LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Orlistat Accord
(orlistat)

SE/H/2256/01/DC

This module reflects the scientific discussion for the approval of Orlistat Accord. The procedure was finalised on 2023-06-14. 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 Orlistat Accord, 120 mg, Capsule, hard.

The active substance is orlistat. 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 Orlistat Accord, 120 mg, capsule, hard, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, IE, NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xenical, 120 mg, capsule, hard authorised in the Union since 1998, with Cheplapharm Arzneimittel GmbH as marketing authorisation holder.

The reference product used in the clinical studies for demonstration of therapeutic equivalence is Xenical, 120 mg, capsule, hard from DE with Cheplapharm Arzneimittel GmbH as marketing authorisation holder.

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 this application.

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 orlistat are well known. As orlistat 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 Orlistat Accord 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 Orlistat Accord from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
Absorption
Studies in normal weight and obese volunteers have shown that the extent of absorption of orlistat was minimal. Plasma concentrations of intact orlistat were non-measurable (< 5 ng/ml) eight hours following oral administration of orlistat.

In general, at therapeutic doses, detection of intact orlistat in plasma was sporadic and concentrations were extremely low (< 10 ng/ml or 0.02 µmol), with no evidence of accumulation, which is consistent with minimal absorption.

Distribution
The volume of distribution cannot be determined because the drug is minimally absorbed and has no defined systemic pharmacokinetics. In vitro orlistat is > 99 % bound to plasma proteins (lipoproteins and albumin were the major binding proteins). Orlistat minimally partitions into erythrocytes.

Metabolism
Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on a study in obese patients, of the minimal fraction of the dose that was absorbed systemically, two major metabolites, M1 (4-member lactone ring hydrolysed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42 % of the total plasma concentration.

M1 and M3 have an open beta-lactone ring and extremely weak lipase inhibitory activity (1000 and 2500 fold less than orlistat respectively). In view of this low inhibitory activity and the low plasma levels at therapeutic doses (average of 26 ng/ml and 108 ng/ml respectively), these metabolites are considered to be pharmacologically inconsequential.

Elimination
Studies in normal weight and obese subjects have shown that faecal excretion of the unabsorbed drug was the major route of elimination. Approximately 97 % of the administered dose was excreted in faeces and 83 % of that as unchanged orlistat.

The cumulative renal excretion of total orlistat-related materials was < 2 % of the given dose. The time to reach complete excretion (faecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese volunteers. Orlistat, M1 and M3 are all subject to biliary excretion.

Pharmacodynamics
Orlistat is a potent, specific and long-acting inhibitor of gastrointestinal lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine site of the gastric and pancreatic lipases. The inactivated enzyme is thus unavailable to hydrolyse dietary fat, in the form of triglycerides, into absorbable free fatty acids and monoglycerides.

Pharmacodynamic and pharmacokinetic study for demonstration of therapeutic equivalence
Introduction
Orlistat acts locally in the gastrointestinal tract by preventing the absorption of dietary fat. Orlistat exerts its therapeutic activity in the lumen of the stomach and small intestine. After oral administration the systemic absorption of orlistat is very low.

According to the "*Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents*" (CPMP/EWP/239/95), bioequivalence generally is not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy, although they may play a role with regard to safety.

According to the "*Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract*" (CPMP/EWP/239/95 Rev. 1, Corr.1*), pharmacokinetic data may however in certain cases be used in order to demonstrate therapeutic equivalence for locally applied products. In this case, however, the systemic absorption of orlistat is very low and conducting a formal bioequivalence study for bridging efficacy data from the originator's formulation is not meaningful. Instead, in accordance with the "*Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract*" (CPMP/EWP/239/95 Rev. 1, Corr.1*) a comparative pharmacodynamic equivalence and pharmacokinetic bioequivalence study has been conducted (Study 0320-21).

Study 0320-21
Methods
This was an open-label, balanced, randomised, two-sequence, two-treatment, two-period, multiple-doses crossover comparative pharmacodynamic equivalence and pharmacokinetic bioequivalence study conducted in 66 healthy volunteers under fed conditions. After the run-in period, subjects received multiple doses of either test or reference orlistat formulations. A single oral dose (120 mg) of either the test product or the reference product was administered with 240 ml of drinking water 10 minutes following the beginning of each meal (breakfast, lunch and dinner), 3 times in a day for ten consecutive days in each period.

Results

Pharmacodynamic Equivalence Results for Orlistat (N = 47)

Parameters (Units)	Geometric Least Squares Mean (n=47)			95% Confidence Interval (Parametric)	Intra Subject CV (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %		
Ln(Baseline corrected $FFE_{24(SS)}$ (%))	746.230	764.185	97.7	90.42 - 105.46	18.6

Relative Bioavailability Results for Metabolite 1 of orlistat (4-member lactone ring hydrolysed) (N = 65)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	46.961	54.126	86.8	81.64 - 92.20	21.0	100.0
$lnAUC_{0-t}$	353.463	406.324	87.0	82.69 - 91.52	17.5	100.0
$lnAUC_{0-\infty}$ ^	1422.078	1355.895	104.9	73.15 - 150.37	67.9	25.8

^N=19.

Discussion and overall conclusion

The comparative pharmacodynamic equivalence and pharmacokinetic bioequivalence study 0320-21 was of adequate design. The analytical methods applied appear adequate. The choice of the percentage of baseline corrected faecal fat excretion ($FFE_{24(SS)}$) as the pharmacodynamic endpoint to assess the pharmacodynamic equivalence between the two orlistat formulations is acceptable. Clarifications on the formulas for calculating $FFE_{24(SS)}$ and baseline corrected faecal fat excretion ($FFE_{24(SS)}$) has been provided. There is no separate statistical analysis plan (SAP), but the statistical methods are described in sufficient detail in the protocol and clinical study report. The statistical methods were adequate.

For baseline corrected $FEE_{24(SS)}$ the 95% confidence interval for the ratio of the geometric mean fell within the acceptance range of 80.00-125.00%. Therefore, therapeutic equivalence can be concluded.

The analysis of pharmacokinetic parameters of metabolite M1 of orlistat (4-member lactone ring hydrolysed) was provided as supportive information. For C_{max} and 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%. For these parameters the ratio of the test and reference products was lower than 1. Hence, systemic safety is not expected to be worse for Orlistat Accord compared to Xenical.

Clinical efficacy/ Clinical safety

No new studies on clinical efficacy or clinical safety have been submitted. A comprehensive review of the literature supporting the efficacy and safety of orlistat has been provided by the Applicant. Provided that therapeutic equivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted an updated risk management plan, version 1.1, 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 Orlistat Accord.

Safety specification

Important identified risks	• None
Important potential risks	• None
Missing information	• None

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 1.1, signed 20th October 2022, 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

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xenical, EMEA/H/C/000154 and Solifenacinsuccinat Accord, DK/H/2339/001-002/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Orlistat Accord, is found adequate. There are no objections to approval of Orlistat Accord, from a non-clinical and clinical point of view. Therapeutic equivalence 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 Orlistat Accord, 120 mg, Capsule, hard was positively finalised on 2023-06-14.

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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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