LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Letrozol Omet Pharma
(letrozole)

This module reflects the scientific discussion for the approval of Letrozol Omet Pharma. The procedure was finalised on 2022-05-23. 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 Letrozol Omet Pharma, 2,5 mg, Film-coated tablet.

The active substance is letrozole. 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 Letrozol Omet Pharma, 2,5 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Omet Pharma AB applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Femara, 2,5 mg, film-coated tablet (FR/H/0110/001) authorised in France since 1997, with NOVARTIS PHARMA SAS as marketing authorisation holder.
The reference product used in the bioequivalence study is the same as above: Femara, 2,5 mg, film-coated tablet (FR/H/0110/001) from France with NOVARTIS PHARMA SAS 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

Pharmacodynamic, pharmacokinetic and toxicological properties of letrozole are well known. As letrozole 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 Letrozol Omet 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 Letrozol Omet 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 Letrozole with the reference product Femara. The study compared the 2.5 mg strength in fasting condition.

Pharmacokinetic properties of the active substance

Absorption: Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max}: 1 hour fasted versus 2 hours fed; and mean C_{max}: 129 ± 20.3 nmol/l fasted versus 98.7 ± 18.6 nmol/l fed) but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken without regard to mealtimes.

Linearity: The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10 mg (dose range: 0.01 to 30 mg) and after daily doses up to 1.0 mg (dose range: 0.1 to 5mg). After a 30 mg single oral dose there was a slightly dose over-proportional increase in AUC value. The dose over-proportionality is likely to be the result of a saturation of metabolic elimination processes. Steady levels were reached after 1 to 2 months at all dosage regimens tested (0.1-5.0 mg daily).

Elimination: The apparent terminal elimination half-life in plasma is about 2 to 4 days. After daily administration of 2.5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Study 70584
Methods
This was a single-dose, two-way crossover study conducted in 22 healthy volunteers (20 completed), comparing Letrozole, 2.5 mg, film-coated tablet with Femara, 2.5 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 240 hours post-dose. Plasma concentrations of letrozole 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 16th of August 2008 and 13th of October 2008.

Results
The results from the pharmacokinetic and statistical analysis are presented in table 1 and table 2 below.

Table 1. Pharmacokinetic parameters (n=20)

Parameters		Test (Letrozole (A)) Mean	SD	CV (%)	Reference (Femara (B)) Mean	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	1585.58	375.28	23.67	1598.60	381.09	23.84
AUC_{0-inf}	(ng·h/mL)	1688.81	417.11	24.70	1701.45	419.12	24.63
C_{max}	(ng/mL)	36.96	8.61	23.31	37.78	8.53	22.58
Residual area	(%)	5.89	2.32	39.44	5.86	2.37	40.44
T_{max}	(h)	1.84	1.15	62.58	1.42	0.70	48.99
T_{max}*	(h)	1.50	0.58	-	1.25	0.92	-
K_{el}	(h^{-1})	0.0138	0.0046	33.22	0.0135	0.0037	27.39
$T_{½ el}$	(h)	54.28	13.75	25.34	54.56	12.27	22.50

*Medians and interquartile ranges are presented.

Table 2. Letrozole (A) vs Femara (B) (n=20)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	99.16%	99.19%	97.55%
90 % Geometric C.I.[2]	97.01 % to 101.37 %	96.77 % to 101.66 %	88.41 % to 107.64 %
Intra-Subject CV	4.01 %	4.50 %	18.09 %

[1]Calculated using least-squares means according to the formula: $e^{(\text{Letrozole (A) - Femara (B)})} \times 100$
[2] 90% Geometric Confidence Interval using 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%.

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.

Based on the submitted bioequivalence study, Letrozol Omet Pharma is considered bioequivalent with Femara.

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 Letrozol Omet Pharma.

Safety specification
The MAH has submitted the version 1.1 RMP dated 04-08-2021 and proposed the following summary safety concerns:

Summary of safety concerns	
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 04-08-2021 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 MPA;
- 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 information leaflet (PL) has been performed on the basis of a bridging report making reference to Letrozole 2,5 mg comprimé pelliculé (FR/H/417-418/01/DC). The bridging report submitted by the applicant is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Letrozol Omet Pharma, is found adequate. There are no objections to approval of Letrozol Omet 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 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

Letrozol Omet Pharma, 2,5 mg, Film-coated tablet was approved in the national procedure on 2022-05-23.

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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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