LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Amorest 28
(ethinylestradiol, norgestimate)

Asp no. 2014-0159

This module reflects the scientific discussion for the approval of Amorest. The procedure was finalised at 2015-02-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Amorest 28, 0.25 mg/0.035 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, CampusPharma 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 Cilest 28, 0.25 mg/0.035 mg, tablet, authorised in Sweden since 2001, with Janssen-Cilag AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Cilest®, 0.25 mg/0.035 mg, tablet from UK with Janssen-Cilag Ltd. UK as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

The medicinal product Amorest 28 consists of 21 blue tablets and 7 light green tablets. Each blue tablet contains 250 micrograms of norgestimate and 35 micrograms of ethinylestradiol. The light green tablets do not contain any active substances and are placebo tablets.

The excipients of the active tablets are microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, povidone, lactose anhydrous, lactose monohydrate, all-rac-alpha-tocopherol, magnesium stearate and indigo carmine aluminium lake (E132). The excipients of the placebo tablets are microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, lactose anhydrous, magnesium stearate, brilliant blue FCF aluminium lake (E133) and iron oxide yellow (E172).

The tablets are packaged in PVC-PVdC/Al-blisters inside a tri-laminated aluminium pouch containing a silica gel desiccant. The blisters are calendar printed and each blister contains 21 active tablets and 7 placebo tablets.

II.2 Drug Substance

The active substances in the blue tablets are norgestimate and ethinylestradiol.

Norgestimate. The drug substance norgestimate has a monograph in the European Pharmacopoeia (Ph. Eur.). Norgestimate drug substance is described as a white or almost-white powder that is practically insoluble in water. Norgestimate is not known to display polymorphism.

The structure of norgestimate has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

Ethinylestradiol. The drug substance ethinylestradiol has a monograph in the European Pharmacopoeia (Ph. Eur.). Ethinylestradiol is described as a white or slightly yellowish-white crystalline powder that is practically insoluble in water.

The structure of ethinylestradiol has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

The active and placebo tablets of Amorest 28 are formulated using excipients described in the current Ph. Eur., except for the included colorants. The colorants indigo carmine aluminium lake (E132) and brilliant blue FCF aluminium lake (E133) comply with acceptable in-house specifications as well as with the specifications set out in Commission Regulation (EU) 231/2012 regarding colorants in foodstuffs while iron oxide yellow (E172) complies with USP/NF.

TSE/BSE statements have been provided for each of the excipients included in the active and placebo tablets. The excipients used can be considered to be of no risk with respect to transmitting TSE.

The product development has taken into consideration the physico-chemical characteristics of the active substances.

The manufacturing process has been sufficiently described and critical steps identified for both the active and placebo tablets. Results from the process validation studies of the active tablets confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification. In addition, an acceptable process validation scheme to be followed for production scale batches of the placebo tablets has been submitted.

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 under ICH conditions have been performed and the data presented support the shelf life as stated in the SPC when stored protected from light.

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 single-dose, two-way crossover study conducted in 34 healthy female volunteers, comparing Norgestimate/Ethinylestradiol, 0.25 mg/0.035 mg, tablets with Cilest, 0.25 mg/0.035 mg, tablets under fasting conditions. The study was conducted at Lambda Therapeutic Research Ltd., Ahmedabad, India between 24th September and 30th October 2010. Blood samples were collected pre-dose and up to 96 hours post-dose. The study design is considered acceptable. Plasma concentrations of 17-deacetylnorgestimate (norelgestromin) and ethinylestradiol were determined with adequately validated LC-MS/MS methods.
The assessment of bioequivalence based on the metabolite 17-deacetylnorgestimate (norelgestromin) is acceptable. It is concluded that norgestimate is rapidly absorbed and extensively metabolised by first pass mechanisms following oral administration resulting in low plasma concentrations of norgestimate and using the metabolite 17-deacetylnorgestimate as surrogate for the parent compound is thus acceptable.

For AUC_{0-t} and C_{max} of both 17-deacetylnorgestimate and ethinylestradiol the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% and bioequivalence was demonstrated.

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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Cilest 21, PT/H/753-755+765/01/DC. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Amorest 28, 0.25 mg/0.035 mg, tablet, is recommended for approval.

VI. APPROVAL

Amorest 28, 0.25 mg/0.035 mg, tablet, was approved in the national procedure on 2015-02-26.

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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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