COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Glycofren 1000 mg effervescent tablets

(metformin hydrochloride)

NL/H/4892/001/DC

Date: 8 April 2021

This module reflects the scientific discussion for the approval of Glycofren 1000 mg effervescent tablets. The procedure was finalised at 17 December 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Glycofren 1000 mg effervescent tablets from Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.

The product is indicated for treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Glycofren may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children from 10 years of age and adolescents, Glycofren may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin hydrochloride as first-line therapy after diet failure (see SmPC section 5.1).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the European reference product Glucophage 1000 mg poudre pour solution buvable en sachet-dose which has been registered in France by Merck Sante S.A.S. since 2 December 2008 (marketing authorisation (MA) numbers: 34009 390 160 8 5 (box of 30 sachets) and 34009 390 161 4 6 (box of 60 sachets)). Glucophage is currently not marketed due to the sunset clause. The use of Glucophage as reference product is adequately justified.

The concerned member states (CMS) involved in this procedure were France and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Glycofren is a white, round, flat-faced, bevel-edged, bisect, effervescent tablet. The effervescent tablet can be divided into equal doses.

The effervescent tablets are packed in Al/PE strips.

One tablet contains 1000 mg of metformin hydrochloride corresponding to 780 mg metformin.

The excipients are povidone (PVP K-30) (E1201), sodium hydrogen carbonate (E500), sodium carbonate (E500), lemon flavour in powder (containing: natural flavouring substances in concentration 20.0%, maltodextrin (maize) in concentration 65.5%, modified starch (E1450) (waxy maize) in concentration 5.0%, sugar (sucrose) in concentration 9.5%), citric acid crystalline (E330), citric acid powder (E330), potassium acesulfame (E950), isomalt (E953), sodium cyclamate (E952), and glycine (E640).

II.2 Drug Substance

The active substance is metformin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride but freely soluble in water.

The CEP procedure is used by both manufacturers for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for one batch of each manufacturer.

Stability of drug substance
The active substance is stable for three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Appreciation/palatability of the drug product in solution is justified with bibliographic data. This is acceptable in view of the fact that there

are sufficient alternative products/formulations with metformin hydrochloride available on the market for patients who dislike the taste of the product. The effervescent tablets contain a score line and it has been demonstrated that the tablets can adequately be split by hand to obtain two halved doses.

The product is an aqueous oral solution at the time of administration and contains metformin hydrochloride, in the same concentration as the reference product; hence no dissolution study is required.
The solubility in water of drug substance, which is a critical characteristic, is adequately discussed. The MAH has adequately justified that the particle size of the drug substance is not critical for the drug product.

Pharmaceutical development is adequately described.

Manufacturing process
The manufacturing process is a wet granulation followed by compression. A sufficiently detailed description of the manufacturing process is provided. Relevant process parameters are included. No intermediates are stored.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients
With the exception of the lemon flavour, all excipients comply to a Ph.Eur. monograph. The quantitative composition of the natural flavouring substance and the natural lemon flavouring preparation have been provided. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, average weight, assay, impurities, uniformity of dosage units, subdivision of tablets, nitrosamine impurities, disintegration, water content, dissolution rate, hardness, and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been submitted for sufficient full scale batches stored for 30 months at 25°C/60% RH, and six months at 40°C/75% RH, in the proposed packaging. The conditions used in the stability studies are according to the ICH stability guideline. After 30 months storage the levels remained well within the specifications. On basis of the data submitted, a shelf life was granted of 30 months with no special temperature storage

conditions. The tablets should be stored in the original package in order to protect from moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Glycofren has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Glycofren is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Glucophage which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Metformin hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The

overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The MAH applied for exemption from the requirements to perform a bioequivalence study of the generic product Glycofren 1000 mg effervescent tablets. The MAH applied for a biopharmaceutics classification system (BCS) based biowaiver.

This is based on the BCS classification (III) of metformin and that metformin is not a narrow therapeutic index drug (NTI). Further, in order to accept the requested biowaiver, in line with the Guideline on Bioequivalence, it should be demonstrated that (1) both test and reference product show very rapid *in vitro* dissolution and (2) excipients that might affect bioavailability are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar.

Regarding the dissolution (1), it was indicated that it could reasonably be assumed that both test (Glycofren 1000 mg, effervescent tablets) and reference product (Glucophage 1000 mg, poudre pour solution buvable en sachet-dose) demonstrate rapid *in vitro* dissolution after administration, as in fact both products are a solution at time of administration. However, this was not formally demonstrated or discussed for the reference product in the initial application.
Subsequently, adequate details of the amount of water used and analytical method have been provided. The MAH indicated that the UK product Glucophage 1000mg powder for oral solution by Merck Serono Ltd (MA number PL 11648/0090) was used in a comparative study in 2014. Note: according to the MAH the French product used as European Reference Product (ERP), i.e. Glucophage 1000 mg poudre pour solution buvable en sachet-dose, was not available at that time. The MAH argued that due to the pharmaceutical form dissolution test cannot be performed. This is correct. A comparison of appearance of the solution, pH and % dissolved metformin hydrochloride between Glycofren 1000 mg effervescent tablet and the UK reference product Glucophage 1000 mg powder for oral solution is provided. Glycofren and Glucophage 1000 mg powder for oral solution were both dissolved in 200 ml water and tested after 5 minutes. The pH of the solutions were found to be comparable and % dissolved quantity of metformin hydrochloride HCl is almost the same. A difference was observed in appearance of the solution; clear solution (Glycofren) vs. clear to slightly cloudy solution (Glucophage). The dissolved quantity of the active ingredient is measured using a validated analytical method. The data confirm the active substance is fully dissolved at the time of administration.

Further (2), initially it could be not concluded that the compositions of test and reference formulations are qualitatively and quantitatively comparable, as it was noted that several excipients are present in the Glucophage formulation (reference product) which are not present in the Glycofren formulation and vice versa.

Subsequently, the MAH has sufficiently discussed the differences between the compositions of Glycofren and the reference product Glucophage. Differences are largely attributed to the different pharmaceutical dosage forms of the effervescent tablet and the powder for oral solution. It is agreed that the differing excipients are not known to influence solubility or bioavailability, or transporter proteins. In the light of the knowledge that polyols can cause intestinal osmotic stress, the MAH convincingly argued that this does not hold true for erythritol as present in the Glucophage product. Erythritol demonstrates fast and complete absorption and thereby a reduced likelihood of causing osmotic stress and alter intestinal transit time. Furthermore, Glycofren contains sodium hydrogen carbonate and sodium carbonate as alkalizing agents, and lemon as a flavouring agent as additional excipients. The sodium hydrogen carbonate and sodium carbonate are necessary for effervescent pharmaceutical dosage forms and are not expected to affect the solubility of metformin hydrochloride. Thus, the MAH sufficiently justified the differences between compositions of Glycofren and the reference product Glucophage.

All aspects above considering, comparable bioavailability between the test and the reference product can be assumed. A BCS-based biowaiver is justified.

IV.3 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 Glycofren.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Lactic acidosis (occurring with or without renal failure/impairment and/or concomitant use with iodinated contrast media)
Important potential risks	--
Missing information	--

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Glucophage 1000 mg, powder for oral solution. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Glycofren 1000 mg effervescent tablets has a proven chemical-pharmaceutical quality and is a generic form of Glucophage 1000 mg, powder for oral solution in single-dose container. Glucophage is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Glycofren with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 December 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse