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Public Assessment Report

Name of the Product:

Aprepitant-Q Pharma

80 mg, 125 mg and (80+125) mg

hard capsules

(aprepitant)

Procedure number: HU/H/0624/001-003/DC

Marketing authorisation holder: Q PHARMA Gyógyszerkereskedelmi és Szolgáltató Kft.

Date: 26th February 2021

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-Q Pharma 80 mg, 125 mg and (80+125) mg hard capsules. The holder of the marketing authorisation is Q PHARMA Gyógyszerkereskedelmi és Szolgáltató Kft.

The active substance is aprepitant.

Aprepitant-Q Pharma 80 mg hard capsules
Each hard capsule contains 80 mg of aprepitant.

Aprepitant-Q Pharma 125 mg hard capsules
Each hard capsule contains 125 mg of aprepitant.

The other ingredients are:

sucrose, cellulose microcrystalline (sphere 500) (E 460), hydroxypropylcellulose (HPC-SL) (E 463), sodium laurilsulfate, gelatin, titanium dioxide (E 171); the 125 mg hard capsule also contains red iron oxide (E 172).

The appearance of the tablets is:

Aprepitant-Q Pharma 80 mg hard capsules
Opaque with a white body and cap, containing white to off-white pellets.

Aprepitant-Q Pharma 80 mg hard capsules are supplied in the following pack sizes:
- OPA/Al/PVC//Al blister containing one 80 mg capsule
- OPA/Al/PVC//Al blister containing two 80 mg capsules
- 3 OPA/Al/PVC//Al blisters each containing one 80 mg capsule
- 5 OPA/Al/PVC//Al blisters each containing one 80 mg capsule

Aprepitant-Q Pharma 125 mg hard capsules
Opaque with a white body and cap, containing white to off-white pellets.

Aprepitant-Q Pharma 125 mg hard capsules are supplied in the following pack sizes:
- OPA/Al/PVC//Al blister containing one 125 mg capsule
- OPA/Al/PVC//Al blister containing two 125 mg capsules
- 3 OPA/Al/PVC//Al blisters each containing one 125 mg capsule
- 5 OPA/Al/PVC//Al blisters each containing one 125 mg capsule

Aprepitant-Q Pharma 125 mg hard capsules + Aprepitant-Q Pharma 80 mg hard capsules are supplied in the following pack size:
- 3-day treatment pack containing one blister of 125 mg capsule and one blister of 80 mg capsules

Not all pack sizes may be marketed.

Aprepitant-Q Pharma contains the active substance aprepitant and belongs to a group of medicines called "neurokinin 1 (NK1) receptor antagonists". The brain has a specific area that controls nausea and vomiting. Aprepitant-Q Pharma works by blocking signals to that area, thereby reducing nausea and vomiting. Aprepitant-Q Pharma 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 using Aprepitant-Q Pharma

Patients should not take Aprepitant-Q Pharma

- if the patient or the child is allergic to aprepitant or any of the other ingredients of this medicine.
- with 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) . Patients should tell their doctor if they or their child is taking these medicines since the treatment must be modified before they or the child start taking Aprepitant-Q Pharma.

Warnings and precautions

Patients should talk to their doctor, pharmacist before they take Aprepitant-Q Pharma or give this medicine to their child.

Before treatment with Aprepitant-Q Pharma, patients should tell their doctor if they have 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 patient’s liver.

Children and adolescents

Aprepitant-Q Pharma 80 mg and Aprepitant-Q Pharma 125 mg should not be given to children under 12 years of age, because the Aprepitant-Q Pharma 80 mg and Aprepitant-Q Pharma 125 mg capsules have not been studied in this population.

Other medicines and Aprepitant-Q Pharma

Aprepitant-Q Pharma can affect other medicines both during and after treatment with aprepitant, the active substance of Aprepitant-Q Pharma. There are some medicines that should not be taken with Aprepitant-Q Pharma (such as pimozide, terfenadine, astemizole, and cisapride) or that require a dose adjustment.

The effects of Aprepitant-Q Pharma or other medicines might be influenced if the patient or the child take Aprepitant-Q Pharmatogether with other medicines including those listed below. Patients should talk to the doctor or pharmacist if they or their 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-Q Pharma. Another or additional non-hormonal form of birth control should be used during treatment with Aprepitant-Q Pharma and for up to 2 months after using Aprepitant-Q Pharma,
- cyclosporine, tacrolimus, sirolimus, everolimus (immunosuppressants),
- alfentanil, fentanyl (used to treat pain),
- quinidine (used to treat an irregular heart beat),
- 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 patients to sleep),
- St. John's Wort (an 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).

Patients should tell their doctor if they or the child are taking, have recently taken, or might take any other medicines.

Pregnancy and breast-feeding

This medicine should not be used during pregnancy unless clearly necessary. If the patient is pregnant or breast-feeding, thinks she may be pregnant or is planning to have a baby, she should ask her doctor for advice before taking this medicine.

For information regarding birth control, see 'Other medicines and Aprepitant-Q Pharma'.

It is not known whether Aprepitant-Q Pharma 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-Q Pharma. If the patient or the child feels dizzy or sleepy, avoid driving, riding a bicycle or using machines or tools after taking Aprepitant-Q Pharma (see 'Possible side effects').

Aprepitant-Q Pharma contains sucrose

Aprepitant-Q Pharma capsules contain sucrose. If the patient or the child have been told by their doctor that he/she or the child have an intolerance to some sugars, they should contact the doctor before taking this medicine.

How to use Aprepitant-Q Pharma?

Patients should always take this medicine or give this medicine to the child exactly as the doctor, pharmacist or nurse has told them. They should check with the doctor, pharmacist or nurse if they are not sure. Aprepitant-Q Pharma should be always taken together with other medicines, to prevent nausea and vomiting. After treatment with Aprepitant-Q Pharma, the doctor may ask the patient or the child to continue taking other medicines including a corticosteroid (such as dexamethasone) and a '5HT3 antagonist' (such as ondansetron) for preventing nausea and vomiting. Patients should check with the doctor, pharmacist or nurse if they are not sure.

The recommended oral dose of Aprepitant-Q Pharma is Day 1:
- one Aprepitant-Q Pharma125 mg capsule 1 hour before the patient starts his/her chemotherapy session

and

Days 2 and 3:
- one Aprepitant-Q Pharma80 mg capsule each day
- If no chemotherapy is given, patients should take Aprepitant-Q Pharmain the morning.
- If chemotherapy is given, take Aprepitant-Q Pharma1 hour before the patient starts his/her chemotherapy session.

Aprepitant-Q Pharma can be taken with or without food. Swallow the capsule whole with some liquid.

What to do if more Aprepitant-Q Pharma was taken that it should have been?

Patients should not take more Aprepitant-Q Pharma than the doctor recommends. If the patient or the child has taken too many capsules, they should contact their doctor immediately.

What to do if taking Aprepitant-Q Pharma was forgotten?

If the patient or the child has missed a dose, they should contact their doctor for advice.

If patients have any further questions on the use of this medicine, they should ask their doctor or pharmacist.

Possible side effects

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

Patients should stop taking Aprepitant-Q Pharma and see a doctor immediately if the patient or the child notice any of the following side effects, which may be serious, and for which he/she or the child may need urgent medical treatment:

- 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 patient's 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.

Reporting of side effects

If the patient or the child gets any side effects, he/she should talk to his/her doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. Side effects can also be reported directly via the national reporting system. By reporting side effects the patients can help provide more information on the safety of this medicine.

How to store Aprepitant-Q Pharma?

This medicine should be kept out of the sight and reach of children.

This medicine should not be used after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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

Patients should not throw away any medicines via wastewater or household waste. Their pharmacist should be asked how to throw away medicines they no longer use. These measures will help protect the environment.

SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Aprepitant-Q Pharma 80 mg, 125 mg and (80+125) mg hard capsules. The procedure was finalised on 04-03-2020 (day210). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for **Aprepitant-Q Pharma 80 mg, 125 mg, (80 + 125) mg hard capsules** from **Q Pharma GmbH.**

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.

A comprehensive description of the indications and posology is given in the SmPC.

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

II. QUALITY ASPECTS

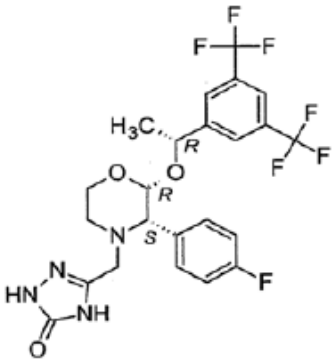
II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Aprepitant Q Pharma 80 mg, 125 mg hard capsules and Aprepitant Q Pharma 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.
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 applicant's submission using the CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: 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.

Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current Ph.Eur. monograph, additional specifications have been set for residual solvents, particle size distribution, polymorphism, impurities and microbial impurities.

The presented specification is in accordance with the Ph.Eur. general monograph on *Substances for Pharmaceutical Use* and the 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 details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the 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 API 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 bioequivalent and pharmaceutically equivalent 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 (Spheres 500), hydroxypropylcellulose (HPC-SL), 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 European Pharmacopoeia monograph. Compliance of the product with

the general monograph of the European Pharmacopoeia 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 4 years with no special storage conditions** is approved.
The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: 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.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of aprepitant are well known, no further non-clinical studies are required in support of this marketing authorisation. The Applicant submitted a nonclinical overview based on a literature review of the pre clinical pharmacology, pharmacokinetic and toxicology characteristics of aprepitant which is considered adequate. No further studies are required.

III.2 Pharmacology

No new non-clinical pharmacological studies were conducted by the Applicant.
Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK1) receptors.

III.3 Pharmacokinetics

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

III.4 Toxicology

Published information on toxicological studies with aprepitant was the basis for the evaluation. No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmnetal risk assessment (ERA)

Since Aprepitant-Q Pharma 80 mg, 125 mg, (80 + 125) mg hard capsules are 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 onthe non-clinical aspects

The dossier concerned an abridged application that avoids the need for repetitive tests on animals and humans.
Aprepitant-Q Pharma 80 mg, 125 mg, (80 & 125) mg hard capsules are considered essentially similar to the innovator products are registered throughout the European Union under the brand name Emend® 80 mg, 125 mg, (80 & 125) mg hard capsules, marketed in Europe by Merck Sharp & Dohme Ltd, UK. Emend® has been centrally authorized in the European community since 13/11/2003.

IV. CLINICAL ASPECTS

IV.1 Introduction

Applicant has not conducted any clinical studies with Aprepitant-Q Pharma 80 mg, 125 mg, (80 & 125) mg hard capsules and all the relevant Clinical information provided in Clinical overview is based on literature.

Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK1) receptors.
The vomiting reflex involves activation of neuronal nuclei in the brainstem by both peripheral (glosophararyngeal and vagal nerves) and central (cortical and cerebellar) pathways that triggers a sequence of events. Incoming signals from the chemoreceptor trigger zone, gastrointestinal tract, cerebral cortex and other areas are coordinated in the emetic center in the CNS. The main neurotransmitter receptors involved in this signaling are 5-HT3, neurokinin-1 (NK-1) and dopamine receptors. Other receptors include corticosteroid, histamine, cannabinoid, acetylcholine, GABA-containing and opiate receptors. This central site of action is the likely explanation for the unique broad antiemetic pharmacological profile of the SPAs.

IV.2 Pharmacokinetics

To support the application, the applicant has submitted as report one pilot and two pivotal (fasting and fed) bioequivalence studies.

• Pilot study was performed between Aprepitant Capsules 125 mg (Test 1), Aprepitant Capsules 125 mg (Test 2) manufactured by Rontis Hellas S.A. Greece) and Emend® 125 mg Capsules (125 mg aprepitant) (Reference) manufactured by Merck Sharp & Dohme Ltd., Netherland.
• The first pivotal study was conducted between Aprepitant Capsules 125 mg (manufactured by Rontis Hellas S.A., Greece) and Emend® 125 mg hard capsules (manufactured by Merck Sharp & Dohme Ltd., UK, from the Netherlands market) in healthy adult volunteers under *fasting conditions*.
• The second pivotal study was conducted between Aprepitant Capsules 125 mg (manufactured by Rontis Hellas S.A., Greece) and Emend® 125 mg hard capsules (manufactured by Merck Sharp & Dohme Ltd., UK, from the Netherlands market) in healthy adult volunteers under *fed conditions*.

Bioequivalence studies:

• Fasting study:
Design: randomized, open label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study in 40 healthy volunteers under fasting conditions with a 9 days wash-out period. For each subject, a total of 24 blood samples were collected in each period, pre-dose sample (within one hour before dosing) and post-dose samples were taken at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 7.00, 9.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after dosing. Blood samples were collected in pre-labelled vacutainer containing K3EDTA as anticoagulant.

Bioequivalence criteria:
was based on the 90% confidence intervals for the ratios of geometric least squares means (Test/Reference), from the ln-transformed parameters Cmax and AUC0-t. The acceptance range for bioequivalence is 80.00-125.00% for the 90% confidence intervals of the geometric least squares means ratio (T/R) for the primary pharmacokinetic parameters Cmax and AUC0-t.

Safety results: no death or serious adverse event occurred during the study. The test and reference products were comparable in their safety and tolerability.

Results:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$[2]	99.88	90.76% - 109.92%	24.34
Cmax	100.18	91.96% - 109.13%	21.69

The 90% confidence intervals of the ratios of LSM derived from analyses on the ln-transformed PK parameters AUC_{0-t} and C_{max} for aprepitant in plasma were within the predefined protocol limits (80% to 125%) indicating bioequivalence with the reference product.

• Fed study:
Design: randomized, open label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study in 62 healthy volunteers under fed conditions with an 11 days wash-out period. For each subject, a total of 24 blood samples (3.2mL) were collected in each period, pre-dose sample (within one hour before dosing) and post-dose samples were taken at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 7.00, 9.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after dosing. Blood samples were collected in pre-labelled vacutainer containing K_3EDTA as anticoagulant.

Bioequivalence criteria:
the acceptance range for bioequivalence was 80.00-125.00% for the 90% confidence intervals of the geometric least squares means ratio (T/R) for the primary pharmacokinetic parameters C_{max} and AUC_{0-t}.

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

Results:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$[2]	101.30	97.03% -105.77%	13.31
Cmax	101.56	94.81% -108.79%	21.36

The 90% confidence intervals of the ratios of LSM derived from analyses on the ln-transformed pharmacokinetic parameters AUC_{0-t} and C_{max} for aprepitant in plasma were within the predefined protocol limits (80.00% to 125.00%) indicating bioequivalence with the reference product in fed conditions.

Biowaiver:
The bioequivalence studies were performed with the highest strength (125 mg), and according to the Bioequivalence Guideline the applicant submitted biowaiver request for the lower strength (80 mg) which was based on the following conditions:

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

Since all criteria of general biowaiver claim were satisfied for the claimed dose strength (80 mg) according to the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Corr**) and similarity of dissolution profiles of the 80 and 125 mg dose strengths was justified, the biowaiver claim for the 80 mg dose strength is acceptable.

Conclusion on bioequivalence studies:
Based on the submitted pivotal bioequivalence studies **Aprepitant 1 A Pharma 125 mg hard capsules** is considered bioequivalent with **Emend® 125 mg capsules** (manufactured by Merck Sharp & Dohme Ltd., UK, from the Netherlands market) in healthy adult volunteers under fasting and fed conditions.

The results of bioequivalence studies with 125 mg hard capsules can be extrapolated to the other 80 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), section 4.1.6.

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

IV.4 Clinical efficacy

No new clinical efficacy studies were presented and no such studies are required for this application. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy profile of aprepitant.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, 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.

No new clinical safety studies were presented and no such studies are required for this application. The applicant has provided an adequate review of clinical trials published in the literature, describing 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 Pharmacovigilance 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

The safety concerns listed by the Applicant are in line with safety specification of the latest accepted version of the originator's RMP. (Version 4.1, dated on 01-July 2015; Assessment report, Procedure No. EMEA/H/C/000527/X/0049/G, 22 October 2015, EMA/787667/2015, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000527/WC500200826.pdf).

There is only one difference that the missing information, "Use in patients < 6 months of age or weighing <6 kg" has been changed to "Use in children less than 12 years of age", since the products under evaluation in this procedure are for treatment adults and adolescent from the age of 12. EMEND 125 mg powder for oral suspension is adequate only for the treatment in children, toddlers and infants from the age of 6 months to less than 12 years.

Note: During the last PSUSA procedure (EMEA/H/C/PSUSA/00000229/201903), the Lead member state recommended to update the RMP of the originator according to the new guidance document but the originator has not submitted an updated RMP.

Q Pharma should continuously check EMA website to notice any change.

Pharmacovigilance plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to the product. No additional activities are proposed.

Risk Minimisation Measures: Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to the product.
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 un-der 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 dossier concerned an abridged application that avoids the need for repetitive tests on animals and humans.
Aprepitant-Q Pharma 80 mg, 125 mg, (80 & 125) mg hard capsules is considered essentially similar to the innovator products are registered throughout the European Union under the brand name Emend® 80 mg, 125 mg, (80 & 125) mg hard capsules, marketed in Europe by Merck Sharp & Dohme Ltd, UK.

The Applicant has adequately demonstrated bioequivalence between the products and reference products.
Based on the submitted pivotal bioequivalence studies **Aprepitant-Q Pharma 125 mg hard capsules are considered bioequivalent** with **Emend® 125 mg capsules** (manufactured by Merck Sharp & Dohme Ltd., UK, from the Netherlands market) in healthy adult volunteers under fasting and fed conditions.

The results of study with 125 mg hard capsules CAN be extrapolated to the other 80 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), section 4.1.6.

All criteria of general biowaiver claim were satisfied for the claimed dose strength (80 mg) according to the bioequivalence guideline (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 was justified; hence, **the biowaiver claim for the 80 mg dose strength can be acceptable.**

Based on the review of the data on safety and efficacy, the Member State have granted a marketing authorization for Aprepitant 80 mg, 125 mg, 80 + 125 mg hard capsules in the treatment of prevention nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

Based on the submitted pivotal bioequivalence studies **Aprepitant 1 A Pharma 125 mg hard capsules is considered bioequivalent** with **Emend® 125 mg capsules** (manufactured by Merck Sharp & Dohme Ltd., UK, from the Netherlands market) in healthy adult volunteers under fasting and fed conditions.

The results of study with 125 mg hard capsules CAN be extrapolated to the other 80 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), section 4.1.6.

All criteria of general biowaiver claim were satisfied for the claimed dose strength (80 mg) according to the bioequivalence guideline (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 was justified; hence, **the biowaiver claim for the 80 mg dose strength can be acceptable.**

Based on the review of the data on safety and efficacy, the RMS considers that the application for Aprepitant 80 mg, 125 mg, 80 + 125 mg hard capsules in the treatment of prevention nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults and adolescents from the age of 12, is approvable.

V.2 Classification

Product on restricted prescription.

V.3 Package Leaflet and 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 **EMEND 125 mg hard capsules** (content) and **Darunavir 400 mg & 800 mg film coated tablets** (layout). The bridging report submitted by the applicant has been found acceptable.

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)