COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levonorgestrel Naari 1.5 mg, tablets

(levonorgestrel)

NL/H/4142/001/DC

Date: 26 November 2019

This module reflects the scientific discussion for the approval of Levonorgestrel Naari 1.5 mg, tablets. The procedure was finalised at 21 May 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levonorgestrel Naari 1.5 mg, tablets from Naari BV.

The product is indicated for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Levonelle 1.5 mg tablets which has been registered in the United Kingdom by Medimpex UK Limited since 16 April 2004 (original product). In the Netherlands, Postinor 1.5 mg tablets is registered via mutual recognition procedure (CZ/H/0939/001/MR) by Gedeon Richter Plc since 11 January 2007. Other levonorgestrel containing medicines are also on the market in the Netherlands.

The concerned member states (CMS) involved in this procedure were Denmark, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Levonorgestrel Naari is a white to off white, round bevel edged, flat faced tablets debossed with “J06” on one side and plain on other side.

And contains as active substance 1.5 mg of levonorgestrel.

The tablets are packed in a clear and transparent PVC/aluminium-blister.

The excipients are maize starch, potato starch, talc, colloidal anhydrous silica, magnesium stearate E470b, and lactose monohydrate.

II.2 Drug Substance

The active substance is levonorgestrel, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Levonorgestrel is practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol and soluble in chloroform.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additional tests and limits for identification and heavy metals have been included in the drug substance specification and are acceptable. It has been demonstrated that additional control of the elemental impurities in the drug substance as well as microbiological quality are not required. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance
Based on the data submitted, a retest period could be granted of 12 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients justified and their functions explained. All excipients used are well known. Formulation development and manufacturing process development have been adequately described.

A bioequivalence study has been performed with a full scale batch having the chosen final composition and the reference product. The *in vitro* dissolution tests complementary to the bioequivalence study have been performed with three dissolution media without surfactant and with the QC medium. The obtained results reflect the bioequivalence as demonstrated *in vivo*.

Manufacturing process
The product is manufactured using a wet granulation technique. It has been classified as a specialized pharmaceutical dosage form in accordance with the Guideline on process validation for finished products.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for full scale batches in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, weight variation, friability, disintegration time, water content, dissolution, uniformity of dosage units, assay, related substances and microbiological tests. The release and end of shelf-life limits are the same for all involved parameters except the limit for water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scale validation batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are in accordance with the ICH stability guideline. The batches were stored in the proposed packaging. The results demonstrate that the product in the chosen packaging material is stable during the tested period. All the tested parameters remain within the proposed specification. No trends are observed. Based on this data, a shelf life of 48 months is granted.

It has been demonstrated, that the tablet outside blister is not sensitive to moisture. The results of the photostability study confirm that the product is photostable. The proposed storage condition for the drug product: “This medicinal product does not require any special storage conditions” is considered acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Levonorgestrel Naari has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levonorgestrel Naari is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Levonelle which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levonorgestrel is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Levonorgestrel Naari 1.5 mg tablets (Naari BV, the Netherlands) is compared with

the pharmacokinetic profile of the reference product Levonelle 1.5 mg tablets (Medimpex UK Limited, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 40 healthy female subjects, aged 18-45 years. Each subject received a single dose (1.5 mg) of one of the two levonorgestrel formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 28 days. The use of oral hormonal contraception was not allowed during the study.

Blood samples were collected at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24, 36, 48 and 72 hours after administration of the products.

The design of the bioequivalence study is acceptable and in accordance with the guidelines on the investigation of bioequivalence. The washout period is sufficient. The sampling scheme covered a period of 72 hours, which is sufficient to estimate the pharmacokinetic parameters of interest.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

37 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levonorgestrel under fasted conditions.

Treatment N=37	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	283.3 ± 25.8	16.8 ±5.8	2.25 (1.0 - 5.0)
Reference	287.6 ±129.6	18.1 ±6.6	2.0 (1.25 - 5.0)
***Ratio (90% CI)**	0.93 (0.88 - 0.98)	0.99 (0.93 - 1.04)	--

CV (%)	92.5 (87.9 - 97.4)	0.97 (0.92 - 1.03)	--
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 concentration			

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Levonorgestrel Naari 1.5 mg tablets is considered bioequivalent with Levonelle 1.5 mg tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Levonorgestrel Naari.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	--
Important potential risks	--
Missing information	--

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Levonelle. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levonorgestrel Naari 1.5 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Levonelle 1.5 mg tablets. Levonelle is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Levonorgestrel Naari with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 May 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4142 /001/DC	New certificate from a new manufacturer	--	28-10-2019	Approval	--