LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Prometazin Actavis
(promethazine hydrochloride)

SE/H/1555/01/DC

This module reflects the scientific discussion for the approval of Prometazin Actavis. The procedure was finalised on 2016-07-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Prometazin Actavis, 25 mg film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Actavis Group PTC ehf. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and IS as concerned member states (CMS). FI was withdrawn at Day 114. The application for the strength 50 mg has been withdrawn. NO was withdrawn at Day 185.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Lergigan, 25 mg, film-coated tablets, authorised in SE since 1953, with Recip AB as marketing authorisation holder.
The reference product used in the bioequivalence study is Lergigan Forte, 50 mg, film-coated tablets from SE with Recip AB as marketing authorisation holder.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence was evaluated in one adequately designed single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Prometazin Actavis 50 mg film-coated tablet with Lergigan 50 mg film-coated tablet under fasting conditions. The study was conducted at Watson Pharma Pvt. Ltd, Navi Mumbai, India between 18/09/14 and 28/09/14. Blood samples were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of promethazine were determined with an adequately validated LC/MS/MS method. An achiral bioanalytical method was justified since the enantiomers have similar pharmacodynamic properties.

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%, see table below.

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

Based on the results from the bioequivalence study, bioequivalence between Prometazin Actavis 50 mg film-coated tablet and Lergigan 50 mg film-coated tablet was satisfactorily demonstrated. Absence of studies with the 25 mg strength is acceptable, since all conditions for biowaiver of additional strength are fulfilled. Conducting the study with the highest strength is justified given that the pharmacokinetics of promethazine is linear or possibly non-linear with a more than dose-proportional increase in exposure with increasing doses.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Prometazin Actavis.

Safety specification

Summary table of safety concerns proposed in the RMP

Important identified risks	Worsening of pre-existing medical conditions (glaucoma, hyperthyroidism, active gastric or duodenal ulcer, pyloric stenosis, severe cardiovascular disease, liver disease, hypertrophy or adenoma of the prostate gland) due to anticholinergic effects of promethazine
Important potential risks	Risk of cerebrovascular events in patients with risk factors for stroke Extrapyramidal symptoms (EPS)
Missing information	NA

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.

Conclusion of the RMP

The RMP is 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 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 benefit/risk ratio is considered positive and Prometazin Actavis, 25 mg film-coated tablets is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The Mutual recognition/Decentralised procedure for Prometazin Actavis, 25 mg film-coated tablets was positively finalised on 2016-07-05.

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Public Assessment Report – Update

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)

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