

# **Public Assessment Report**

## **Scientific discussion**

**Halyone 1500 micrograms, tablets  
(levonorgestrel)**

**NL/H/2670/001/DC**

**Date: 6 May 2014**

This module reflects the scientific discussion for the approval of Halyone 1500 micrograms, tablets. The procedure was finalised on 25 October 2013. For information on changes after this date please refer to the module 'Update'.

## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Halyone 1500 micrograms, tablets from Laboratorios León Farma S.A.

The product is indicated for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraception 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 1500 micrograms. This product has been registered in the Netherlands under the trade name Postinor 1500 micrograms (NL License RVG 32253) through MRP UK/H/0803/001 since January 2007. Other levonorgestrel containing medicines are also on the market in the Netherlands.

The concerned member states (CMS) involved in this procedure were Czech Republic, Hungary, Poland and Slovakia.

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

## II. QUALITY ASPECTS

### II.1 Introduction

Halyone 1500 micrograms is a round, white tablet, marked "C" on one side and "1" on the other.

The tablets are packed in blisters of PVC/PVDC/Aluminium.

Each box contains one blister one 1500 microgram tablet.

The excipients are: microcrystalline cellulose, lactose monohydrate, poloxamer 188, croscarmellose sodium, magnesium stearate

### II.2 Drug Substance

The active substance is levonorgestrel, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder, which is practically insoluble in water and freely soluble in anhydrous ethanol and in methylene chloride. Polymorphic forms of levonorgestrel were not detected.

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 European Pharmacopoeia.

#### Manufacturing process

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

#### Quality control of drug substance

The drug substance specification was included. The specifications are in line with the Ph.Eur. with additional tests for residual solvents and particle size. Batch analytical data have been provided, demonstrating compliance with the drug substance specifications.

#### Stability of drug substance

The MAH has submitted stability data on the drug substance stored at 25°C/60%RH (up to 5 years) and 40°C/75%RH (6 months). All parameters remain stable throughout the test periods at both

temperatures. On the basis of the available stability data the claimed re-test period of 4 years, without temperature restriction, was granted.

## **II.3 Medicinal Product**

### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained.

An *in vivo* bioequivalence study has been performed demonstrating bioequivalence. Sufficient comparative dissolution data have been provided. The product development has been sufficiently described from a chemical-pharmaceutical point of view.

### Manufacturing process

The manufacturing process of the drug product consists of direct compression. Since the drug product consists of less than 2% active substance, the manufacturing process is considered to be a non-standard process. Process validation data have been submitted on three full-scaled batches.

### Control of excipients

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

### Quality control of drug product

The product specification includes tests for appearance, identification, assay, dissolution, content uniformity, related substances and microbiological control. The release and shelf-life limits are identical with the exception of the limits for related substances which are widened in the shelf-life specifications. The specification is considered acceptable.

The analytical methods have been adequately described and validated. Batch analytical data of 3 full-scale batches have been provided, demonstrating compliance with the release specification.

### Stability of drug product

Stability data on the drug product have been provided three pilot-scale batches stored at 25°C/60% RH (24 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 materials. A slight decrease in assay within 6 months at accelerated conditions was observed, and at long term conditions no trends were observed. The product was demonstrated to be photostable. Based on the submitted data the shelf life of 36 months without any special storage requirements can be granted.

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

The drug product contains lactose monohydrate sourced from milk of healthy animals collected under the same conditions as milk suitable for human consumption. Magnesium stearate is derived from vegetable source.

## **II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Halyone 1500 micrograms, tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH committed to continue the currently on-going studies on the first three development and bioequivalence batches up to at least 36 months.

## **III. NON-CLINICAL ASPECTS**

### **III.1 Ecotoxicity/environmental risk assessment (ERA)**

Since Halyone 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 a bioequivalence study, which is discussed below.

### **IV.2 Pharmacokinetics**

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Halyone 1500 micrograms (Laboratorios León Farma S.A., Spain) is compared with the pharmacokinetic profile of the reference product Postinor 1.5 mg tablets (Medimpex UK Ltd, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

#### Bioequivalence studies

##### *Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy female subjects, aged 19-45 years. Each subject received a single dose (1.5 mg) of one of the 2 levonorgestrel formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting continued for at least 4 hours following drug administration. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable. Fasted conditions are appropriate in view of the 'Note for Guidance on the investigation of bioavailability and bioequivalence' (CPMP/EWP/QWP/1401/98), as levonorgestrel may be taken without reference to food intake.

##### *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*

One subject did not show up for the second period. The remaining 39 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=39	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	282 $\pm$ 123	315 $\pm$ 132	19.5 $\pm$ 5.7	2.0 (1 – 6)	24.5 $\pm$ 5.7
<b>Reference</b>	284 $\pm$ 124	320 $\pm$ 137	22.4 $\pm$ 6.6	1.75 (0.75 - 4.0)	24.6 $\pm$ 5.9
<b>*Ratio (90% CI)</b>	1.0 (0.94 - 1.06)	--	0.87 (0.83 - 0.91)	--	--
<b>CV (%)</b>	15.4	--	11.6	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

#### Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC<sub>0-t</sub> and C<sub>max</sub> are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Halyone 1500 micrograms is considered bioequivalent with Postinor 1.5 mg tablets. The formulations were well tolerated, with no major side effects.

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 indicated that the current application concerns a generic product, with an active ingredient that has been in use for many years and has a well-established safety profile. Routine pharmacovigilance activities in accordance with EU regulations will be undertaken. As the safety profile of the drug is well-established, a Risk Minimisation Plan (RMP) is not considered necessary. The absence of an RMP is accepted, as this was not required when the application was made.

### **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. An appropriate pharmacovigilance system is in place. This generic medicinal product can be used instead of the reference product.

## **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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The studied population consisted of potential users of levonorgestrel, women over 18 years of age. Safety issues specific to levonorgestrel were addressed using questions that used imaginary situations to verify that the participant comprehended and was able to apply the information to make the correct decision. The technical readability, comprehensibility of the text, traceability of information and the applicability were investigated. In both rounds, the results showed that for each question, 90% of all participants were able to find the information requested within the PL, and 90% of all participants showed that they understand and can act upon it. Based on quantitative and qualitative results from testing, no edits were suggested to the PIL after the user test.

In conclusion, the test 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**

Halyone 1500 micrograms, tablets has a proven chemical-pharmaceutical quality and are generic forms of Levonelle 1500 micrograms, 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 Halyone 1500 micrograms, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 October 2013.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached