LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Buprenorphine G.L. Pharma
(buprenorphine, buprenorphine hydrochloride)

SE/H/2385/01-02/DC

This module reflects the scientific discussion for the approval of Buprenorphine G.L. Pharma. The procedure was finalised on 2025-03-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Buprenorphine G.L. Pharma, 0,2 mg, 0,4 mg, Sublingual tablet.

The active substance is buprenorphine, buprenorphine hydrochloride. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Buprenorphine G.L. Pharma, 0.2 mg, 0.4 mg, sublingual tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, NL and NO as concerned member states (CMS). The application was withdrawn in FR on 2024-09-09 (during clockstop).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Temgesic, sublingual tablet, 0.2 mg, authorised in Sweden since 1986, with Eumedica Pharmaceuticals GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Temgesic forte sublingual, 0.4 mg, sublingual tablet from Germany with Indivior Europe Limited, as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS NL: Temgesic, 0.4 mg, sublingual tablet, authorised in Sweden since 1990, with Eumedica Pharmaceuticals GmbH as marketing authorisation holder. The justification to use this product is based on RMS's own files. The ERP information was shared during the validation period. (Previously true also for CMS FR before the withdrawal of application in FR.)

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of buprenorphine are well known. As buprenorphine is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Buprenorphine G.L. Pharma is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Buprenorphine G.L. Pharma from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Buprenorphine G.L Pharma with the reference products Temgesic and Subutex.

Pharmacokinetic properties of the active substance
Absorption: Buprenorphine has an oral bioavailability of 50 % when administered sublingually. Following an oral dose of buprenorphine maximal plasma concentrations occur at approximately 2 hours.

There are no restrictions with respect to food in the SmPC of the originator.

Study 049B19
Methods
This was a single-dose, three-way crossover study conducted in 15 healthy volunteers, comparing Buprenorphine, 0.4 mg, sublingual tablets with Subutex, 0.4 mg, sublingual tablets (reference product 1) and with Temgesic, 0.4 mg, sublingual tablets (reference product 2) under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of buprenorphine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2021-03-26 and 2021-05-27.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for buprenorphine.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (N=14)	**2.4797 ± 0.6988**	**0.3714 ± 0.1422**	**1.25 (0.83-3.00)**
Reference 1 (N=14)	**2.4189 ± 0.6043**	**0.3270 ± 0.1171**	**1.38 (0.83-4.00)**
Reference 2 (N=13)	**2.5014 ± 0.7237**	**0.3730 ± 0.1245**	**1.50 (0.83-3.00)**
***Ratio T/R1 (90% CI)**	**100.85 (90.60-112.25)**	**111.51 (95.87-129.71)**	**-**
***Ratio T/R2 (90% CI)**	**96.96 (88.37-106.39)**	**97.35 (86.58-109.46)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For comparison with reference 2, for AUC_{0-t} and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

For comparison with reference 1, for AUC_{0-t} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %. However, C_{max} was outside 125.00 %.

A biowaiver was sought for the additional strength of 0.2 mg.

Discussion and overall conclusion

The bioequivalence study was performed in accordance with accepted standards for bioequivalent testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the result, the applicant decided to claim the bridge to Temgesic only. However, by using two reference products the study had two chances to show equivalence, and the strategy for testing prespecified in the protocol does not control for multiplicity. At Day 120, the Applicant has provided additional statistical calculations for the comparison of T/R2 by using Bonferroni correction of a/2 instead of a, which leads to the calculation of 95% confidence intervals. The 95% confidence intervals for absorption: AUC_{0-t}, $AUC_{0-\infty}$, and the rate of absorption (C_{max}) of T vs. R2 are within the acceptance range of 80.00% - 125.00% for buprenorphine. The multiplicity strategy was not pre-specified and other strategies than Bonferroni correction could, in theory, have been applied. However, for this procedure, the results are considered sufficiently conservative, and can be accepted as claim for equivalence.

Absence of studies with the additional strength of 0.2 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of buprenorphine can be considered linear between 0.075 mg and 1.200 mg based on submitted literature data.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Buprenorphine G.L. Pharma.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 2023-08-07 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	- Respiratory depression - Drug dependence and withdrawal - Abuse, misuse and diversion - Fatal overdose - Paediatric intoxication - Use during pregnancy and lactation (effects on newborn and infant) - Use in patients with severe hepatic impairment - CNS depression
Important potential risks	- Medication error
Missing information	- Elderly patient > 65 years old - Children < 15 years old

Assessor´s comment: The summary of safety concerns are based on the PRAC PSUR assessment report from procedure EMEA/H/C/PSUSA/00000459/202007. This is agreed.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 2023-08-07 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet 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 language used for the purpose of user testing the PL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Buprenorphine G.L. Pharma, is found adequate. There are no objections to approval of Buprenorphine G.L. Pharma, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated.
The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Buprenorphine G.L. Pharma, 0,2 mg, 0,4 mg, Sublingual tablet was positively finalised on 2025-03-12.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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