicine and is bioequivalent to the reference medicine Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK), the benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Glucient SR, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Glucient SR approved?

In accordance with the EU requirements, Glucient SR has been shown to have comparable quality and clinical characteristics to the originator Glucophage prolonged release tablets (Merck Serono Limited). Based on this evaluation, the MHRA concluded that the benefits of Glucient SR outweigh the identified risks and recommended Glucient SR for approval.

What measures are being taken to ensure the safe and effective use of Glucient SR?

A risk management plan has been developed to ensure that Glucient SR is used as safely as possible. The relevant safety information has been included in the Summary of Product Characteristics and the package leaflet for Glucient SR, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored / reviewed continuously.

Other information about Glucient SR

A Marketing Authorisation was granted in the UK on 18 December 2014.

The full PAR for Glucient SR follows this summary.

For more information about treatment with Glucient SR read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2015.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Consilient Health Limited a Marketing Authorisation for the medicinal product Glucient SR 1000 mg prolonged-release tablets (PL 24837/0060) on 18 December 2014. The product is a prescription-only medicine (POM) indicated for the 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.

Glucient SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

The application for Glucient SR 1000 mg prolonged-release tablets was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application, cross-referring to the reference medicinal product Glucophage 500 mg film-coated tablets (PL 11648/0085; Merck Serono Limited, UK), which was first authorised in the UK on 21 September 1982 to Lipha Pharmaceuticals Limited. The original Marketing Authorisation for Glucophage 500 mg film-coated tablets (PL 03759/0012) was transferred to Merck Serono Limited, the parent company of Lipha Pharmaceuticals Limited (PL 11648/0085), on 01 April 2010. The application for Glucient SR 1000 mg prolonged-release tablets also cross-refers to Glucophage SR 1000 mg prolonged-release tablets (PL 11648/0067; Merck Serono Limited, UK), which were authorised in the UK on 16 September 2008.

Glucient SR 1000 mg prolonged-release tablets contain the active ingredient, metformin hydrochloride, which is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. Metformin is believed to 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. The exact mechanism remains speculative.

Three bioequivalence studies were submitted to support this application, comparing the applicant's test product Glucient SR 1000 mg prolonged release tablets with the reference product Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK) under fasting, fed and steady-state conditions. The bioequivalence studies are stated to have been conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/95).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Glucient SR 1000 mg prolonged-release tablets outweigh the risks.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Each Glucient SR 1000 mg prolonged-release tablet contains 1000 mg of metformin hydrochloride, corresponding to 780 mg of metformin. Each tablet is 22.25 x 9 mm, white, shallow convex, 22.25 x 9 mm, with marking “SR2” on one side and without marking on the other side.

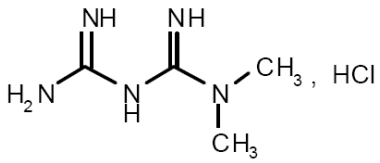
The product also contain the pharmaceutical excipients carmellose sodium 2000, Hypromellose 100M, colloidal anhydrous silica and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in polvinylchloride/polvinylidene chloride/aluminium blisters, in pack sizes of 28, 30, 56, 60 and 100 prolonged-release tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Metformin hydrochloride

INN:	Metformin hydrochloride
Chemical name:	N,N-dimethyl imido-dicarbonimidicdiamide*) 1,1-dimethyl biguanide*) N-N dimethyl diguanide*) N' – dimethyl guanylguanidine*) *) as hydrochloride
Structure:	
Molecular formula:	$C_4H_{12}ClN_5$
Molecular weight:	165.6
Appearance:	White or almost white crystals.
Solubility	Freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in acetone and in methylene chloride.

Metformin hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, metformin hydrochloride, except for the proposed packaging specifications and stability data, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable, prolonged-release tablet that was bioequivalent to the reference medicinal product Glucophage1000 mg prolonged release tablets (Merck Pharmaceuticals). Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution profiles have been provided for this product and the reference product. The dissolution profiles were satisfactory.

All the excipients comply with their respective European Pharmacopoeia monographs.

Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Based on full-scale batches, the manufacturing process has been validated and has shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months, with the special storage conditions ‘Do not store above 30°C.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section IV, Clinical Aspects.

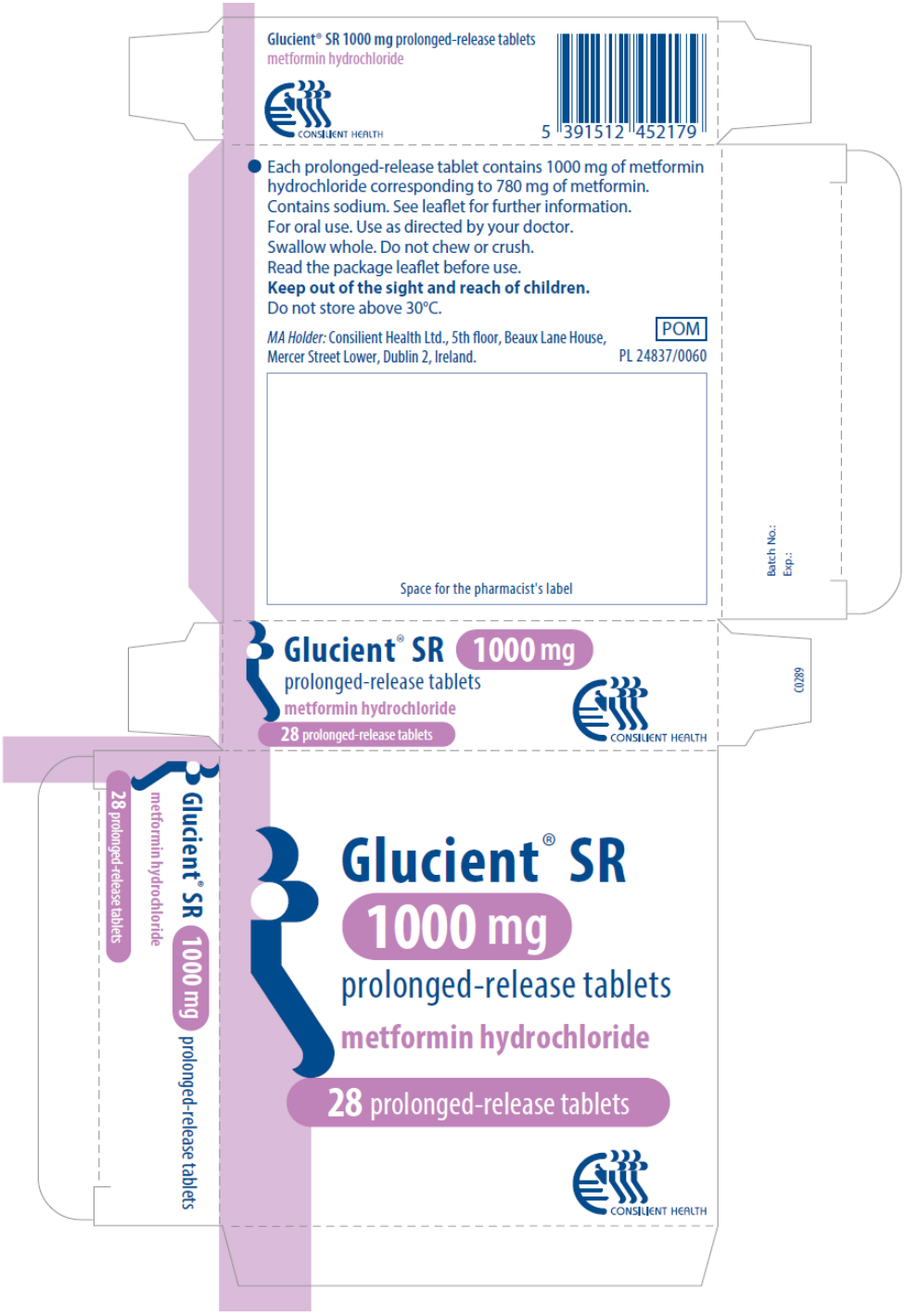
II.4 Discussion on chemical, pharmaceutical and biological aspects

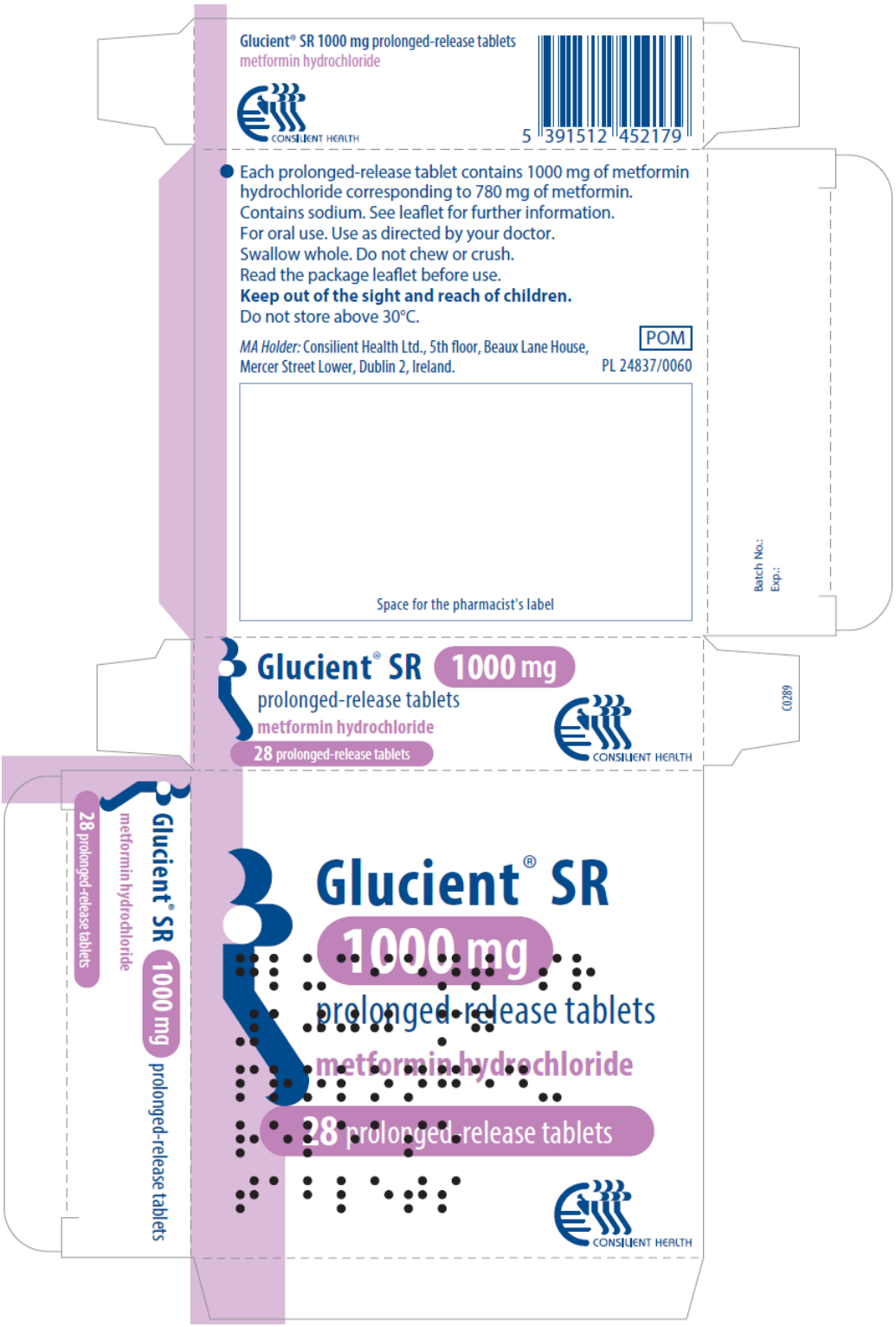
It is recommended that a Marketing Authorisation is granted for the application for Glucient SR 1000 mg prolonged-release tablets, from a quality point of view.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:


Glucient® SR 1000 mg prolonged-release tablets
metformin hydrochloride
CONSILIENT HEALTH
5 391512 452179
Each prolonged-release tablet contains 1000 mg of metformin hydrochloride corresponding to 780 mg of metformin.
Contains sodium. See leaflet for further information.
For oral use. Use as directed by your doctor.
Swallow whole. Do not chew or crush.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 30°C.
MA Holder: Consilient Health Ltd., 5th floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland.
POM
PL 24837/0060
Space for the pharmacist's label
Batch No.:
Exp.:
C0289
Glucient® SR 1000 mg
prolonged-release tablets
metformin hydrochloride
28 prolonged-release tablets
CONSILIENT HEALTH
Glucient® SR 1000 mg prolonged-release tablets
metformin hydrochloride
28 prolonged-release tablets
Glucient® SR
1000 mg
prolonged-release tablets
metformin hydrochloride
28 prolonged-release tablets
CONSILIENT HEALTH


Glucient® SR 1000 mg prolonged-release tablets
metformin hydrochloride
CONSILIENT HEALTH
5 391512 452179
Each prolonged-release tablet contains 1000 mg of metformin hydrochloride corresponding to 780 mg of metformin.
Contains sodium. See leaflet for further information.
For oral use. Use as directed by your doctor.
Swallow whole. Do not chew or crush.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 30°C.
MA Holder: Consilient Health Ltd., 5th floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland.
POM
PL 24837/0060
Space for the pharmacist's label
Batch No.:
Exp.:
Glucient® SR 1000 mg
prolonged-release tablets
metformin hydrochloride
28 prolonged-release tablets
CONSILIENT HEALTH
C0289
Glucient® SR 1000 mg prolonged-release tablets
metformin hydrochloride
28 prolonged-release tablets
Glucient® SR
1000 mg
prolonged-release tablets
metformin hydrochloride
28 prolonged-release tablets
CONSILIENT HEALTH


Glucient® SR 1000 mg
prolonged-release tablets
metformin hydrochloride
MA Holder: Consilient Health Ltd.
F0182


Glucient® SR 1000 mg
prolonged-release tablets
metformin hydrochloride
MA Holder: Consilient Health Ltd.
F0182


Glucient® SR 1000 mg prolonged-release tablets
metformin hydrochloride
CONSILIENT HEALTH
5 391512 452186
Each prolonged-release tablet contains 1000 mg of metformin hydrochloride corresponding to 780 mg of metformin.
Contains sodium. See leaflet for further information.
For oral use. Use as directed by your doctor.
Swallow whole. Do not chew or crush.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 30°C.
POM
MA Holder: Consilient Health Ltd., 5th floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland.
PL 24837/0060
Space for the pharmacist's label
Batch No.:
Exp.:
Glucient® SR 1000 mg
prolonged-release tablets
metformin hydrochloride
56 prolonged-release tablets
CONSILIENT HEALTH
C0290
Glucient® SR
prolonged-release tablets
1000 mg
metformin hydrochloride
56 prolonged-release tablets
Glucient® SR
1000 mg
prolonged-release tablets
metformin hydrochloride
56 prolonged-release tablets
CONSILIENT HEALTH


Glucient® SR 1000 mg prolonged-release tablets
metformin hydrochloride
CONSILIENT HEALTH
5 391512 452186
Each prolonged-release tablet contains 1000 mg of metformin hydrochloride corresponding to 780 mg of metformin.
Contains sodium. See leaflet for further information.
For oral use. Use as directed by your doctor.
Swallow whole. Do not chew or crush.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 30°C.
POM
MA Holder: Consilient Health Ltd., 5th floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland.
PL 24837/0060
Space for the pharmacist's label
Batch No.:
Exp.:
Glucient® SR 1000 mg
prolonged-release tablets
metformin hydrochloride
56 prolonged-release tablets
CONSILIENT HEALTH
CD290
Glucient® SR
prolonged-release tablets
1000 mg
metformin hydrochloride
56 prolonged-release tablets
Glucient® SR
1000 mg
prolonged-release tablets
metformin hydrochloride
56 prolonged-release tablets
CONSILIENT HEALTH

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of metformin hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics

Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology

Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental exposure to metformin hydrochloride is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Glucient SR 1000 mg prolonged release tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of metformin hydrochloride is well-known.

In accordance with the regulatory requirements for a modified release generic product claiming to be bioequivalent to a reference product (CPMP/EWP/QWP/280/96. Corr), the applicant submitted three bioequivalence studies (single dose fasted, single dose fed and multiple dose). The results of the bioequivalence studies are discussed in Section IV.2, Pharmacokinetics.

With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for this application.

IV.2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence studies:

Study 1

An open randomised, single dose, two-period, crossover study to compare the pharmacokinetics of the test product Glucient SR 1000 mg prolonged release tablets (Consilient Health Limited, UK) versus the reference product Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK) in healthy, male and female subjects under fasting conditions.

The subjects were administered one tablet of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 30 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (ratios of geometric means, confidence intervals and coefficients of variation) of metformin

Parameter	% Ratio of Geometric Means (T/R)	90% Confidence Interval (T/R)		% CV
		Lower Limit	Upper Limit	
AUC_t ($ng.h.mL^{-1}$)	105.86	94.01	119.20	28.90
AUC_{inf} ($ng.h.mL^{-1}$)	105.85	94.21	118.93	28.35
C_{max} ($ng.mL^{-1}$)	102.89	93.92	112.72	22.18

*) Bioequivalence criteria (90%CI): 80.00 – 125.00 %

C_{max} maximum plasma concentration
AUC_t area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from ln-transformed data

The Note for Guidance on the Investigation of Bioavailabilty and Bioequivalence (CPMP/EWP/QWP/1401/98 Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and C_{max} values. Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK) under fasting conditions.

STUDY 2

A randomised, single blind (investigators blind) single dose, two-period, two sequence crossover study to compare the pharmacokinetics of the test product Glucient SR 1000 mg prolonged release tablets (Consilient Health Limited, UK) versus the reference product Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK) in healthy, adult male and female subjects under fed (high fat meal) conditions.

The subjects were administered one tablet of either the test or the reference product with 240 ml of

water, 30 minutes after the start of a high fat and high calorie breakfast. The subjects fasted for at least 10 hours prior to the scheduled time for breakfast. Blood samples were collected before and up to and including 30 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (ratios of geometric means, confidence intervals and coefficients of variation) of metformin

Parameter	% Ratio of Geometric Means (T/R)	90% Confidence Interval (T/R)		% CV
		Lower Limit	Upper Limit	
AUC_t ($ng.h.mL^{-1}$)	97.43	92.73	102.36	12.00
AUC_{inf} ($ng.h.mL^{-1}$)	97.57	93.21	102.13	11.09
C_{max} ($ng.mL^{-1}$)	104.09	98.00	110.55	14.63

*) Bioequivalence criteria (90%CI): 80.00 – 125.00 %

C_{max} maximum plasma concentration
AUC_t area under the plasma concentration-time curve from time zero to t hours
AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from ln-transformed data

The Note for Guidance on the Investigation of Bioavailabilty and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) defines the confidence limits as 80.00 to 125.00 % for AUC and C_{max} values. Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK) under fed conditions.

STUDY 3
A randomised, single blind (investigators blind), two-period, two sequence crossover multiple dose study to compare the pharmacokinetics of the test product Glucient SR 1000 mg prolonged release tablets (Consilient Health Limited, UK) versus the reference product Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK) in healthy, adult male and female subjects under fed conditions.

The subjects were administered one tablet of either the test or the reference product with 240 ml of water for four consecutive days (Days 1 to 4), 30 minutes after a standardised normal diabetic meal. The subjects fasted for at least 10 hours prior to the scheduled time for breakfast. Blood samples were collected before each administration on Days 1-3 and before and up to 30 hours after administration on Day 4. The washout period between the treatment phases was 11 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (ratios of geometric means, confidence intervals and coefficients of variation) of metformin

Parameter	% Ratio of Geometric Means (T/R)	90% Confidence Interval (T/R)		% CV
		Lower Limit	Upper Limit	
AUC_{tau} ($ng.mL^{-1}.h$)	100.14	92.12	108.86	21.84
C_{max} ($ng.mL^{-1}$)	100.74	97.16	104.45	9.47
C_{min} ($ng.mL^{-1}$)	100.73	81.12	125.09	56.68

*) Bioequivalence criteria (90%CI): 80.00 – 125.00 %

AUC_{tau} area under the plasma concentration-time curve at steady state
C_{min} minimum (non zero) observed plasma concentration of the drug at steady-state phase
C_{max} maximum observed plasma concentration at steady state
Ratios and 90% CI calculated from ln-transformed data

The Note for Guidance on the Investigation of Bioavailabilty and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) defines the confidence limits as 80.00 to 125.00 % for AUC and C_{max} values. The 90% confidence limits for C_{max} and AUC_{tau} ratios were within the 80% - 125% range. However, the 90% upper confidence limit for C_{min} is 125.09%, which is marginally outside the acceptance range of 80.00-125.00%; this finding is considered of little clinical relevance. Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK) under steady-state conditions.

Overall bioequivalence conclusion
The data support the claim that the applicant's test product is bioequivalent to the reference Glucophage SR 1000 mg prolonged release tablets (Merck Serono Limited, UK) under fasting, fed and steady-state conditions.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of metformin hydrochloride are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of metformin hydrochloride is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety
With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence studies.

IV.6 Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Glucient SR 1000 mg prolong-release tablets.

A summary of safety concerns is listed in the table below:

Summary of safety concerns	
Important identified risks	• Renal failure or renal dysfunction • Lactic acidosis • Hepatic insufficiency • Surgery • Hypoglycaemia associated with 1) co-administration with other antidiabetic agents and 2) co-administration with drugs with intrinsic sympathomimetic activity, including glucocorticoids and sympathomimetics • Use in patients on sodium controlled diet
Important potential risks	• Co-administration of drugs with intrinsic hyperglycaemic activity
Missing information	• Use of Glucient in children • Effect on fertility, and use in pregnancy and lactation

No additional risk minimisation activities were required beyond those included in the product information.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Glucient SR 1000 mg prolong-release tablets, from a clinical point of view.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the PIL for Glucient SR 500 mg prolonged-release tablets (Consilient Health Limited). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Glucient SR 1000 mg 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.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of metformin hydrochloride are well-known, no additional data were required.

EFFICACY

With the exception of the bioequivalence studies, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant's product and the reference product Glucophage 1000 mg prolonged release tablets (Merck Serono Limited UK) under fasting, fed and steady-state conditions.

SAFETY

With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for this type of application. As the safety profile of metformin hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with metformin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION

The grant of a Marketing Authorisation is recommended.

Annex 1 - Table of content of the PAR update

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

(Type II variations, PSURs, commitments)

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)