1 April 2015
EMA/287566/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Palonosetron Accord

International non-proprietary name: palonosetron

Procedure No. EMEA/H/C/004129/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-HT_3 receptor	serotonin receptor
ASMF	Active substance master file
AUC	Area under the curve
BCS	Biopharmaceutics classification system
CHMP	Committee for Medicinal Products for Human use
CFU	Colony forming units
Cmax	Maximum observed concentration
CQA	Critical quality attribute
EC	European Commission
EURD	EU reference dates
GC	Gas chromatography
HPLC	High performance liquid chromatography
HS-GC	Headspace gas chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometry
IR	Infrared
IV	Intravenous
LDPE	Low density polyethylene
MAH	Marketing authorisation holder
mL	millilitre
NMR	Nuclear magnetic resonance
NMT	Not more than
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PP	Polypropylene
PRAC	Pharmacovigilance Risk Assessment Committee
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative humidity
RMP	Risk management plan
SmPC	Summary of product characteristics
USP	United States Pharmacopoeia
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 4 May 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Palonosetron Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 December 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy,
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

in paediatric patients 1 month of age and older for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data with the reference medicinal product Aloxi 250 micrograms solution for injection instead of non-clinical and clinical.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Aloxi 250 micrograms solution for injection
  - Marketing authorisation holder: Helsinn Birex Pharmaceuticals Ltd, Ireland
  - Date of authorisation: (22-05-2005)
  - Marketing authorisation granted by:
    - Community

      Community Marketing authorisation number: EU/1/04/306/001

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Aloxi 250 micrograms solution for injection
  - Marketing authorisation holder: Helsinn Birex Pharmaceuticals Ltd, Ireland

- Date of authorisation: (22-05-2005)
- Marketing authorisation granted by:
  - Community
    Community Marketing authorisation number: EU/1/04/306/001

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

N/A (this medicinal product is a parenteral preparation. Therefore a bioequivalence study is not applicable according to CPMP/EWP/QWP/1401/98 Rev.1)

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alar Irs

- The application was received by the EMA on 4 May 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2016.
- During the meeting on 24 September 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 8 December 2015.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 4 February 2016.
- PRAC assessment overview, adopted by PRAC on 11 February 2016.
- During the CHMP meeting on 25 February 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 1 March 2016.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 15 March 2016.
- During the meeting on 1 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Palonosetron Accord.

2. Scientific discussion

2.1. Introduction

Palonosetron Accord 250 micrograms solution for injection is a generic medicinal product containing the active substance palonosetron. Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Palonosetron is an antiemetic agent. It is presented as a white to off white crystalline powder. It is freely soluble in water and soluble in methanol. Chemically it is (3aS)-2-[(3S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6- hexahydro-1H-benz[de]isoquinolin-1-one hydrochloride.

The reference medicinal product is Aloxi, palonosetron hydrochloride, 250 micrograms solution for injection of Helsinn Birex Pharmaceuticals Ltd, Ireland, authorised on 22/03/2005 via centralised procedure (authorisation number: EU/1/04/306). Therefore, according to the legislation, the applicant is not required to provide the results of pre-clinical tests and clinical trials as the medicinal product is a generic of a reference product, which has been authorised in the Community for at least 10 years.

The applicant is applying for a marketing authorisation for Palonosetron Accord, which has the same qualitative and quantitative composition in terms of the active pharmaceutical ingredient and also is of the same pharmaceutical form as the reference product.

The safety and efficacy profile of palonosetron for the prevention of acute nausea and vomiting associated with emetogenic chemotherapy has been demonstrated in several clinical trials for the reference medicinal product. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance.

The indications for Palonosetron Accord are identical to the indications of Aloxi and are as follows:

Palonosetron Accord is indicated in adults for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy,
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Palonosetron Accord is indicated in paediatric patients 1 month of age and older for.

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Palonosetron Accord should be used only before chemotherapy administration. This medicinal product should be administered by a healthcare professional under appropriate medical supervision.

The posology is 250 micrograms of palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Palonosetron Accord should be injected over 30 seconds.

The efficacy of Palonosetron Accord in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy may be enhanced by the addition of a corticosteroid administered prior to chemotherapy.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 250 µg of palonosetron (as hydrochloride salt) as active substance.

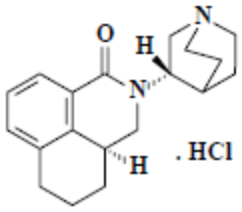
Other ingredients are: mannitol, citric acid monohydrate, sodium citrate, disodium edetate, sodium hydroxide (for pH adjustment), hydrochloric acid concentrated (for pH adjustment) and water for injections.

The product is available in a 6 ml type I tubular clear glass vial, closed with chlorobutyl rubber stopper and sealed with a flip-off aluminium seal. It is available in a pack of 1 vial containing 5 ml of solution.

2.2.2. Active substance

The information on palonosetron hydrochloride was provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of palonosetron hydrochloride is (3aS)-2-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1H-benz[de]-isoquinolin-1-one hydrochloride corresponding to the molecular formula $C_{19}H_{24}N_{2O}$·HCl and has a relative molecular mass of 332.87 g/mol. It has the following structure:



The structure of the active substance was elucidated by ^{1}H NMR spectroscopy, mass spectroscopy, infrared spectroscopy and elemental analysis.

Palonosetron hydrochloride is white to off-white, non-hygroscopic, crystalline powder, freely soluble in water and soluble in methanol. It has two chiral centres whereas the active substance in the product consists of a single stereoisomer. The absolute configuration of the active substance is (3*aS*,3*S*). Palonosetron hydrochloride is known to exhibit polymorphism. The manufacturing process, employed by the ASMF holder consistently yields Form I.

Manufacture, characterisation and process control

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and was considered satisfactory.

Palonosetron hydrochloride is synthesized in 5 stages using 2 starting materials with acceptable specifications.

The proposed starting materials have been sufficiently justified and reassuring information has been provided with regard to their origin, specifications and evaluation of impurities.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products and reagents have been presented and are satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. No class I solvents are used in the manufacturing process and a discussion as well as sufficient reassurance on absence of genotoxic impurities has been provided.

The container closure system consisting of low-density polyethylene (LDPE) bags, has been described and found acceptable.

Specification

The active substance specification includes tests for description, solubility (Ph. Eur.), identification (IR, HPLC), pH (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (USP method), (3aR, 3R)-enantiomer content (HPLC), related substance (HPLC), assay (HPLC), chloride content (titrimetry), palladium content (ICP-OES), lithium content (ICP-OES), residual solvents (GC), bacterial endotoxins (Ph. Eur.) and microbial examination (Ph. Eur.).

Additional information on potential impurities was requested and the suitability of applied limits in active substance specifications was scrutinised and was justified in an acceptable manner. The proposed limits for metal catalysts are justified based on PDE for parenteral use as per ICH Q3D.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data on 3 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial active substance package, low-density polyethylene bag, for 36 months under long term conditions at 25 ºC / 60% RH and for to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested*:* Description, identification by IR (Initial, third and sixth month in accelerated and initial and further annually during long term study), loss on drying, pH, assay, related substances, (3aR, 3R)-enantiomer content. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. No significant changes were observed in any of the batches under the stability study.

Photostability testing following the ICH guideline Q1B was performed on one batch and no degradation was observed when exposed to light. Results on stress conditions (acid, base, peroxide, thermal, humidity) were also provided on one batch and degradation was observed with peroxide.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is a 5 ml vial of sterile aqueous, clear, colourless solution containing 250 micrograms palonosetron (as hydrochloride).

The active ingredient, route of administration, dosage form, and concentration of palonosetron hydrochloride injection are similar to the reference product Aloxi 250 micrograms solution for injection marketed by Helsinn Birex Pharmaceuticals Ltd, Ireland. All ingredients were formulated to match the reference product for each specific attribute. No alternative formulations were investigated.

The development activities were aimed towards achieving a generic, stable formulation of Palonosetron Hydrochloride Injection 0.05 mg/ml (5 ml) in glass vial which is similar to that of the EU innovator product.

All excipients are well known pharmaceutical ingredients and are in line with innovator product Aloxi 250 micrograms solution for injection. Their quality is compliant with Ph. Eur standards. The list of excipients is included in section 6.1 of the SmPC. The finished product does not contain any preservative.

Physicochemical properties of the finished product such as description, assay and osmolality as well as the impurity profile are comparable with those of the innovator product.

The pH range of the finished product is lower than the measured pH of reference product (5.07) and lower than the physiological range and could cause adverse reactions to the patients during administration. Justification for the suitability of pH range has been provided. As a further measure, injection site reactions as a potential risk were included to the RMP based on precautionary principles and the finished product is added to the EURD list due to its lower pH compared to the reference product.

Terminal sterilisation was selected as manufacturing process and critical steps of manufacturing process were optimised. A number of studies were performed to optimise the manufacturing process of finished product, including a solubilisation study, a study on the selection of sterilisation method, a study on flushing, an excipient optimisation study, a pH extreme study, a bulk holding and surface compatibility study, filter compatibility studies, a freeze thaw study and performance testing.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Based on information of the innovator product clear glass vials of 6 ml furnished with chlorobutyl rubber stoppers, for which compatibility studies have been conducted, were selected as containers for finished product. The material complies with Ph.Eur. and EC requirements.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: preparation of bulk solution, filtration, vial filling & stoppering, vial sealing, terminal sterilisation and labeling & packaging.

The process is considered to be a standard manufacturing process. Hold time study results on unfiltered and filtered bulk solutions support the proposed holding times.

Major steps of the manufacturing process have been validated by studies on three batches of finished product. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Finished Product Specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description, identification (HPLC), pH (Ph. Eur.) extractable volume (Ph. Eur.), particulate contamination (Ph. Eur.), bacterial endotoxin (Ph. Eur.), sterility (Ph. Eur.), related substance (HPLC), assay (HPLC), clarity and color of solution (Ph. Eur.).

The specifications are considered adequate for individual impurities set according to ICH thresholds taking into account the maximum daily dose. Upon CHMP request, the total impurities limit (related substances) at the end of shelf life was tightened in line with batch data.

Details on specified impurities have been provided in the ASMF.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards including their preparation and qualification has been presented.

Batch analysis results are provided for three exhibit batches (commercial scale) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 exhibit batches of finished product stored under long term conditions for up to 36 months at 25 ºC / 60% RH and for to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of finished product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, pH (Ph.Eur.), clarity & colour of solution, assay, related substances, particulate contamination (sub visible), sterility and bacterial endotoxin.

The analytical methods for stability studies are the same as used for release testing and are stability indicating.

The stability study was performed on the samples in the inverted position. Test results both at long term and accelerated conditions were in accordance with the applied acceptance criteria and no significant changes have been observed. In addition, one batch was exposed to light as required by ICH Guideline on Photostability Testing of New Drug Substances and Products and results were in accordance with applied acceptance criteria.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

None of the excipients is of human or animal origin.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant did not submit non-clinical studies. 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 provides the justification as to why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed based on the Guideline CPMP/ICH/2738/99 and was considered generally acceptable. The limit for total impurities has been tightened.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Palonosetron Accord manufactured by Accord Healthcare Limited is considered unlikely to result in any significant increase in the combined sales volumes for all palonosetron containing products and the exposure of the environment to the active substance. Thus, the environmental risk is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The applicant provided a justification for not conducting any toxicological and pharmacological studies as the indications proposed and the pharmaceutical form and strength of Palonosetron Accord are the same as for the reference product Aloxi. Instead, the applicant provided a review of the literature for the *in vitro* and *in vivo* pharmacological and toxicological studies of palonosetron to support the claim

that the generic product Palonosetron Accord is similar to the reference product Aloxi. The information in the SmPC section 5.3 is the same as for the reference product.

2.3.4. Conclusion on the non-clinical aspects

The CHMP is of the opinion that the applicant has justified the lack of non-clinical studies based on the literature review and the claim that Palonosetron Accord is a generic of the reference product Aloxi. The literature data presented in the dossier is considered acceptable and sufficient for the assessment of non-clinical aspects of Palonosetron Accord in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of palonosetron hydrochloride based on published literature. The relevant SmPC sections are in line with the SmPC of the reference product.

No formal scientific advice by the CHMP has been requested for this medicinal product.

GCP

The applicant did not submit clinical trials with this application.

Exemption

Palonosetron Accord has been developed as a pharmaceutical equivalent of Aloxi solution for injection, (Helsinn Birex Pharmaceuticals Limited, Ireland). Palonosetron Accord is essentially similar to the approved reference product, Aloxi. Palonosetron Accord is qualitatively and quantitatively identical in composition to that of Aloxi. The active ingredient, dosage form, route of administration and strength of Palonosetron Accord are identical to those of the reference medicinal product. Palonosetron Accord is presented in packs of 1 vial containing 5 mL of solution, which is the same as Aloxi.

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were submitted. The applicant provided a literature review of the PK aspects of palenosetron.

Following palonosetron intravenous administration, an initial decline in plasma concentrations is followed by slow elimination from the body with a mean terminal elimination half-life of approximately 40 hours. Mean maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC0-∞) are generally dose-proportional over the dose range of 0.3- 90 μg/kg in healthy subjects and in cancer patients.

Palonosetron at the recommended dose is widely distributed in the body with a volume of distribution of approximately 6.9 to 12.5 l/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Palonosetron is eliminated by dual route, about 40% eliminated through the kidney and with approximately 50% metabolised to form two primary metabolites, which have less than 1% of the 5HT3 receptor antagonist activity of palonosetron. In vitro metabolism studies have shown that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 isoenzymes are involved in the metabolism of palonosetron.

Radiolabeled metabolic characterization of a single i.v. [14C]-palonosetron (10 µg/kg) reveals that unchanged palonosetron accounts for 71.9% of the total radioactivity in plasma over 96 h. Approximately 83% of the dose was recovered in urine (~40% as unchanged drug, with 50% metabolized; M9 [N-oxide metabolite] and M4 were the major metabolites) and 3.4% in feces. Both renal and hepatic routes are involved in the elimination of palonosetron from the body. The mean CLT for palonosetron is 160 ml/h/kg. The mean renal clearance of palonosetron is 66.5 ml/h/kg. Mean CLT of palonosetron ranges from 1.51 to 2.23 ml/min/kg at palonosetron doses of 0.3, 1, 3, 10, 30 or 90 µg/kg, indicating low clearance compared with hepatic blood flow (approximately 20 ml/min/kg). The low CLT and large Vd resulted in a long T1/2, with mean values ranging from 43.7 to 128 h.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. Post marketing experience

2.4.1. Post marketing experience

No post-marketing data were submitted by the applicant. The medicinal product has not been marketed in any country.

2.4.2. Discussion on clinical aspects

No new pharmacokinetic and pharmacokinetic studies were submitted. A summary of the literature with regard to clinical data of Palonosetron Accord and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. The summary of literature referred to the proposed indications.

Palonosetron Accord is to be administered as an aqueous intravenous injection and contains the same active ingredient in the same concentration and pharmaceutical formulation using the same route of administration as for the reference product. It has an identical qualitative and quantitative composition in terms of the active substance as its reference medicinal product and also contains the same excipients. As it is indicated for intravenous administration and in accordance to CPMP/EWP/QWP/1401/98 Rev.1, Appendix II, Parenteral solutions, bioequivalence can be concluded without the need for further studies. There are no differences in non-clinical or clinical effects that are expected. Main safety concerns identified with the reference product were severe constipation and severe hypersensitivity reactions. Important potential risks (as for other 5HT3 antagonists) are QT/QTc prolongation and serotonin syndrome.

2.4.3. Conclusions on clinical aspects

The CHMP is of the opinion that the applicant has justified the lack of clinical studies based on the claim that Palonosetron Accord is a generic of the reference product Aloxi. As the product contains the

same active ingredient in the same concentration and pharmaceutical formulation using the same route of administration as for the reference product, the lack of bioequivalence studies is considered acceptable. The literature data and the publicly available information presented in the dossier are considered acceptable and sufficient for the assessment of clinical aspects of Palonosetron Accord in the applied indications.

2.5. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The CHMP and PRAC considered that the RMP version 3.0 (dated 8 February 2016) is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Table 1: Summary of safety concerns

Important identified risks	• Severe constipation • Severe hypersensitivity reactions
Important potential risks	• QT/QTc prolongation • Convulsive events • Serotonin syndrome • Injection site reactions
Missing information	• Effect in pregnancy • Effect in lactating women • Effects on fertility • Effect in children aged less than 1 month (potential off-label use for CINV prevention) • Effects in patients with end stage renal disease undergoing haemodialysis

Pharmacovigilance plan

No studies required.

Risk minimisation measures

Table 2: Summary table of additional Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Severe constipation	Section 4.4 and 4.8 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None
Severe hypersensitivity reactions	Section 4.3 and 4.8 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None
Important potential risks		
QT/QTc prolongation	Section 4.4, 4.8 and 5.1 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None
Convulsive events	None proposed	None
Serotonin syndrome	Section 4.4 and 4.5 of proposed SPC has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None
Injection site reactions	Section 4.8 of proposed SPC has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None
Missing information		
Effect in pregnancy	Section 4.6 and 5.3 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None
Effect in lactating women	Section 4.6 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	status of the product as "prescription only".	
Effects on fertility	Section 4.6 of proposed SPC has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None
Effect in children aged less than 1 month (potential off-label use for CINV prevention)	Section 4.2 of proposed SPC has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None
Effects in patients with end stage renal disease undergoing haemodialysis	Section 4.2 and 5.2 of proposed SPC has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	None

2.6. PSUR submission

An important potential safety concern of "injection site reactions" was raised during the assessment. The product Palonosetron Accord has a low pH compared to the reference product. It is known that the incidence of injection site reactions (including phlebitis) is higher with a lower pH level and longer duration of IV administration. Hence, "injection site reaction" and close monitoring through routine pharmacovigilance was added to the RMP. In light of this safety concern, the applicant shall submit PSURs in line with the reference product PSUR submission requirements (EURD list). This need for PSUR submission will continue to be reassessed as further market experience is acquired.

2.7. Pharmacovigilance

Pharmacovigilance system

The Applicant has submitted a signed Summary of the Pharmacovigilance System. The CHMP considered that the Summary of the Pharmacovigilance System submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Aloxi. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of palonosetron hydrochloride, 250 microgram solution for injection. The reference product Aloxi is indicated in adults for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, and is indicated in paediatric patients 1 month of age and older for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient and acceptable.

A bioequivalence study was not submitted and this was considered acceptable as Palonosetron Accord contains the same active ingredient in the same concentration and pharmaceutical formulation using the same route of administration (parenteral) as for the reference product.

The CHMP, having considered the quality data provided as well as the non-clinical and clinical information submitted in the application, is of the opinion that Palonosetron Accord is comparable to the reference product Aloxi in the applied indication and that no additional risk minimisation activities are required beyond those included in the product information. Therefore, the benefit risk balance for Palonosetron Accord is considered positive.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Palonosetron Accord in adults for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy, the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, and in paediatric patients 1 month of age and older for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.