Public Assessment Report

Decentralised Procedure

Glucient SR 750 mg Prolonged-Release Tablets

(Metformin hydrochloride)

UK/H/5129/001/DC

UK licence no: PL 24837/0036

Consilient Health Limited

LAY SUMMARY
Glucient SR 750 mg prolonged-release tablets
(**Metformin hydrochloride**)

This is a summary of the public assessment report (PAR) for Glucient SR 750 mg prolonged-release tablets (PL 24837/0036). It explains how Glucient SR 750 mg prolonged-release tablets were assessed and their authorisations recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Glucient SR 750 mg prolonged-release tablets.

For practical information about using Glucient SR 750 mg prolonged-release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Glucient SR 750 mg prolonged-release tablets and what are they used for?
Glucient SR 750 mg prolonged-release tablets is a 'generic medicine'. This means that Glucient SR 750 mg prolonged-release tablets are similar to a 'reference medicine' already authorised in the UK called Glucophage Film-coated tablets (Merck Serono Limited; PL 11648/0085).

Glucient SR 750 mg prolonged-release tablets are used for the treatment of Type 2 (non-insulin dependant) diabetes mellitus when diet and exercise changes alone have not been enough to control blood glucose (sugar).

How are Glucient SR 750 mg prolonged-release tablets used?
Glucient SR 750 mg Prolonged-release tablets are taken by mouth. A single tablet should be swallowed (without chewing) with a glass of water. The patient should take one or two tablets a day, depending on doctor's recommendation, with an evening meal.

The maximum recommended daily dose is 1500 milligrams of Glucient SR 750 mg prolonged-release tablets.

Glucient SR 750 mg prolonged-release tablets can only be obtained on prescription from a doctor.

For further information on how Glucient SR 750 mg prolonged-release tablets are used, please see the Summary of Product Characteristics and the package leaflet available on the MHRA website.

How do Glucient SR 750 mg prolonged-release tablets work?
Glucient SR 750 mg prolonged-release tablets contain 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. As a result, the absorption of sugar from the intestines into the bloodstream is delayed.

How have Glucient SR 750 mg prolonged-release tablets been studied?
Because Glucient SR 750 mg prolonged-release tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the medicinal product, Glucophage SR 750 mg prolonged-release tablets (Merck Serono Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Glucient SR 750 mg prolonged-release tablets?
As Glucient SR 750 mg prolonged-release tablets is a generic medicine that is bioequivalent to Glucophage SR 750 mg prolonged-release tablets (Merck Serono Limited), its benefits and risks are taken as being the same as Glucophage SR 750 mg prolonged-release tablets (Merck Serono Limited).

Why are Glucient SR 750 mg prolonged-release tablets approved?
It was concluded that, in accordance with EU requirements, Glucient SR 750 mg prolonged-release tablets have been shown to have comparable quality and to be bioequivalent to Glucophage SR 750 mg prolonged-release tablets (Merck Serono Limited). Therefore, the view was that, as for Glucophage SR 750 mg prolonged-release tablets (Merck Serono Limited) the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Glucient SR 750 mg prolonged-release tablets?
A risk management plan has been developed to ensure that Glucient SR 750 mg prolonged-release tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Glucient SR 750 mg prolonged-release tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Glucient SR 750 mg prolonged-release tablets
Republic of Ireland and the UK agreed to grant a Marketing Authorisation for Glucient SR 750 mg prolonged-release tablets on 13th July 2014. A Marketing Authorisation was granted in the UK on 12th August 2014.

The full PAR for Glucient SR 750 mg prolonged-release tablets follows this summary. For more information about treatment with Glucient SR 750 mg prolonged-release tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in October 2014.

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Module 1
Information about initial procedure

Product Name	Glucient SR 750 mg prolonged-release tablets
Type of Application	Generic, Article 10.1
Active Substance	Metformin hydrochloride
Form	Prolonged-release tablets
Strength	750 mg
MA Holder	Consilient Health Limited, 5th Floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland
RMS	UK
CMS	Republic of Ireland
Procedure Number	UK/H/5129/001/DC
Timetable	Day 209 – 13th July 2014

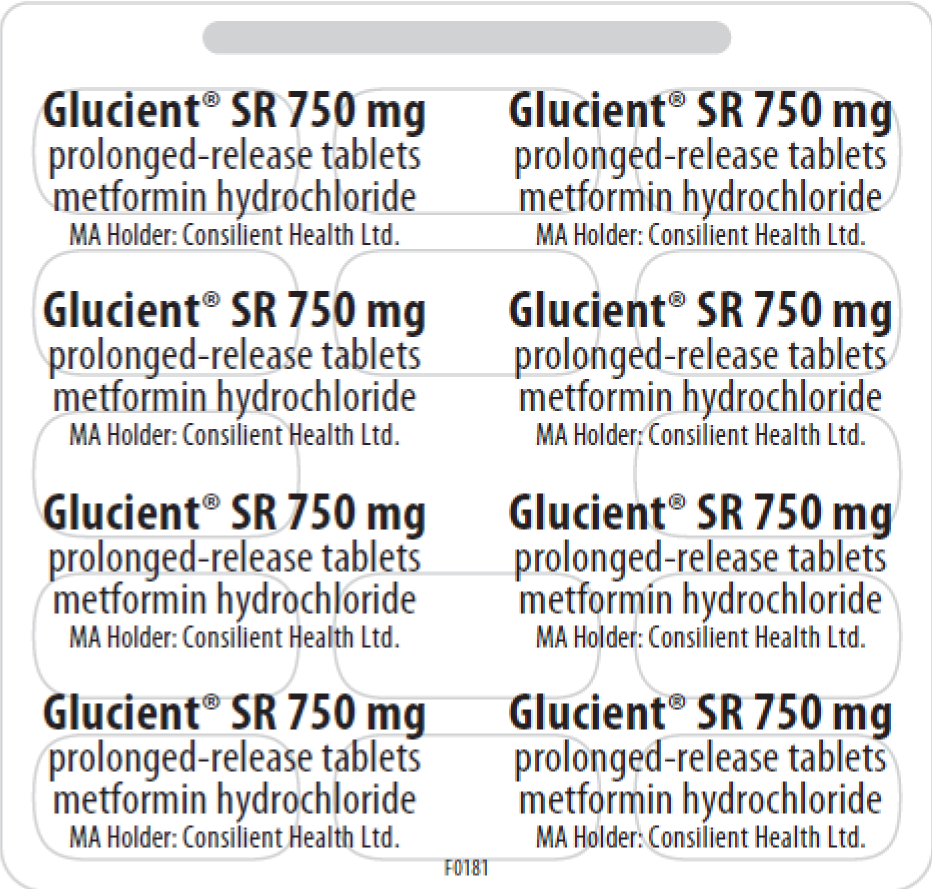
Module 2
Summary of Product Characteristics

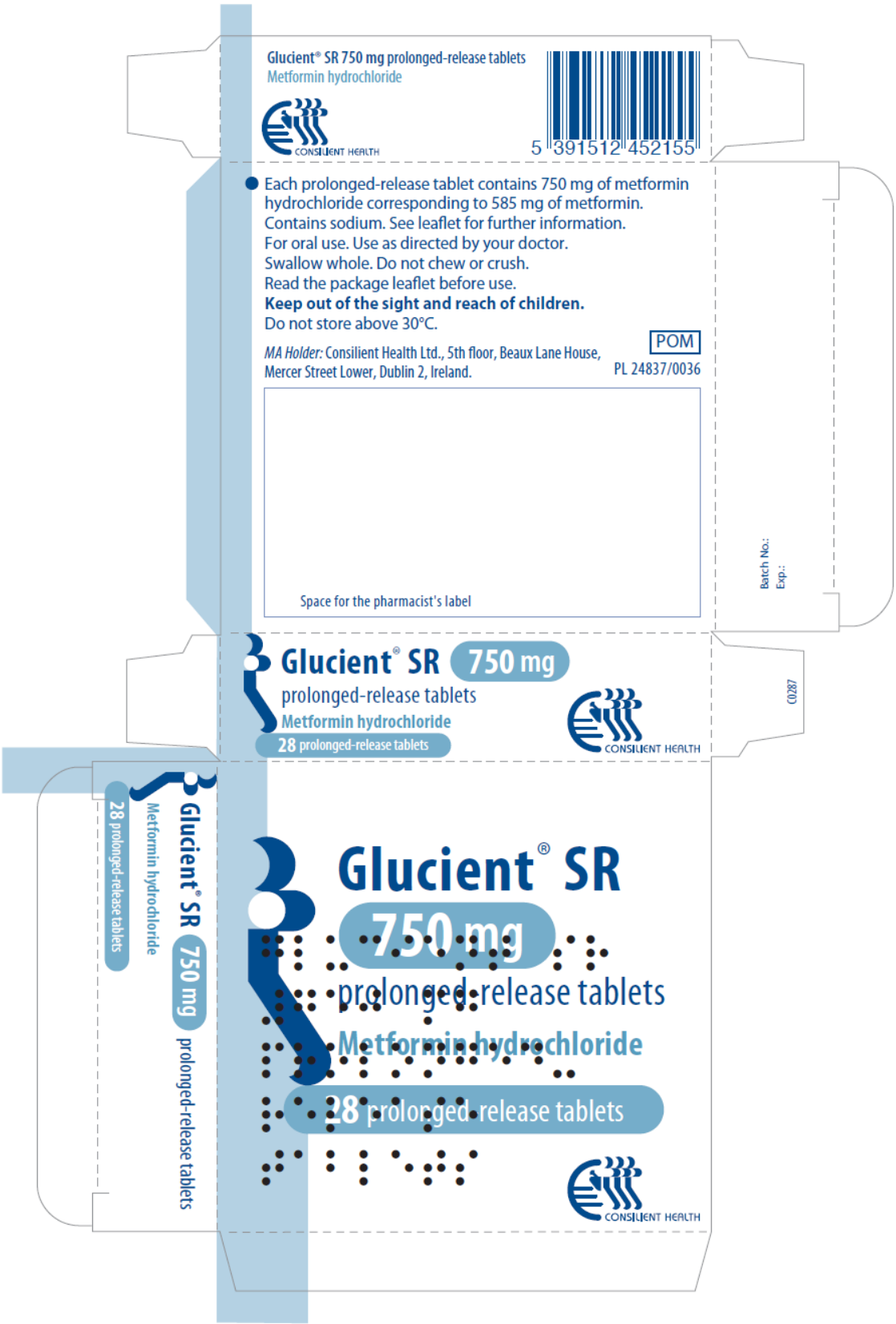
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4
Labelling




Glucient® SR 750 mg prolonged-release tablets
Metformin hydrochloride
CONSILIENT HEALTH
5 391512 452155
Each prolonged-release tablet contains 750 mg of metformin hydrochloride corresponding to 585 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 24837/0036
Space for the pharmacist's label
Batch No.:
Exp.:
Glucient® SR 750 mg
prolonged-release tablets
Metformin hydrochloride
28 prolonged-release tablets
C0287
Glucient® SR
750 mg
prolonged-release tablets
Metformin hydrochloride
28 prolonged-release tablets
CONSILIENT HEALTH


Glucient® SR 750 mg prolonged-release tablets
Metformin hydrochloride
CONSILIENT HEALTH
5 391512 452162
Each prolonged-release tablet contains 750 mg of metformin hydrochloride corresponding to 585 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 24837/0036
Space for the pharmacist's label
Batch No.:
Exp.:
Glucient® SR 750 mg
prolonged-release tablets
Metformin hydrochloride
56 prolonged-release tablets
CONSILIENT HEALTH
Glucient® SR 750 mg prolonged-release tablets Metformin hydrochloride 56 prolonged-release tablets
Glucient® SR
750 mg
prolonged-release tablets
Metformin hydrochloride
56 prolonged-release tablets
CONSILIENT HEALTH

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Glucient SR 750 mg prolonged-release tablets (PL 24837/0036; UK/H/5129/001/DC) 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, is approvable.

This application was submitted under the Decentralised Procedure (DCP) according to Article 10(1) of Directive 2001/83/EC, as amended, as a generic equivalent of Glucophage SR 750 mg prolonged-release tablets authorised to Merck Serono Limited (PL 11648/0066) on 21st of February 2008. This reference product was submitted as a hybrid (line extension) application referring to Glucophage SR 500 mg prolonged-release tablets, first authorised to Merck Serono Limited (PL 11648/0054) on 26th November 2004, which was a line extension of the originator product, Glucophage 500 mg Film-coated Tablets (PL 03759/0012). This application represented a change in pharmacokinetics compared to the immediate-release presentation and the product was first authorised in the UK on 21st of September 1982 to Lipha Pharmaceuticals Ltd and hence have been marketed in the EEA for at least 10 years. The Marketing Authorisation for Glucophage 500 mg film-coated tablets was transferred to Merck Serono, the parent company of Lipha Pharmaceuticals Ltd (PL 11648/0085), on 1st April 2010.

With the UK as the RMS in this Decentralised Procedure (UK/H/5129/001/DC), Consilient Health Limited applied for the Marketing Authorisation for Glucient SR 750 mg prolonged-release tablets in the Republic of Ireland.

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

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

Bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those

countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 209 – 13th July 2014). After a subsequent national phase, the UK granted a Marketing Authorisation for this product on 12th August 2014 (PL 24837/0036).

II. ABOUT THE PRODUCT

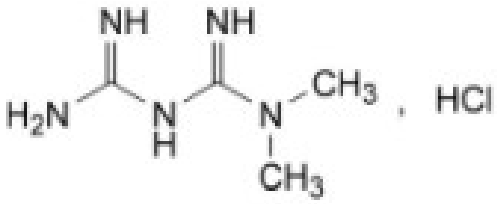
Name of the product in the Reference Member State	Glucient SR 750 mg prolonged-release tablets
Name(s) of the active substance(s) (INN)	Metformin hydrochloride
Pharmacotherapeutic classification (ATC code)	Gastrointestinal tract and metabolism A10BA02
Pharmaceutical form and strength(s)	Prolonged-release tablets, 750 mg
Reference numbers for the Decentralised Procedure	UK/H/5129/001/DC
Reference Member State	UK
Concerned Member State	Republic of Ireland
Marketing Authorisation Number(s)	PL 24837/0036
Name and address of the authorisation holder	Consilient Health Limited, 5th Floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

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: $C_4H_{12}CIN_{15}$
Molecular Weight: 165.6 g/mol
Appearance: White or almost white crystals.
Solubility: Freely soluble in water, slightly soluble in alcohol 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients carmellose sodium 2000, hypromellose 100M, silica, colloidal anhydrous and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

It had been confirmed that the excipients used are free of TSE/BSE and the corresponding certificates issued by each supplier were suitably provided. This is acceptable.

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable prolonged-released tablets that contain the same active ingredient as , Glucophage SR 750 mg prolonged-release tablets (Merck Serono Limited).

Comparative impurity and dissolution profiles have been presented for test and reference products.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has

been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided and comply with the specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packaged in a PVC/PVDC aluminium blisters with 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 have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months with a storage condition of 'Do not store above 30ºC' have been set and these are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labels are pharmaceutically acceptable.

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Glucient SR 500 mg prolonged-release tablets (parent PIL). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

The Marketing Authorisation holder (MAH) has stated that not all licensed pack sizes may be marketed. However, they have committed to submit mock-ups of any pack size to the relevant regulatory authorities before marketing.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert report/Quality Overall Summary
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS

The pharmacological, pharmacokinetic and toxicological properties of metformin hydrochloride are well-known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for not submitting the environmental risk assessment. This is satisfactory.

There are no objections to the approval of this product from a non-clinical point of view.

III.3 CLINICAL ASPECTS

Clinical Pharmacology

Pharmacokinetics

In support of this application, the Marketing Authorisation holder has submitted the following three bioequivalence studies.

Single dose fasted study

This is an open, randomised, single dose, 2-period cross-over comparative bioavailability study of Glucient SR 750 mg prolonged-release tablets (test) and Glucophage® SR 750 mg prolonged-release tablets (reference) in 40 healthy, male and female volunteers under fasting conditions.

A single dose of the investigational products (1 tablet of 750 mg) was administered orally to each subject in each period after a supervised overnight fast.

Serial blood sampling before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 9, 12, 16, 24 and 30 hours after drug administration was carried out in each group. A washout period of 7 days was maintained.

Table 1. Pharmacokinetic Summary data for Metformin hydrochloride (N=40)

Parameter	% Ratio of Geometric Means (T/R)	90% Confidence Interval (T/R)		% CV	Conclusion
		Lower Limit	Upper Limit		
AUC_t ($ng.h.mL^{-1}$)	99.69	91.35	108.78	23.15	Bioequivalent*)
AUC_{inf} ($ng.h.mL^{-1}$)	99.93	91.63	108.98	22.98	
C_{max} ($ng.mL^{-1}$)	98.91	89.66	109.13	26.06	

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

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (Glucient SR 750 mg prolonged-release tablets) and the reference formulation (Glucophage® SR 750 mg prolonged-release tablets) for single dose under fasted conditions.

A single dose under high fat meal

This is an open, randomised, single dose, 2-period cross-over comparative bioavailability study of Glucient SR 750 mg prolonged-release tablets (test) and

Glucophage® SR 750 mg prolonged-release tablets (reference) in 23 healthy, male and female volunteers under high fat meal condition.

A single dose of the investigational products (1 tablet of 750 mg either test or reference drug) was administered orally to each subject in each period with 240 ml of water after a supervised overnight fast of at least 10 hours, the subjects received a high fat, high calorie breakfast.

Serial blood sampling before dosing and at 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 9, 12, 16, 24 and 30 hours after drug administration was carried out in each group. A washout period of 7 days was maintained between the two 2 phases of the study.

Table 2. Pharmacokinetic Summary data for Metformin hydrochloride (N=23)

Parameter	% Ratio of Geometric Means (T/R)	90% Confidence Interval (T/R)		% CV	Conclusion
		Lower Limit	Upper Limit		
AUC_t ($ng.h.mL^{-1}$)	101.31	95.15	107.88	12.40	Bioequivalent*)
AUC_{inf} ($ng.h.mL^{-1}$)	100.51	95.20	106.12	10.72	
C_{max} ($ng.mL^{-1}$)	106.14	95.59	113.13	12.60	

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

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (Glucient SR 750 mg prolonged-release tablets) and the reference formulation (Glucophage® SR 750 mg prolonged-release tablets) for single dose under fed conditions.

A multiple dose study

This is a randomized, single blind (investigators blind), two-period, two-sequence cross-over multiple dose bioavailability study of Glucient SR 750 mg prolonged-release tablets (test) and Glucophage® SR 750 mg prolonged-release tablets (reference) in 37 healthy, male and female volunteers under normal diabetic meal condition.

The treatment was consisted of 2 periods of 2 phases each. Each period included a multiple dose phase under fed condition using a normal diabetic meal.

Blood samples were collected prior to study drug administration and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 9, 12, 16, 24 and 30 hours post-dose. A washout period of 11 days was maintained between two periods.

Table 3. Pharmacokinetic Summary data for Metformin (N=37)

Parameter	% Ratio of Geometric Means (T/R)	90% Confidence Interval (T/R)		% CV	Conclusion
		Lower Limit	Upper Limit		
AUC_{tau} ($ng.mL^{-1}.h$)	97.52	91.85	103.53	15.11	Bioequivalent*)
C_{min} ($ng.mL^{-1}$)	104.30	88.93	122.34	41.67	
C_{maz} ($ng.mL^{-1}$)	101.62	98.03	105.34	9.04	

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

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (Glucient SR 750 mg prolonged-release tablets) and the reference formulation (Glucophage® SR 750 mg prolonged-release tablets) for multiple dose under fed conditions.

Pharmacodynamics
No new data have been submitted and none are required for this generic application.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

Expert Report
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form
The MAA form is medically satisfactory.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Glucient SR 750 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 applications of this type.

CLINICAL

Bioequivalence have been demonstrated between the applicant's Glucient SR 750 mg prolonged-release tablets and the reference product, Glucophage® SR 750 mg prolonged-release tablet.

No new or unexpected safety concerns arose from this application.

The SmPC and PIL are satisfactory and consistent with those of the reference product. Satisfactory labelling has also been submitted.

BENEFIT-RISK ASSESSMENT

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

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome