COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Aprepitant Zentiva 80 mg, 125 mg, 80 mg + 125 mg, hard capsules

# (aprepitant)

# NL/H/4431/001-003/DC

# Date: 7 May 2019

**This module reflects the scientific discussion for the approval of Aprepitant Zentiva 80 mg, 125 mg, 80 mg + 125 mg, hard capsules. The procedure was finalised at 14 December 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| 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 Aprepitant Zentiva 80 mg, 125 mg, 80 mg + 125 mg, hard capsules, from Zentiva k.s.

The product is indicated for the prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12.

Aprepitant Zentiva 125 mg + 80 mg is given as part of combination therapy (see SmPC section 4.2).

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 Emend 80 mg, 125 mg, 80 mg+125 mg which has been centrally registered (EU/1/03/262) in the EEA by Merck Sharp & Dohme Ltd. since 11 November 2003.

The concerned member states (CMS) involved in this procedure were Germany, France (only the 80 mg + 125 mg strength) 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

Aprepitant Zentiva is a hard capsule in two strengths:

- The 80 mg hard capsules are presented as opaque hard gelatin capsules, with a white cap and white body, imprinted in black ink with “80mg” on the body.
- The 125 mg hard capsules are presented as opaque hard gelatin capsules, with a pink cap and white body, imprinted in black ink with “125mg” on the body.

The product contains as active substance 80 mg or 125 mg of aprepitant.

The hard capsules are packed in OPA/ALU/PVC-Aluminium foil blisters

The excipients are:

*Capsule content*

- Hypromellose
- Poloxamer
- Sucrose
- Cellulose, microcrystalline

*Capsule shell*
- Gelatin
- Sodium laurilsulfate (E487)
- Titanium dioxide (E171)
- Iron oxide yellow and red (E172) (40 mg and 125 mg respectively)

*Black printing ink*
- Shellac
- Iron oxide black (E172)
- Propylene glycol (E1520)

The three tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is aprepitant, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder. Aprepitant is very slightly soluble in water, sparingly soluble in anhydrous ethanol and practically insoluble in heptane.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process has been adequately described. It consists of four stages. The four starting materials are considered acceptable, and adequate specifications have been set. No class I organic solvents are used.

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. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at long term (25°C/60% RH) and accelerated conditions (40°C/75% RH) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 36 months.

## 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 has been justified and their functions have been explained. General properties of the drug substance have been described. The aim of the pharmaceutical development was to develop a stable hard capsule formulation which is comparable in performance to the reference product Emend hard capsules. The manufacturing process development is described in detail. The drug substance is classified as BCS Class IV drug exhibiting both poor solubility and poor permeability. A solubility enhancement method is applied so that a product with comparable bioavailability to the originator is obtained. For this reason the particle size reduction to the nano-range of the active ingredient has been chosen. The reduction is obtained as a part of the drug product manufacturing process. A media milling technique is applied resulting in a desirable particle size distribution.

Two bioequivalence studies have been preformed in which the 125 mg strength has been compared with the reference product Emend 125 mg. The first bioequivalence study was performed under the fed conditions and the second study under the fast conditions. The satisfactory results of in vitro dissolution tests complementary to bioequivalence studies in three different buffers (pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media) have been reported (profiles of the biobatches are comparable).

The MAH performed dissolution studies to support a biowaiver for the additional strength (80 mg). Based on the provided data the biowaiver of strength for the 80 mg strength is acceptable.

Manufacturing process

The manufacturing process is considered a non-standard process, because it concerns a nano-particulate preparation. In addition the spray coating is considered a step which may give rise to scale-up difficulties. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches per product strength in accordance with the relevant European guidelines.

Control of excipients

All excipients except for the capsules used for 80 mg and 125 mg strength are of the Ph.Eur. quality. 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 appearance, average mass & mass uniformity, loss of drying, disintegration, identification, assay, uniformity of dosage units (by mass variation), related substances and degradation products, Dissolution and microbiological quality. 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 batches for each strength 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 batches of each strength at long term (25°C/60% RH), accelerated (40°C/75% RH) and intermediate conditions (30°C/65% RH) in accordance with applicable European guidelines demonstrating the stability of the product. On basis of the data submitted, a shelf life was granted of 30 months. The statement "the product should be kept in the original package in order to protect from moisture" is supported as capsules are generally known to be sensitive to moisture.

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 Aprepitant Zentiva 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 Aprepitant Zentiva 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 Emend 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

Aprepitant 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 two bioequivalence studies, which are discussed below.

### IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Aprepitant Zentiva 125 mg is compared with the pharmacokinetic profile of the reference product Emend 125 mg (Merck Sharp & Dohme Ltd., United Kingdom) under fasted and fed conditions.

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.

<u>Biowaiver</u>
The MAH has requested a biowaiver for the lower strength 80 mg, based on the provided bioequivalence study with the 125 mg formulation. The biowaiver was granted on the following conditions:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the strengths is quantitatively proportional.
- Appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

<u>Bioequivalence studies</u>

*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.

**Pivotal single dose bioequivalence study under fasting conditions**
*Design*
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 82 healthy male subjects, aged 20-43 years. Each subject received a single dose (125 mg) of one of the two aprepitant formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 16 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 3.75, 4, 4.25, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The pharmaceutical form used by the MAH is considered a product with specific formulation characteristics. For these products, a bioequivalence study needs to be performed under both fasted and fed conditions unless the product must be taken only in the fasted state or only in the fed state. As aprepitant can be taken both in fasted and fed state, bioequivalence under fasted and fed conditions should be shown. The MAH performed bioequivalence studies under both fasted and fed conditions as recommended in the EMA bioequivalence guideline.
Aprepitant has non-linear pharmacokinetics, which is characterised by a more than proportional increase in AUC with increasing dose over the therapeutic dose range. Therefore, the bioequivalence studies were conducted at the highest strength, which is appropriate.

*Results*
One subject was withdrawn due to vomiting in Period I, one subject withdrew voluntarily after check-in from Period II, and four subjects did not report for check-in at period II. Therefore 76 subjects were eligible for pharmacokinetic analysis.

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

| **Treatment N=76** | **$AUC_{0-t}$** (ng.h/ml) | **$AUC_{0-\infty}$** (ng.h/ml) | **$C_{max}$** (ng/ml) | **$t_{max}$** (h) |
|---|---|---|---|---|
| **Test** | 52960 ± 13399 | 73487 ± 34332 | 1841 ± 425 | 4.0 (2.5 - 4.5) |
| **Reference** | 53865 ± 15011 | 82853 ± 66330 | 1875 ± 485 | 4.0 (2.0 - 12.0) |
| ***Ratio (90% CI)** | 0.99 (0.95 – 1.03) | 0.96 (0.90 – 1.03) | 0.99 (0.94 – 1.04) | -- |

| | |
|---|---|
| **$AUC_{0-\infty}$** | area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{0-t}$** | area under the plasma concentration-time curve from time zero to t hours |
| **$C_{max}$** | maximum plasma concentration |
| **$t_{max}$** | time for maximum concentration |
| **$t_{1/2}$** | half-life |
| **CV** | coefficient of variation |

**ln-transformed values*

**Pivotal single dose bioequivalence study under fed conditions**

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 32 healthy male subjects, aged 19-38 years. Each subject received a single dose (125 mg) of one of the two aprepitant formulations. The tablet was orally administered with 240 ml water after the intake of a high caloric and fat breakfast. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The breakfast is a high caloric, high fat breakfast and is therefore suitable to investigate the bioequivalence under fed conditions.

*Results*

Two subjects did not complete the study: one subject was withdrawn from the study due to vomiting in Period I and one subject did not report for Period II check-in. Therefore 30 subjects were eligible for pharmacokinetic analysis.

**Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of aprepitant under fed conditions.**

| **Treatment N=30** | **$AUC_{0-t}$** (ng.h/ml) | **$AUC_{0-\infty}$** (ng.h/ml) | **$C_{max}$** (ng/ml) | **$t_{max}$** (h) |
|---|---|---|---|---|
| **Test** | 96297 ± 26928 | 138554 ± 78399 | 3541 ± 675 | 4.5 (3.5-6.0) |
| **Reference** | 96895 ± 22461 | 134476 ± 61797 | 3495 ± 593 | 4.5 (4.0-5.5) |
| ***Ratio (90% CI)** | 0.99 (0.94 – 1.04) | -- | 1.01 (0.97 – 1.06) | -- |

| | |
|---|---|
| **$AUC_{0-\infty}$** | area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{0-t}$** | area under the plasma concentration-time curve from time zero to t hours |
| **$C_{max}$** | maximum plasma concentration |
| **$t_{max}$** | time for maximum concentration |
| **$t_{1/2}$** | half-life |
| **CV** | coefficient of variation |

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Aprepitant Zentiva 125 mg is considered bioequivalent with Emend 125 mg.

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 Aprepitant Zentiva.

**Table 3. Summary table of safety concerns as approved in RMP**

| | |
|---|---|
| Important identified risks | • Hypersensitivity<br>• Drug interaction: hormonal contraceptives |
| Important potential risks | • Potential for medication errors |
| Missing information | • Use in pregnancy<br>• Use in patients with moderate or severe hepatic impairment |

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 Emend. 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) for the 80 mg and 125 mg capsules 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

Aprepitant Zentiva 80 mg, 125 mg, 80 mg + 125 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Emend 80 mg, 125 mg, 80 mg + 125 mg, hard capsules. Emend 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 Aprepitant Zentiva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 December 2018.

## 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 |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |