Public Assessment Report
Scientific discussion

Navalem 10 mg/10 mg Modified Release Hard Capsules

Doxylamine Succinate
Pyridoxine Hydrochloride

ES/H/0343/001/DC

This module reflects the scientific discussion for the approval of **Navalem 10 mg/10 mg Modified Release Hard Capsules**. The procedure was finalised on January 2018.

I. INTRODUCTION

This decentralized application concerns a generic version of doxylamine succinate and pyridoxine hydrochloride under Navalem 10 mg/10 mg modified release hard capsules trade name. In this Assessment Report, the name Navalem is used.

This application has been submitted as a generic application under Article 10.1 of Directive 2001/83/EC as amended by Directive 2004/27/EC.

The application submitted is an auto-generic application of Cariban also from Laboratorios Inibsa that was first registered in Spain in March 1967.

With Spain as the Reference Member State in this Decentralized Procedure, Inibsa Ginecologia, S.A., is applying for the Market Authorization for Navalem 10 mg/10 mg Modified Release Hard Capsules in AT, BE, DE, IT, PL and PT.

Doxylamine is an ethanolamine derivative, a first-generation antihistamine that competitively, reversibly and non-specifically blocks H_1 receptors. It is also a non-specific antagonist that can block other receptors, such as central or peripheral muscarinic receptors, although it is less potent than other ethanolamines. The antiemetic action of doxylamine is also associated with blocking of the central cholinergic and H_1 receptors.

Pyridoxine is a water-soluble vitamin factor (vitamin B_6) whose active form is pyridoxal 5ô-phosphate. It acts as an enzyme co-factor in numerous biochemical reactions involved in the digestive breakdown of proteins and amino acids and, to a lesser extent, lipids and carbohydrates. Pyridoxine is also involved in the metabolism of unsaturated fatty acids (conversion of linoleic acid into arachidonic acid). It is a coenzyme for transaminases and decarboxylases and allows the conversion of tryptophan into nicotinic acid.

Navalem is indicated for the symptomatic treatment of nausea and vomiting during pregnancy (NVP) in adults who do not respond to conservative management.

Limitations of use: The combination doxylamine/pyridoxine has not been studied in case of hyperemesis gravidarum.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Navalem 10 mg/10 mg modified release hard capsules** for Inibsa Ginecologia, S.A.

II. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

DRUG SUBSTANCE - Doxylamine hydrogen succinate

Doxylamine hydrogen succinate is an active ingredient that is described in the European Pharmacopoeia, Product Monograph number 1589, current edition. There is one supplier of active substance, the manufacturer of Doxylamine hydrogen succinate has a CEP for the drug substance.

DRUG SUBSTANCE ï Pyridoxine hydrochloride

Pyridoxine hydrochloride is an active ingredient that is described in the European Pharmacopoeia, current edition. There is one supplier of active substance, the manufacturer of pyridoxine hydrochloride has a CEP for the drug substance.

DRUG PRODUCT

Description of the product

The product is composed of two types of modified-release pellets one for each active ingredient, one containing Pyridoxine hydrochloride and the other containing Doxylamine succinate. Those pellets are packed together in size 3 green gelatine capsules.

The qualitative composition of the capsules is as follows:

Sucrose, corn starch, shellac, povidone, talc, methacrylic acid ï methyl methacrylate copolymer and silica colloidal anhydrous.

Hard gelatine capsule: gelatine, indigo carmine, quinoline yellow and titanium dioxide.

The type of primary packaging selected is a blister made of PVC coated with PVDC material on one side and aluminum foil on the other side.

Pharmaceutical development

The pharmaceutical development has been properly described. The function of the excipientes has been discussed. The manufacturing process is described in detail.

The validation studies show that the manufacturing process for the product is suitable for routine production of the medicinal product.

Excipients

The information provided is adequate. These excipients are described in European Pharmacopoeia and they are analysed according to the corresponding monographs. The composition of the gelatin capsules is properly described.

Product specification

Specifications proposed are adequate. The product specifications cover appropriate parameters for this dosage form. The limits proposed for the different parameters have been adequately justified.

All analytical methods have been correctly validated following the ICH Q2 (R1) Guideline.

Container closure system

Information about container closure system is correct. The type of primary packaging selected is a blister made of PVC coated with PVDC material on one side and aluminum foil on the other side.

Stability

Stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life (*24 months when stored below 25ºC in the proposed container closure system*).

II-2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of doxylamine succinate and pyridoxine hydrochloride are well known. As doxylamine succinate and pyridoxine hydrochloride are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

The submitted Environmental Risk Assessment includes a Phase I Pre-Screening Estimation of Exposure. The $PEC_{surfacewater}$ values for both components are all above the action limit of 0.01 ε g/L (0.2 µg/L for Pyridoxine Hydrochloride and Doxylamine Succinate). However, Pyridoxine Hydrochloride due to its nature is not expected to pose a risk to the environment. For Doxylamine Succinate active substance, an ERA Phase II was required. The Applicant committed to submit a complete ERA.

II.3 Clinical aspects

Introduction

Navalem 10 mg/10 mg modified release hard capsules and the reference product are identical. The active and inactive pharmaceutical ingredient used, the manufacturing process and manufacturing site for the finished dosage form are the same.

A bioavailability study is therefore not required to demonstrate bioequivalence, and none is provided in this application.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Efficacy and safety of the active substances doxylamine succinate and pyridoxine hydrochloride are well documented for the reference medicinal product.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

No bioequivalence study is necessary since Navalem 10 mg/10 mg modified release hard capsules is identical to the reference medicinal product Cariban 10 mg/10 mg modified-release hard capsules.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance is considered to be positive.

Agreement between Member States was reached during the procedure. The decentralized procedure was finalised with a positive outcome in January2018.