LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Farghess
(promethazine hydrochloride)

SE/H/2101/01/DC

This module reflects the scientific discussion for the approval of Farghess. The procedure was finalised on 2021-12-15. 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 Farghess, 25 mg, Film-coated tablet.

The active substance is promethazine hydrochloride, promethazine. 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 Farghess, 25 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, New.Fa.Dem. S.r.l., apply through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IT as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Lergigan, 25 mg, film-coated tablet, authorised in Sweden since 1953, with Meda AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Lergigan Forte, 50 mg, film-coated tablets from Sweden with Meda AB as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS IT: Lergigan, 25 mg, film-coated tablets authorised in Sweden since 1953, with Meda AB as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information from Sweden was circulated during validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in these applications.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since product name 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 product name 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 promethazine hydrochloride (Farghess) 50 mg film-coated tablet with the reference product Lergigan Forte 50 mg film-coated tablet.

Pharmacokinetic properties of the active substance
The applicant claims that the pharmacokinetics of the product is linear over the range of 25-50 mg. There are no restrictions with respect to food in the SmPC of the originator and the terminal half-life is around 13 hours.

Study BE-1231-14*Methods*
This was an open-label, randomized, single-dose, two-way crossover bioequivalence study conducted in 36 healthy volunteers, comparing promethazine hydrochloride (Farghess), 50 mg, film-coated tablet with Lergigan Forte, 50 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of promethazine 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 18/09/14 and 28/09/14.

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for promethazine hydrochloride, n=31.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	434.13 ± 295.52	30.58 ± 14.53	2.67 (1.50 - 6.00)
Reference	403.44 ± 238.39	28.97 ± 11.54	2.33 (1.50 - 8.00)
***Ratio (90% CI)**	105.52 (99.62 - 111.78)	104.00 (96.54 - 112.05)	-
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 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 %.

A biowaiver was sought for the strength of 25 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence 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.

Absence of studies with the strength of 25 mg is acceptable, as all conditions for biowaiver for the applied strength, 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 promethazine hydrochloride is linear or possibly non-linear with a more than dose proportional increase in exposure with increasing doses between 25 mg and 50 mg.

Based on the submitted bioequivalence study, Farghess 50 mg film-coated tablet is considered bioequivalent with reference product Lergigan Forte 50 mg film-coated tablet and, as stated above, biowaiver of the 25 mg strength is acceptable.

Pharmacodynamics/Clinical efficacy/Clinical safety

Initially no new studies on pharmacodynamics, clinical efficacy or clinical safety had been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data was deemed not necessary.

On request from IT, studies were submitted for further assessment of certain indications of the reference product (in SE) not previously approved in IT, and certain indications were withdrawn**.** Further those indications of the reference product which include a recommended lower dose than 25 mg are considered not adequate as the tablet applied for cannot be split and there was no other strength applied for**.**

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 Farghess.

Safety specification

The MAH has submitted the version 0.2 RMP dated 22/10/2021 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risk	none
Important potential risk	none
Missing information	none

Assessors comment's: The proposed summary of safety concerns is in line with that of the other promethazine-containing products. This is considered acceptable.

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

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

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 22/10/2021 is considered acceptable.

The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

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 PIL 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, Farghess, is found adequate. There are no objections to approval of Farghess, 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 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 Farghess, 25 mg, Film-coated tablet was positively finalised on 2021-12-15.

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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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