25 February 2016
EMA/215640/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Palonosetron Hospira

International non-proprietary name: palonosetron

Procedure No. EMEA/H/C/004069/0000

## 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 |
| 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 |
| UV | Ultraviolet |
| XRPD | X-ray powder diffraction |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Hospira UK Limited submitted on 25 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Palonosetron Hospira, 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 23 October 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 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 indication:

Palonosetron Hospira 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.

**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 and complete quality data. There is no requirement for bioequivalence testing according to CPMP/EWP/QWP/1401/98 Rev.1.

***Information on paediatric requirements***

Not applicable.

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/5ml Solution for injection
  - Marketing authorisation holder: Helsinn Birex Pharmaceuticals Limited
  - Date of authorisation: (22-03-2005)
  - 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/5ml Solution for injection
- Marketing authorisation holder: Helsinn Birex Pharmaceuticals Limited
- Date of authorisation: (22-03-2005)
- 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:

This medicinal product is a parenteral preparation. Therefore 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***

An application was filed in the following country: USA.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur appointed by the CHMP was:

Rapporteur: Kolbeinn Gudmundsson Co-Rapporteur: N/A

CHMP Peer reviewer: N/A

- The application was received by the EMA on 25 March 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 August 2015.
- During the meeting on 24 September 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 December 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 February 2016.
- PRAC assessment overview, adopted by PRAC on 11 February 2016.
- During the meeting on 25 February 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 Hospira.

# 2. Scientific discussion

## *2.1. Introduction*

Palonosetron Hospira 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, was 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 Hospira, 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 Hospira are identical to the indications of Aloxi and are as follows:

Palonosetron Hospira 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 Hospira 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 Hospira 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 Hospira should be injected over 30 seconds.

The efficacy of Palonosetron Hospira 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, disodium edetate, sodium citrate, citric acid monohydrate, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

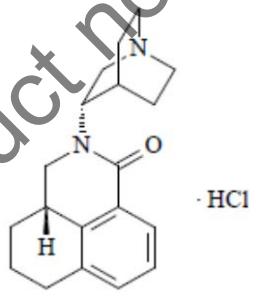
The product is available in type I glass vials with chlorobutyl rubber stoppers and aluminium seals as described in section 6.5 of the SmPC.

### 2.2.2. Active substance

#### *General information*

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

The chemical name of palonosetron hydrochloride is (3a*S*)-2-[(*S*)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-*1H*-benz[de]isoquinoline hydrochloride corresponding to the molecular formula $C_{19}H_{24}N_2O$ and a relative molecular mass of 332.8 g/mol. It has the following structure:




The structure of the active substance was elucidated by a combination of $^{1}H$ and $^{13}C$ NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry and elemental analysis. The polymorphic form was characterised by XRPD.

The active substance is a white to off-white non-hygroscopic crystalline powder, very soluble in aqueous media across the physiological pH range.

Palonosetron exhibits stereoisomerism due to the presence of two chiral centres which originate in the starting materials. Enantiomeric and diastereomeric purity is controlled routinely by chiral HPLC.

Polymorphism has not been observed for palonosetron hydrochloride.

#### *Manufacture, characterisation and process controls*

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

Palonosetron hydrochloride is synthesized in three main steps using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and have been demonstrated to adequately control any stereoisomeric impurities.

The characterisation of the active substance and its impurities is 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. Limits for several impurities have been set in intermediates, which ensures they are adequately purged by subsequent steps. The absence of genotoxic impurities has been adequately demonstrated.

The active substance is doubly packaged in low-density polyethylene (LDPE) bags inside polypropylene (PP) drums, the materials of which comply with the EC directive 2002/72/EC and EC 10/2011.

***Specification***

The active substance specification as shown below includes tests for appearance, identity (IR, HPLC), water content (KF), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), impurities (HPLC), enantiomeric impurities (chiral HPLC), assay (HPLC), residual solvents (GC and HS-GC), chloride content (potentiometric titration), bacterial endotoxins (Ph. Eur.) and microbial content (Ph. Eur.). Impurities levels are set in accordance with the ICH Q3A thresholds for a daily posology of 0.25 mg.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. However, according to Ph. Eur. 2.6.12, the ability of the test for microbial quality to detect microorganisms in the presence of the active substance needs to be established. Further validation work to address this omission is on-going and the applicant committed to providing the data prior to product launch. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

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

***Stability***

Stability data on six production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. Data on four of the batches stored for 6 months under accelerated conditions (40 ºC / 75% RH) were also provided. The following parameters were tested: appearance, identity, water content, impurities, enantiomeric impurities and assay. The analytical methods used were the same as for release and are stability indicating. No trends were observed and all measured parameters remained within their specification limits throughout the study.

Photostability testing following the ICH guideline Q1B was performed on one batch. Forced degradation studies were carried out in solution at reflux in water, aqueous acid, base or with peroxide and in the solid state at high temperature. Palonosetron is stable to light and high temperature. It degrades to an extent in solution, more so in base than in acid, although the greatest degradation is observed under oxidative conditions.

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, without special storage conditions.

## 2.2.3. Finished medicinal product

***Description of the product and Pharmaceutical development***

The finished product is a sterile aqueous solution containing 0.25 mg palonosetron (as hydrochloride salt) in 5 ml solution. The aim of development was to deliver a finished product qualitatively and quantitatively identical to the reference product, Aloxi. The quality target product profile (QTPP) was defined to ensure the product is pharmacologically equivalent to Aloxi, meeting or exceeding the relevant quality standards. Accordingly, the QTPP was defined as a clear colourless solution for injection in an appropriate primary container containing 0.05 mg/ml palonosetron with a suitable shelf-life and meeting the required specifications for impurities, assay, volume, pH, osmolarity, oxygen content and sterility. Following a risk assessment and subsequent investigations, critical quality attributes (CQAs) were defined as appearance, pH, assay, impurities and sterility.

Palonosetron hydrochloride is freely soluble across the physiologically relevant pH range and highly permeable (BCS I). A risk assessment was carried out to assess the active substance attributes with the potential to impact finished product quality, and those considered important, (appearance, impurities, assay, microbiological quality), are controlled in the active substance specification. Since the formulation is identical to that of the reference product which has a shelf-life of 5 years and is thus very stable, no excipient compatibility studies were deemed necessary. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Given the route of administration and the formulation relative to Aloxi, no bioequivalence study was required.

QbD principles were applied to the development of the manufacturing process. An overall risk assessment was carried out to identify the individual steps with potential to impact the CQAs of the finished product. Additional risk assessments were carried out on the individual process steps to evaluate the potential impact of process parameters of unit operations and input material attributes on the quality of the output materials. This was used to guide development of the process and define parameters in order to ensure the quality of the finished product. Terminal sterilisation is used to ensure sterility of the product as it has been shown to be thermally stable.

The primary packaging is a type I glass vial with a chlorobutyl rubber stopper and aluminium seal. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

***Manufacture of the product and process controls***

The manufacturing process consists of six main steps: preparation of bulk solution; sterile filtration; filling; sealing; sterilisation; packaging.

The process is considered to be a standard manufacturing process. In-process controls are carried out after critical operations and are considered adequate. The applied process parameters are well justified. Holding times for intermediates have been investigated and defined. The sterilisation process has been validated whilst a validation scheme for the rest of the process has been provided and is considered acceptable.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form and comprise tests for appearance, extractable volume (Ph. Eur.), identification (UV, HPLC), osmolarity (Ph. Eur.), pH (Ph. Eur.), assay (HPLC), impurities (HPLC), extractables (HPLC), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and particulate matter (Ph. Eur.). The levels set for impurities are in line with the ICH thresholds for a daily posology of 0.25 mg and historic data.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

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

***Stability of the product***

Stability data on three production scale batches of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH), for up to 18 months under intermediate conditions (30 ºC / 60% RH and 30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Palonosetron Hospira are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, osmolarity, pH, assay, impurities, sterility, particulate matter and bacterial endotoxins. The analytical procedures used are stability indicating. There were no significant trends to any of the measured parameters and all remained within specification throughout the studies. A maximum of 0.2% total impurities was observed under accelerated testing.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. A slight increase in one stereoisomer and an unspecified impurity was observed although both were within specification.

Based on available stability data, the proposed shelf-life of 30 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

***Adventitious agents***

No excipients derived from animal or human origin have been used.

## 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

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The ability of the test for microbial quality to detect microorganisms in the presence of the active substance should be demonstrated. Validation data should be provided prior to commercialisation of the product.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. 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.

Therefore, the CHMP agreed that no further non-clinical studies were required.

### 2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Palonosetron Hospira manufactured by Hospira UK 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 Hospira 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 Hospira 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 claim that Palonosetron Hospira 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 Hospira 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***

The Marketing Authorisation Application for 250 micrograms per vial (5ml) of Palonosetron Hospira is classified as an abridged 'generic' application under Article 10(1) of Directive 2001/83/EC (as amended).

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

As per the guideline CPMP/EWP/QWP/1401/98 Rev.1, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous (IV) solution containing the same active drug substance in the same concentration as the currently authorised product. Palonosetron hydrochloride solution is intended for IV use and contains the same active drug substance in the same concentration as the currently authorised product and therefore, no bioequivalence studies were required.

### 2.4.2. Pharmacokinetics

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 ($C_{max}$) and area under the concentration-time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0.3- 90 $\mu$g/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 7.9 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 $5HT_3$ 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.

After a single intravenous dose of 10 micrograms/kg [$^{14}$C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose, as unchanged active substance. After a single intravenous bolus administration in healthy subjects the total body clearance of palonosetron was 173 ± 73 ml/min and renal clearance was 53 ± 29 ml/min. The low total body clearance and large volume of distribution resulted in a terminal elimination half-life in plasma of approximately 40 hours. Ten percent of patients have a mean terminal elimination half-life greater than 100 hours.

### 2.4.3. Pharmacodynamics

No new pharmacodynamic studies were submitted by the applicant.

### 2.4.4. Post marketing experience

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

### 2.4.5. Discussion on clinical aspects

No new pharmacokinetic and pharmacodynamic studies were presented. A summary of the literature with regard to clinical data of Palonosetron Hospira was provided and was accepted by the CHMP. No post-marketing data were submitted by the applicant as this product has not been marketed in any country.

The summary of literature referred to the proposed indications in adult patients. During the procedure, the applicant aligned the indication with the indication of the reference product Aloxi which included paediatric patients 1 month of age and older.

The product Palonosetron Hospira 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. It also contains the same excipients are used. 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 expected differences in non-clinical or clinical effects 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.

### 2.4.6. 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 Hospira 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 Hospira in the applied indications.

## *2.5. Risk management plan*

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

The PRAC considered that the RMP version 1.0 (dated 17 February 2016) is acceptable.

The CHMP endorsed this advice without changes.

***Safety concerns***

**Table 2 - Summary of safety concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Severe hypersensitivity reactions.<br>• Severe constipation. |
| Important potential risks | • QT/QTc prolongation.<br>• Serotonin syndrome.<br>• Convulsive events |
| Missing information | • Use in pregnancy.<br>• Use in patients with end stage renal disease undergoing haemodialysis.<br>• Effect in lactating women.<br>• Effect on fertility.<br>• Effect in children aged less than 1 month (potential off-label use for CINV prevention) |

***Pharmacovigilance plan and Risk minimisation measures***

There are no pharmacovigilance studies, activities, or additional risk minimisation measures ongoing or planned.

**Table 3 - Summary table of risk minimisation measures**

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| Severe hypersensitivity reactions. | Proposed text in SmPC – Section 4.3 "Contraindications":<br><br>*"Hypersensitivity to the active substance or to any of the excipients listed in section 6.1."*<br><br>List of excipients in section 6.1 include *"mannitol, disodium edetate, sodium citrate, citric acid monohydrate, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections".*<br><br>Proposed text in SmPC – Section 4.8 *"Undesirable effects"* under | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Immune system disorders system organ class (SOC), *"Hypersensitivity"* has been reported to be very rare (<1/10,000).<br><br>Other routine risk minimisation measures:<br><br>PIL as stated under Section 2 "What you need to know before you use Palonosetron Hospira":<br><br>*"Do not use palonosetron Hospira if you are allergic to palonosetron or any of the other ingredients of this medicine."*<br><br>PIL as stated under Section 4 "Possible side effects":<br><br>*"Very rare side effects: (may affect up to 1 in 10,000 people): Allergic reactions to palonosetron Hospira (The signs may include swelling of the lips, face, tongue or throat, having difficulty breathing or collapsing, you could also notice an itchy, lumpy rash (hives), burning or pain at the site of injection."* | |
| Severe constipation. | Proposed text in SmPC – Section 4.4 "Special warnings and precautions for use".<br><br>"*As palonosetron may increase large bowel transit time, patients with a history of constipation or signs of sub-acute intestinal obstruction should be monitored following administration. Two cases of constipation with faecal impaction requiring hospitalisation have been reported in association with palonosetron 750 µg*."<br><br>Proposed text in SmPC – Section 4.8 *"Undesirable effects"* under Gastrointestinal disorders SOC: *"Constipation"* has been reported to be common ARs (≥ 1/100 to<1/10).<br><br>Other routine risk minimisation measures<br><br>PIL as stated under Section 2 "What you need to know before you use Palonosetron Hospira" under warnings and precautions: | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | *"Talk to your doctor or pharmacist before using Palonosetron Hospira. If you have acute bowel obstruction or a history of repeated constipation."*<br><br>PIL as stated under Section 4 "Possible side effects":<br><br>*"Possible side effects and their frequencies are listed below:*<br>*Adults*<br>*Common (may affect up to 1 in 10 people): constipation."* | |
| QT/QTc prolongation. | Proposed text in SmPC – Section 4.4 "Special warnings and precautions for use".<br><br>"*At all dose levels tested, palonosetron did not induce clinically relevant prolongation of the QTc interval. A specific thorough QT/QTc study was conducted in healthy volunteers for definitive data demonstrating the effect of palonosetron on QT/QTc.*<br><br>*However, as for other 5-$HT_3$ antagonists, caution should be exercised in the use of palonosetron in patients who have or are likely to develop prolongation of the QT interval. These conditions include patients with a personal or family history of QT prolongation, electrolyte abnormalities, congestive heart failure, bradyarrhythmias, conduction disturbances and in patients taking anti-arrhythmic agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalemia and hypomagnesemia should be corrected prior to 5-$HT_3$ -antagonist administration*."<br><br>Proposed text in SmPC – Section 4.8 *"Undesirable effects"* under Investigations SOC: *"electrocardiogram QT prolonged" has been reported to be uncommon ARs Uncommon ARs (≥ 1/1,000 to <1/100).*<br><br>Proposed text in SmPC – Section 4.8 *"Undesirable effects"* – Paediatric population under Cardiac disorders SOC: *"electrocardiogram QT prolonged conduction disorder" has been reported to be uncommon ARs Uncommon ARs (≥ 1/1,000 to* | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | *<1/100).*<br><br>Other routine risk minimisation measures:<br><br>PIL as stated under Section 2 "What you need to know before you use Palonosetron Hospira" under warnings and precautions:<br><br>*"Talk to your doctor or pharmacist before using Palonosetron Hospira. If you have a personal or family history of alterations in heart rhythm (QT prolongation)."*<br><br>PIL as stated under Section 4 "Possible side effects":<br><br>Uncommon side effects: (may affect up to 1 in 100 people): electrocardiogram abnormalities (QT prolongation). | |
| Serotonin syndrome. | Proposed text in SmPC – Section 4.4 "Special warnings and precautions for use":<br><br>"*There have been reports of serotonin syndrome with the use of 5-$HT_3$ antagonists either alone or in combination with other serotonergic drugs (including SSRI and SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.*"<br><br>Proposed text in SmPC – Section 4.5 "Interaction with other medicinal products and other forms of interaction":<br><br>*"Serotonergic Drugs (e.g. SSRIs and SNRIs):*<br><br>*There have been reports of serotonin syndrome following concomitant use of 5-HT3 antagonists and other serotonergic drugs (including SSRIs and SNRIs)."*<br><br>Other routine risk minimisation measures<br><br>PIL as stated under Section 2 "What you need to know before you | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | use Palonosetron Hospira" under other medicines and Palonosetron Hospira:<br><br>*"Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including: SSRIs used to treat depression and/or anxiety including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram SNRIs used to treat depression and/or anxiety including venlafaxine, duloxetine."* | |
| Convulsive events | None proposed.<br><br>Prescription only medicine. | Not applicable |
| Use in pregnancy. | Proposed text in SmPC – Section 4.6 "Fertility, pregnancy and lactation".<br><br>"*For palonosetron no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer. There is no experience of palonosetron in human pregnancy. Therefore, palonosetron should not be used in pregnant women unless it is considered essential by the physician.*"<br><br>Proposed text in SmPC – Section 5.3 "Preclinical safety data":<br><br>*"Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer."*<br><br>Other routine risk minimisation measures<br><br>PIL as stated under Section 2 "What you need to know before you use Palonosetron Hospira":<br><br>*"Pregnancy:*<br>• *If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist* | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | *for advice before taking this medicine.*<br>• *If you are pregnant or think you might be, your doctor will not administer Palonosetron Hospira to you unless it is clearly necessary.*<br>*It is not known whether Palonosetron Hospira will cause any harmful effects when used during pregnancy."* | |
| Use in patients with end stage renal disease undergoing haemodialysis. | Proposed text in SmPC – Section 4.2 "Posology and method of administration".<br>"*No dose adjustment is necessary for patients with impaired renal function.*<br>*No data are available for patients with end stage renal disease undergoing haemodialysis.*" | None |
| Effect in lactating women. | Proposed text in SmPC – Section 4.6 "Fertility, pregnancy and lactation".<br>"*As there are no data concerning palonosetron excretion in breast milk, breast-feeding should be discontinued during therapy.*"<br>Other routine risk minimisation measures<br>PIL as stated under Section 2 "What you need to know before you use Palonosetron Hospira":<br>*"Breast-feeding:*<br>*It is not known if Palonosetron Hospira is found in breast milk.*<br>*Ask your doctor or pharmacist for advice before using Palonosetron Hospira if you are breast-feeding."* | None |
| Effect on fertility. | Proposed text in SmPC – Section 4.6 "Fertility, pregnancy and lactation".<br>"*There are no data concerning the effect of palonosetron on fertility.*" | None |
| Effect in children | Proposed text in SmPC – Section 4.2 "Posology and method of | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| aged less than 1 month (potential off-label use for CINV prevention) | administration"<br><br>*"The safety and efficacy of palonosetron in children aged less than 1 month have not been established. No data are available.*<br><br>*There are limited data on the use of palenosetron in the prevention of nausea and vomiting in children under 2 years of age."* | |

### *2.6. PSUR submission*

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.

### *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. The product Palenosetron Hospira applied for the following indication: 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. During the procedure, the applicant aligned the indication with the reference product and included paediatric patients 1 month of age and older. No nonclinical studies have been submitted 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 Hospira 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 Palenosetron Hospira 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 Palenosetron Hospira 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 Hospira 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.