COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Aprepitant Teva 80 mg, 125 mg, and 125 mg + 80 mg, hard capsules

(aprepitant)

NL/H/3854/001-003/DC

Date: 5 December 2018

This module reflects the scientific discussion for the approval of Aprepitant Teva 80 mg, 125 mg, and 125 mg + 80 mg, hard capsules. The procedure was finalised at 31 May 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
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 Teva 80 mg, 125 mg, and 125 mg + 80 mg, hard capsules from Teva B.V.

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

Aprepitant Teva 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 and 125 mg hard capsules(EU/1/03/262) which has been registered in the EEA by Merck Sharp & Dohme Ltd, UK since 11 November 2003 (original product).

The concerned member states (CMS) involved in this procedure were Austria, Belgium (only the 125 mg + 80 mg strength), Czech Republic (only the 125 mg + 80 mg strength), France (only the 80 mg and 125 mg + 80 mg strength), Germany, Croatia (only the 125 mg + 80 mg strength), Italy (only the 125 mg + 80 mg strength), Poland (only the 125 mg + 80 mg strength), Portugal (only the 80 mg and 125 mg strength), Slovenia (only the 125 mg + 80 mg strength) and Slovakia (only the 80 mg and 125 mg + 80 mg strength).

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

II. QUALITY ASPECTS

II.1 Introduction

Aprepitant Teva is a hard capsule.
The 80 mg capsules are opaque, with a white body and cap, containing white to off-white pellets.
The 125 mg capsules are opaque, with a white body and pink cap containing white to off-white pellets.

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

The hard capsules are packed in Aluminium-OPA/Alu/PVC blisters.

The excipients are:
Capsule content – sucrose, microcrystalline cellulose (E460), hydroxypropylcellulose (E463), and sodium laurilsulfate
Capsule shell (125 mg) - gelatin, titanium dioxide (E171), and red iron oxide (E172)
Capsule shell (80 mg) – gelatin and titanium dioxide (E 171)

The two capsule fillings 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 to cream coloured crystalline powder. Aprepitant is soluble in methanol, slightly soluble in acetonitrile, and practically insoluble in water. Aprepitant exists in two monotropically related crystal forms designated as form I, which is orthorhombic and form II, which is monoclinic. The drug substance is manufactured as a mixture of the polymorphic forms.

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
Sufficient information regarding the manufacturing process of the drug substance is 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. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability studies have been performed with the drug substance. No significant change beyond the specification limits in any parameters was observed. The proposed retest period of two years is accepted in the proposed packaging with the storage restriction "Store in airtight container below 25°C, protect from light and moisture".

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 is accepted, and their functions are adequately explained. The development work followed the Quality by Design approach. Throughout the pharmaceutical development Preliminary Hazard Analysis was used as risk assessment tool. Comparative impurity profiles to the originator product are also presented.

Two pivotal bioequivalence studies have been performed comparing the 125 mg test product with the reference product Emend 125 mg hard capsules. Comparative dissolution profiles at three different pHs have been provided for the biobatch and the original product used in the bioequivalence studies. Similarity of in vitro dissolution between test and reference product is demonstrated at three dissolution medium. More than 85% of aprepitant is dissolved within 15 minutes in QC medium. The development of the dissolution method has been adequately discussed. A biowaiver for the 80 mg strength is claimed.

Manufacturing process

The manufacturing process is adequately described. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches for each strength in accordance with the relevant European guidelines.

Control of excipients

All excipients, except for red iron oxide, used in the manufacturing process comply with respective Ph.Eur. monograph. Red iron oxide complies with commission regulation 231/2012/EU. 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 weight, average filled weight, uniformity of dosage units, identification of colours and the drug substance, dissolution, assay, related substances, chiral purity, water content and microbiological purity. 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 batches of 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 per strength in accordance with applicable European guidelines demonstrating the stability of the product for 24 months at long-term conditions and six months at accelerated conditions. On basis of the data submitted, a shelf life was granted of 36 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is of animal origin. 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 Teva 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 Teva 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 three bioequivalence studies of which two are regarded pivotal. The pilot study comparing two earlier initial formulations of the test product with the reference product did not show bioequivalence and will not be further discussed in this report.

IV.2 Pharmacokinetics

Bioequivalence studies

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Aprepitant Teva 125 mg hard capsules (Teva B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Emend 125 mg hard capsules (Merck, Sharp & Dohme Ltd., United Kingdom/The Netherlands).

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

Biowaiver

A biowaiver for the additional strength 80 mg is being applied for on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):

- Both strengths are manufactured by the same manufacturer and using the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The quantitative compositions of the different strengths are dose- proportional.
- In vitro dissolution data confirm the *in vivo* similarity between the claimed strengths. Similarity at pH 1.2, 4.5 and 6.8 between the test biobatch 125 mg and the additional strength 80 mg has been shown.
- Aprepitant exhibits non-linear (more than proportional) pharmacokinetics in the therapeutic range of 80-125 mg.

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.

Design

The design of the fasted and fed study is acceptable. In general, a study in the fasting condition can be considered sufficient for products which can be taken with and without food. However, the effect of food on the pharmacokinetics of aprepitant is largely dependent on the manufacturing process of the product. Hence, the studies under fasting and fed conditions submitted are agreed. The use of the high strength 125 mg is acceptable since aprepitant has a non-linear pharmacokinetics characterised by a more than proportional increase in AUC with increasing dose over the therapeutic dose range.

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 40 healthy male subjects, aged 20-42 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 nine days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 7, 9, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results

Four subjects did not complete the study: one subject withdrew consent in period I post-dosing, two subjects did not report to facility during period 2 admission, and one subject due to an adverse event during period 2. Therefore, 36 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of aprepitant 125 mg under fasted conditions.

Treatment N=36	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	48886 ± 17846	56441 ± 25290	1900 ± 683	4.00 (1.50 – 12.00)
Reference	47445 ± 15781	54624 ± 21644**	1894 ± 731	4.00 (2.50 – 12.00)
***Ratio (90% CI)**	1.00*** (0.91 – 1.10)	0.99 (0.89 – 1.09)	1.00 (0.92 – 1.09)	--

$AUC_{0-\infty}$ 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

** ln-transformed values*
*** n=35*
**** in some cases $AUC_{(0-72)}$*

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 fasted conditions in 62 healthy male subjects, aged 20-44 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 30 minutes after the start of a high-fat high-calorie breakfast. There were two dosing periods, separated by a washout period of eleven days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 7, 9, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results

Nine subjects were withdrawn from the study:

- One subject did not complete the high fat, high calorie breakfast before period 1 dosing.
- Two subjects did not report to the facility during period 2 admission.
- One subject had taken chocolate.
- One subject had taken tea.
- Two subjects tested positive for drugs of abuse during period 2 admission.
- Two subjects tested positive for an alcohol breath test during period 2 admission.
- One subject withdrew due to an adverse event before dosing in period 1 and was replaced.

Therefore, 53 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of aprepitant 125 mg under fed conditions.

Treatment N=53	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	77414 ± 28101	100306 ± 73117	3152 ± 1027	5.00 (3.00 - 24.00)
Reference	76229 ± 24166	104295 ± 91560	3109 ± 1009	4.7 (4.00 – 24.00)
***Ratio (90% CI)**	1.01 (0.97 - 1.06)	0.99 (0.93 - 1.06)	1.02 (0.95 - 1.09)	--

$AUC_{0-\infty}$ 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

** 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 Teva 125 mg hard capsules is considered bioequivalent with Emend 125 mg hard capsules.

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 Teva.

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

Important identified risks	• Hypersensitivity • Drug interaction hormonal contraceptives
Important potential risks	• Potential for medication errors
Missing information	• Use in pregnancy • Use in patients <6 months of age or <6 kg • 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) 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 two rounds. The 20 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 Teva 80 mg, 125 mg, and 125 mg + 80 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Emend 80 mg, 125 mg, and 125 mg + 80 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 Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 31 May 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