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Public Assessment Report

Name of the Product:

Aprepitant Rontis

80 mg, 125 mg, 125 mg + 80 mg hard capsule

(aprepitant)

Procedure number: HU/H/0499/001-003/DC

Marketing authorisation holder: Rontis Medical and Pharmaceutical Products S.A.

Date: 23 March 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Aprepitant Rontis 80 mg, 125 mg, 125 mg + 80 mg hard capsules. The holder of the marketing authorisation is Rontis Medical and Pharmaceutical Products S.A., Greece.

The active substance is aprepitant. Each hard capsule contains 80 mg or 125 mg of aprepitant

The other ingredients are sucrose, cellulose microcrystalline (E 460), hydroxypropylcellulose (E 463), sodium laurilsulfate, gelatin, titanium dioxide (E 171); only the 125 mg hard capsule contains also red iron oxide (E 172).

The 80 mg hard capsules are opaque with a white body and cap, the 125 mg hard capsules are opaque with a white body and pink cap. The capsules contain white to off-white pellets.

The capsules are in Aluminium-OPA/Alu/PVC blister.

There is also a 3-day treatment pack containing one 125 mg capsule and two 80 mg capsules.

The active substance of Aprepitant Rontis hard capsules (further on: Aprepitant Rontis) belongs to a group of medicines called "neurokinin 1 (NK1) receptor antagonists". The brain has a specific area that controls nausea and vomiting. Aprepitant Rontis works by blocking signals to that area, thereby reducing nausea and vomiting. Aprepitant Rontis capsules are used in adults and adolescents from the age of 12 years in combination with other medicines to prevent nausea and vomiting caused by chemotherapy (cancer treatment) that are strong and moderate triggers of nausea and vomiting (such as cisplatin, cyclophosphamide, doxorubicin or epirubicin).

What patients need to know before taking or giving Aprepitant Rontis?

Those who
- are or their child is allergic to aprepitant or any of the other ingredients of this medicine,
- are taking medicines containing pimozide (used to treat psychiatric illnesses), terfenadine and astemizole (used for hay fever and other allergic conditions), cisapride (used for treating digestive problems)

should not take (give the child) Aprepitant Rontis. They should tell their doctor if they or if their child is taking these medicines since the treatment must be modified before taking Aprepitant Rontis.

Warnings and precautions

Before treatment with Aprepitant Rontis, the doctor must be informed if the patient (or the child) has liver disease because the liver is important in breaking down the medicine in the body. The doctor may therefore have to monitor the condition of the patient's liver.

Children and adolescents

Children 12 years of age should not be given Aprepitant Rontis 80 mg and 125 mg capsules, because these strengths have not been studied in this population.

Other medicines and Aprepitant Rontis

Aprepitant Rontis can affect other medicines both during and after treatment with aprepitant. There are some medicines that should not be taken with aprepitant (such as pimozide, terfenadine, astemizole, and cisapride) or that require a dose adjustment (see also 'Do not take Aprepitant Rontis').

The effects of aprepitant or other medicines might be influenced if the patient takes Aprepitant Rontis together with other medicines including those listed below. The doctor should be informed if the patient (or the child) is taking any of the following medicines:
- birth control medicines which can include birth control pills, skin patches, implants, and certain Intrauterine devices (IUDs) that release hormones may not work adequately when taken together with aprepitant. Another or additional non-hormonal form of birth control should be used during treatment with aprepitant and for up to 2 months after using Aprepitant Rontis,
- cyclosporine, tacrolimus, sirolimus, everolimus (immunosuppressants),
- alfentanil, fentanyl (used to treat pain),
- quinidine (used to treat an irregular heartbeat),
- irinotecan, etoposide, vinorelbine, ifosfamide (medicines used to treat cancer),
- medicines containing ergot alkaloid derivatives such as ergotamine and diergotamine (used for treating migraines),
- warfarin, acenocoumarol (blood thinners; blood tests may be required),
- rifampicin, clarithromycin, telithromycin (antibiotics used to treat infections),
- phenytoin (a medicine used to treat seizures),
- carbamazepine (used to treat depression and epilepsy),
- midazolam, triazolam, phenobarbital (medicines used to produce calmness or help to sleep),
- St. John's Wort (a herbal preparation used to treat depression),
- protease inhibitors (used to treat HIV infections),
- ketoconazole except shampoo (used to treat Cushing's syndrome - when the body produces an excess of cortisol),
- itraconazole, voriconazole, posaconazole (antifungals),
- nefazodone (used to treat depression),
- corticosteroids (such as dexamethasone and methylprednisolone),
- anti-anxiety medicines (such as alprazolam),
- tolbutamide (a medicine used to treat diabetes).

Pregnancy and breast-feeding

This medicine should not be used during pregnancy unless clearly necessary. Those who are pregnant or breast-feeding, may be pregnant or are planning to have a baby, ask the doctor for advice before taking this medicine.

For information regarding birth control, see 'Other medicines and Aprepitant Rontis'.

It is not known whether Aprepitant Rontis is excreted in human milk; therefore, breast-feeding is not recommended during treatment with this medicine. It is important to tell the doctor if the patient is breast-feeding or is planning to breast-feed before taking this medicine.

Driving and using machines

It should be taken into account that some people feel dizzy and sleepy after taking Aprepitant Rontis. If the patient feels dizzy or sleepy, avoid driving, riding a bicycle or using machines or tools after taking this medicine (see 'Possible side effects').

Aprepitant Rontis contains sucrose

If the patient has been told by the doctor that he/she (or the child) has an intolerance to some sugars, the doctor should be contacted before taking this medicine.

How to take Aprepitant Rontis?

Aprepitant Rontis should always be taken together with other medicines, to prevent nausea and vomiting. After treatment with Aprepitant Rontis, the doctor may ask the patient to continue taking other medicines including a corticosteroid (such as dexamethasone) and a '5-HT3 antagonist' (such as ondansetron) for preventing nausea and vomiting.

The recommended oral dose of Aprepitant Rontis is as follows.

Day 1: one 125 mg capsule 1 hour before starting the chemotherapy session.
Days 2 and 3: one 80 mg capsule each day.

If no chemotherapy is given, Aprepitant Rontis should be taken in the morning. If chemotherapy is given, Aprepitant Rontis should be taken 1 hour before starting the chemotherapy session.

Aprepitant Rontis can be taken with or without food.

The capsule should be swallowed whole with some liquid.

What to do if more Aprepitant Rontis has been taken that it should have been?

Patients should not take more Aprepitant Rontis than the doctor recommends. If the patient (or the child) has taken too many capsules, the doctor must be contacted immediately.

What to do when taking Aprepitant Rontis has been forgotten?

If the patient has missed a dose, the doctor should be contacted for advice.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody experiences them.

Patients must stop taking Aprepitant Rontis and see a doctor immediately if noticing any of the following side effects, which may be serious, and for which urgent medical treatment may be needed: hives, rash, itching, difficulty breathing or swallowing (frequency not known, cannot be estimated from the available data); these are signs of an allergic reaction.

Other side effects that have been reported are listed below.

Common side effects (may affect up to 1 in 10 people):
- constipation, indigestion,
- headache,
- tiredness,
- loss of appetite,
- hiccups,
- increased amount of liver enzymes in the blood.

Uncommon side effects (may affect up to 1 in 100 people):
- dizziness, sleepiness,
- acne, rash,
- anxiousness,
- burping, nausea, vomiting, heartburn, stomach pain, dry mouth, passing wind,
- increased painful or burning urination,
- weakness, generally feeling unwell,
- hot flush/reddening of the face or skin,
- fast or irregular heartbeats,
- fever with increased risk of infection, lowering of red blood cells.

Rare side effects (may affect up to1 in 1,000 people):
– difficulty thinking, lack of energy, taste disturbance, sensitivity of the skin to sun, excessive sweating, oily skin, sores on skin, itching rash, Stevens-Johnson syndrome/toxic epidermal necrolysis (rare severe skin reaction),
– euphoria (feeling of extreme happiness), disorientation,
– bacterial infection, fungal infection,

- severe constipation, stomach ulcer, inflammation of the small intestine and colon, sores in mouth, bloating,
- frequent urination, passing more urine than normal, presence of sugar or blood in urine,
- chest discomfort, swelling, change in the manner of walking,
- cough, mucus in back of throat, throat irritation, sneezing, sore throat,
- eye discharge and itching,
- ringing in the ear,
- muscle spasms, muscle weakness,
- excessive thirst,
- slow heartbeat, heart and blood vessel disease,
- lowering of white blood cells, low sodium levels in the blood, weight loss.

How to store Aprepitant Rontis?

This medicine does not require any special storage conditions bit it must be kept out of the sight and reach of children.

The capsule should not be removed from its blister until the patient is are ready to take it.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Aprepitant Rontis 80 mg, 125 mg, 125 mg + 80 mg hard capsule. The procedure was finalised at 17 April 2018. For information on changes after this date, please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Greece and Malta) concerned the generic version of aprepitant 80 mg, 125 mg and 125 mg + 80 mg hard capsules (Aprepitant Rontis hard capsules).

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Aprepitant Rontis 80 mg, 125 mg, 80 + 125 mg hard capsules (Rontis Medical and Pharmaceutical Products S.A.).

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

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary.

The applicant has adequately demonstrated bioequivalence between the products applied for and the reference products. The originator (and reference) products are Emend® 80 mg & 125 mg hard capsules by Merck Sharp & Dohme Ltd. UK, authorised for marketing since 2003 in the European Economic Area.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Aprepitant Rontis 80 mg, 125 mg hard capsules and Aprepitant Rontis 80 mg & 125 mg hard capsules via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e, a generic application). The products have been developed by Rontis Hellas Medical and Pharmaceutical Products S.A.

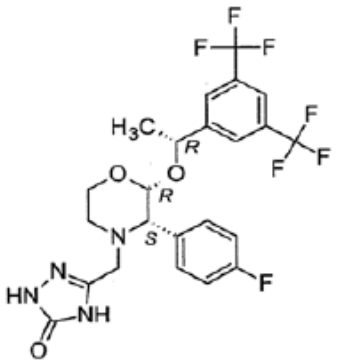
The reference products are Emend 80 mg, 125 mg, 80 mg &125 mg hard capsules (containing 80 mg and 125 mg aprepitant as active ingredient) which were the original products of Merck Sharp & Dohme Ltd. UK.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

International Non-proprietary Name (INN): aprepitant
Chemical name: 5-[[(2R,3S)-2-[(1R)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

Structure:



The active substance is white to cream coloured crystalline powder, Soluble in methanol, slightly soluble in acetonitrile, practically insoluble in water. It shows polymorphism, the manufacturers consistently produce the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by NMR, MS, FT-IR, XRDP, UV spectroscopy and elemental analysis. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current European Pharmacopoeia (Ph. Eur.) monograph, additional specification has only been set for residual solvents, particle size distribution, polymorphism, impurities and microbial impurities.

The Ph. Eur. specification includes the following tests for aprepitant: appearance, solubility, identification by IR, specific optical rotation, water content, sulphated ash, related substances, enantiomeric purity and assay.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council of Harmonisation (ICH) Q6A guideline. The specification reflects all relevant quality attributes of the active substance and was found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in detail in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicine Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable with the proposed storage condition.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop hard capsules containing aprepitant as drug substance in 80 mg and 125 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal product Emend 80 mg and 125 mg hard capsules, the branded original products of Merck Sharp & Dohme Ltd., UK.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

> 80 mg: size 2, opaque hard gelatin capsule with a white body and cap containing white to off-white pellets.
> 125 mg: size 1, opaque hard gelatin capsule with a white body and pink cap containing white to off-white pellets.

The excipients used in the finished product are sucrose, microcrystalline cellulose, hydroxypropylcellulose , sodium laurilsulfate and capsule shell (titanium dioxide (E171), talc, red iron oxide (E172) (only for 125 mg) and gelatin). All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on *the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 30 months with no special storage conditions is approved.

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of aprepitant are well known. As aprepitant is a widely used, well-known active substance, no further studies are required, and the applicant has provided none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient.

III.2 Pharmacology

Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK1) receptors.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of aprepitant.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Aprepitant Rontis 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.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of aprepitant are well-known. As Aprepitant Rontis mg hard capsules is a generic product, there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of aprepitant is well known.

Except for demonstrating bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

The mean absolute oral bioavailability of aprepitant is 67 % for the 80 mg capsule and 59 % for the 125 mg capsule. The mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (t_{max}). Oral administration of the capsule with an approximately 800 Kcal standard breakfast resulted in an up to 40 % increase in AUC of aprepitant. This increase is not considered clinically relevant.

The pharmacokinetics of aprepitant is non-linear across the clinical dose range. In healthy young adults, the increase in AUC_{∞} was 26 % greater than dose proportional between 80 mg and 125 mg single doses administered in the fed state. Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3, the $AUC_{0\text{-}24hr}$ (mean±SD) was 19.6 ± 2.5 μg·h/mL and 21.2 ± 6.3 μg ·h/mL on Days 1 and 3, respectively. C_{max} was 1.6 ± 0.36 μg/mL and 1.4 ± 0.22 μg/mL on Days 1 and 3, respectively.

Aprepitant is highly protein bound, with a mean of 97 %. The geometric mean apparent volume of distribution at steady state (Vdss) is approximately 66 L in humans.

Aprepitant undergoes extensive metabolism. In healthy young adults, aprepitant accounts for approximately 19 % of the radioactivity in plasma over 72 hours following a single intravenous administration 100 mg dose of [14C]-fosaprepitant, a prodrug for aprepitant, indicating a substantial presence of metabolites in the plasma. Twelve metabolites of aprepitant have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains and the resultant metabolites were only weakly active. In vitro studies using human liver microsomes indicate that aprepitant is metabolised primarily by CYP3A4 and potentially with minor contribution by CYP1A2 and CYP2C19.

Aprepitant is not excreted unchanged in urine. Metabolites are excreted in urine and via biliary excretion in faeces. Following a single intravenously administered 100 mg dose of [14C]-fosaprepitant, a prodrug for aprepitant, to healthy subjects, 57 % of the radioactivity was recovered in urine and 45 % in faeces.

The plasma clearance of aprepitant is dose-dependent, decreasing with increased dose and ranged from approximately 60 to 72 mL/min in the therapeutic dose range. The terminal half-life ranged from approximately 9 to 13 hours.

IV.2.2 Bioequivalence studies

One pilot and two pivotal bioequivalence studies (one in fasting, one in fed conditions) have been performed to support essential similarity between the test and the reference preparations in healthy adult subjects. The 125 mg strengths were used in each case. The reference product was Emend® 125 mg capsules manufactured by Merck Sharp & Dohme Ltd., Netherland.

By the Sponsor's statement the studies were conducted in compliance with the requirements of guideline on *Good Clinical Practice* ICH Topic E6 (R1) (CPMP/ICH/135/95), Guideline on *the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, January 2010) and ethical principles stated in the last revision of Declaration of Helsinki.

Pilot study

It was a randomized, open label, single dose, crossover bioequivalence study in healthy adult human subjects under fasting conditions. The subjects were administered two kinds of formulations of Test or the Reference products, one capsule each. The main objective of this study was to compare the rate and extent of absorption of aprepitant from the Test and Reference products and also to estimate intra-subject variability of the primary pharmacokinetic parameters (C_{max} and AUC_{0-t}).

The results of the pilot study were used to select the proper Test product and to plan the two pivotal studies.

Pivotal study under fasting conditions

It was a single-dose, randomized, open-label, crossover study in healthy adult male subjects under fasting condition. Its main objective was to compare the rate and extent of absorption of aprepitant of the Test and Reference products.

The following pharmacokinetic parameters were determined:
- primary: AUC_{0-t}, AUC_{0-inf}, C_{max},
- other: T_{max}, $t_{1/2}$, kel.

Statistical methods used in evaluations used were as follows:

- descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric LS (least squares) means for test (T) and reference (R) pharmacokinetic data;
- log-transformation of AUC and C_{max} data;
- calculation of 90% confidence intervals for the difference between the least square means for primary parameters at $\alpha = 0.05$ significance level,
- applying non-parametric analysis of T_{max} on untransformed data;
- descriptive statistics of safety data collected during the whole study period.

Bioequivalence criteria: the Test product can be considered bioequivalent to the Reference product when the ln-transformed Test/Reference least-squares mean ratios and their 90% confidence intervals of the AUC_{0-t} and C_{max} parameters fall entirely within the acceptance interval of 80.00 - 125.00% for aprepitant.

Summary of the results_

Pharmacokinetic parameter	Geometric Mean Ratio T/R	90% Confidence Intervals
AUC_{0-t}	99.88	90.76 – 109.92
C_{max}	100.18	91.96 – 109.13

Safety results: no death, serious or clinically significant adverse events occurred during the study.

On the basis of results of this bioequivalence study the single dose of the Test and Reference products are bioequivalent in healthy adult human subjects under fasting conditions.

Pivotal study under fed conditions

The design of this investigation was a pivotal, single-dose, randomized, open-label, crossover one in healthy adult male subjects under fed condition. The subjects were administered the Test or Reference products as a single oral dose of one capsule each 30 minutes after the start of the high-fat high-calorie breakfast with a glass of water at ambient temperature.

Main objective of this study was to compare the rate and extent of absorption of aprepitant of the Test and Reference products administered to healthy volunteers in a single dose, under fed conditions.

Pharmacokinetic parameters, statistical methods applied, and bioequivalence criteria were the same as in the previous pivotal study.

The results are shown in the Table below.

Pharmacokinetic parameter	Geometric Mean Ratio T/R	90% Confidence Intervals
AUC_{0-t}	101.30	97.03 – 105.77
C_{max}	101.56	94.81 – 108.79

Safety results: no death, serious or clinically significant or unexpected adverse events occurred during the study.

Results derived from analysis of log-transformed primary parameters (C_{max}, AUC_{0-t}) for aprepitant show that the Test/Reference ratios of least-squares mean values and their 90% confidence intervals are entirely included within the acceptance range of 80%-125%. Thus, results support the bioequivalence between the Test and Reference treatments.

Biowaiver

The applicant claimed for biowaiver for the dose strength of 80 mg hard capsules on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**), as follows:

- both strengths i.e. 80 and 125 mg of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The compositions of the claimed two strengths are proportionally similar.
- *In vitro* dissolution data confirm the *in vivo* similarity between the claimed strengths.
- Aprepitant exhibits non-linear (more than proportional) pharmacokinetics in the therapeutic range of 80-125 mg.

All criteria of general biowaiver claim were satisfied for the claimed dose strength (80 mg) according to the bioequivalence guideline in force (CPMP/EWP/1401/98 Rev.1 Corr** and EMA/CHMP/600958/2010/Corr.*). Similarity of dissolution profiles of the 80 and 125 mg dose strengths could be justified in accordance to the above bioequivalence guideline. Thus, the biowaiver claim for the 80 mg dose strength is justified.

Conclusion on bioequivalence studies

On the basis of results of the bioequivalence studies the single doses of the applicant's Aprepitant Rontis 125 mg hard capsules and EMEND® 125 mg capsules (Merck Sharp & Dohme Ltd.) are considered bioequivalent in healthy adult human subjects under fasting and fed conditions.

The results of above studies with 125 mg formulations can be extrapolated to the other strength 80 mg.

IV.3 Pharmacodynamics

New clinical pharmacology studies to evaluate the pharmacodynamics of Aprepitant Rontis 80 & 125 mg hard capsules were not performed and not needed.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate literature review to describe the efficacy profile of aprepitant.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted, and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

The applicant has provided an adequate literature review to describe the safety profile of aprepitant.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	Hypersensitivity
	Drug interaction: hormonal contraceptives
Important potential risks	Potential for medication errors
Missing information	Use in pregnancy
	Use in children less than 12 years of age
	Use in patients with moderate or severe hepatic impairment

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Aprepitant Rontis 80 mg, 125 mg hard capsule and 80 mg + 125 mg hard capsules. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in the Summary of Product Characteristics, Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Aprepitant Rontis 80 mg, 125 mg hard capsule and 80 mg + 125 mg hard capsules. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application concerns a generic product. Abridged applications avoid the need for repetitive tests on animals and humans. For these applications the bioequivalence studies described in section IV.2 are pivotal.

Based on the submitted bioequivalence studies Aprepitant Rontis 80 mg and 125 mg capsules and the reference product Emend® capsules (Merck Sharp & Dohme Ltd.) are bioequivalent in healthy adult human subjects under fasting and fed conditions.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Aprepitant Rontis 80 mg, 125 mg and 80 mg + 125 mg hard capsules, generic versions of aprepitant. The applicant and the future holder of authorisation is Rontis Medical and Pharmaceutical Products S.A.

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

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference product was Emend® capsule (Merck Sharp & Dohme Ltd.) The applicant demonstrated bioequivalence of the 125 mg strengths of Test and Reference products that could be extended to the 80 mg strength according to the bioequivalence guideline (*CPMP/EWP/QWP/1401/98/rev 1/Corr***).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Aprepitant Rontis 80 mg, 125 mg and 80 mg + 125 mg hard capsules.

V.2 Classification

Prescription-only medicine

V.3 Package Leaflet and 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 language used for the purpose of user testing the patient information leaflet was English.

The 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. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
IB B.III.1.a.1. Replacement of ASMF, submission of a new Certificate of Suitability of the Ph. Eur. for the drug substance (the holder is the already approved manufacturer)	OGYÉI/9422, 9426, 9429/2019 HU/H/0499/001-003/IB/001	yes	11. 03. 2019	10. 04. 2019	approved	no