EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2011
EMA/708931/2011
Patient Health Protection

Assessment report pursuant to Article 30 of Directive 2001/83/EC, as amended

Kytril and associated names

INN: granisetron

Marketing authorisation holder: Roche group of companies and associated companies

Procedure no: EMEA/H/A-30/1155

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 3 June 2010 the European Commission on behalf of all marketing authorisation holders presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, as amended (Annex 3.1), in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products:

Kytril and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the June 2010 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr O. Slanar as rapporteur (later replaced by Dr D. Valik) and Dr J. Ersbøll as co-rapporteur.

Kytril medicinal products are registered in the following EU Members States: Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom.

Kytril medicinal products are currently not registered in the following EU Member States: Denmark, Cyprus and Poland.

2. Scientific discussion during the referral procedure

2.1. Introduction

Granisetron, the active ingredient of Kytril is a highly selective antagonist of 5-hydroxytryptamine (5-HT3) receptors, which displays potent antiemetic activity. Serotonin receptors of the 5-HT3 subtype are located both peripherally in vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT3 receptors and induces vomiting by invoking vagal afferent discharge.

Nausea and vomiting are common adverse events of certain types of chemotherapy. Clinical and basic research over the past 25 years has lead to steady improvements in the control of chemotherapy-induced nausea and vomiting (CINV). The development of the 5-HT3-receptor-antagonists (5-HT3-RAs) such as Kytril have been used in the treatment of CINV in cancer patients.

Kytril was first approved in Europe in France, through the nationally authorised procedure on 12 April 1991. Thereafter national approval was obtained in most of the EU countries. Kytril has recently been withdrawn in two countries (Denmark and Iceland). No marketing authorisations exist in Cyprus, Norway and Poland. Currently no new Marketing Authorisation Applications are pending within Europe.

In Europe, the product is available as film-coated tablets (1 mg and 2 mg) and solutions for injection (1 mg/1 ml, 3 mg/3 ml, 3 mg/1 ml and 3 mg/5 ml). Not all strengths may be registered in all EU Member States. The oral solution (granisetron HCl 6 mg/30 ml) has recently been withdrawn in Italy. As a consequence this formulation is no longer available in the EU and therefore has not been taken into consideration in this clinical overview.

As Kytril (granisetron) was included in the list of products for SmPC harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended, due to the divergent national decisions taken by Member States, the European Commission notified the European Medicines Agency of an official referral under Article 30(2) of Directive 2001/83/EC, as amended in order to resolve divergences amongst the nationally authorised Summary of Product Characteristics (SmPC), and thus to harmonise its divergent SmPC across the EU.

2.2. Clinical aspects

2.2.1. Introduction

Nausea and vomiting is experienced in most patients undergoing chemotherapy and radiotherapy, and may be classified as:

- Acute onset; occurring within 24 h of initial administration of chemotherapy or radiotherapy

- Delayed onset; occurring 24 h after administration of chemotherapy or radiotherapy and persisting for up to 5-7 days.

Postoperative nausea and vomiting (PONV), is defined as nausea and/or vomiting occurring within 24 hours after surgery, and is thought to be multifactorial involving involving individual, anaesthetic, and surgical risk factors.

Harmonisation of the existing SmPCs relating to the clinical sections, for Kytril film-coated tablets and solutions for injection, is discussed below.

2.2.2. Critical Evaluation

Section 4.1 – Therapeutic Indications

- **Chemotherapy-Induced Nausea and Vomiting (CINV)**

Prevention of CINV

Prevention of CINV is approved in all member states.

Numerous trials have been published in the field to evaluate the role of 5-HT3-receptor-antagonists (5-HT3-RAs) in the prevention of acute CINV. All studies demonstrated that 5-HT3-RAs are advantageous in comparison to other antiemetics (e.g., metoclopramide, dexamethasone and aprepitant) in the prevention of acute CINV in both highly and moderately emetogenic chemotherapies.

Treatment of CINV

In response to the List of Outstanding Issues (LoOI) an extensive discussion on the efficacy of granisetron, both tablets and solutions, in the treatment of CINV was provided by the MAH.

The MAH cited 8 studies in total (n = 2 642) with oral use of granisetron, 3 studies (n = 669) with intramuscular administration, and 12 studies (n = 3 073), where granisetron was used as an intravenous solution. Across all these studies the efficacy was demonstrated and the presented data were considered to be sufficient.

Prevention and treatment of delayed CINV

The CHMP was of the view that a distinction between prevention and treatment of CINV and the acute and delayed form of CINV should be made.

In the MAH's response to the LoOI it is stated that most studies were so designed that granisetron or comparator were administered immediately prior to the chemotherapy schedule and subsequently injected twice a day for the duration of the particular cycle for up to 15 days. There was no study actually designed to address delayed onset nausea and vomiting as a stand alone indication.

It is clear from the above that treatment of delayed CINV has not been addressed in a clinical study. (Treatment of delayed CIVN is defined as administration of granisetron after symptoms of delayed CINV have surfaced in patients with no prophylactic anti-emetic treatment – or in patients' breakthrough of symptoms despite prophylactic anti-emetic treatment). Hence, the CHMP agreed that the wording in the SmPC should not comprise treatment of delayed CINV.

Therefore the evidence provided appears to support only the prevention of delayed CINV.

- **Radiotherapy-Induced Nausea and Vomiting (RINV)**

Prevention of RINV

RINV indication is approved in all countries except for Romania. However discrepancies concerning "prevention" or "prevention and treatment" exist.

The literature concerning the prevention of radiotherapy-induced nausea and vomiting is limited, as only few randomized studies have been performed and only a small number of patients are included in each trial. Overall data are supportive that 5-HT3 RA are effective in preventing (moderately and highly emetogenic) RINV with or without corticosteroids.

Treatment of RINV

In response to the LoOI, the MAH provided information on the available data for the treatment of RINV. In total, four trials including 134 patients treated by intravenous granisetron and three studies including 544 patients treated by oral forms of granisetron are cited.

Prevention and treatment of delayed RINV

In the MAH's response to the LoOI the MAH states that most studies were so designed that granisetron or comparator were administered immediately prior to the radiotherapy schedule and that although RINV was indeed controlled throughout the period for consideration, there was no study actually designed to address delayed onset nausea and vomiting as a stand alone indication.

- **Post-Operative Nausea and Vomiting (PONV)**

There is lack of published data supporting the registration of Kytril film-coated tablets in the treatment of PONV. In response to the LoOI, the MAH performed a review of the available data, and agreed that the use of granisetron tablets orally in PONV should not be recommended.

Based on the evidence provided, the use of Kytril in PONV was restricted to the solution for injection formulation only.

Paediatric population

Tablets

The safety and efficacy of Kytril tablets in children have not yet been established and no data are available.

Solution for injection

The MAH also proposed Kytril solution for injection in children aged 2 years and above for the prevention and treatment of acute CINV, which was accepted by the CHMP.

The treatment of delayed CINV has not been investigated in clinical trials. Based on the available data, the indication for Kytril solution for injection in the treatment and prevention of delayed CINV was not agreed by the CHMP.

The SmPC does not recommend administration of Kytril solution for injection for paediatric use in RINV and PONV.

Therefore the following paediatric indication was agreed by the CHMP, only for Kytril solution for injection:

'Kytril solution for injection is indicated in children aged 2 years and above for the prevention and treatment of acute nausea and vomiting associated with chemotherapy.'

CHMP conclusion

The CHMP endorsed the treatment and prevention of CINV and RINV for both formulations – tablets and solution for injection.

Further evidence provided by the MAH support the use of granisetron only in the prevention of delayed CINV and RINV, and not in the treatment of delayed CINV and RINV for both formulations.

Based on the evidence provided, the use of Kytril in PONV was restricted to the solution for injection formulation only. The use of granisetron orally in PONV is not recommended.

In children aged 2 years and above, the indication for Kytril solution for injection was accepted by the CHMP for the prevention and treatment of acute CINV only. The indication for Kytril solution for injection in the treatment and prevention of delayed CINV was not accepted by the CHMP.

The MAH does not recommend administration of Kytril solution for injection for paediatric use in RINV and PONV.

Taking into account the recommendation of the CHMP and the MAH's proposals, the following wording was agreed for the indication in adults, for the following pharmaceutical forms - tablets and solution for injection:

Tablets:

'Kytril film-coated tablets are indicated in adults for the prevention and treatment of acute nausea and vomiting associated with chemotherapy and radiotherapy.

Kytril film-coated tablets are indicated in adults for prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.'

Solution for injection:

'Kytril solutions for injection are indicated in adults for the prevention and treatment of

-acute nausea and vomiting associated with chemotherapy and radiotherapy.
-post-operative nausea and vomiting.

Kytril solution for injection is indicated for the prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.'

Section 4.2 - Posology and method of administration

- **Solution for injection**

CINV & RINV

Some countries restrict use of the parenteral formulations to CINV (UK, Ireland, Malta).

Most countries mention the concomitant administration of corticosteroid as advisable and suggest dexamethazone 8- 20 mg or methylprednisolone 250 mg.

Italy is the only country to recommend administration via the i.m. route. The MAH submitted 3 clinical trials in support of the efficacy of the i.m. route in the prevention of CINV. The first was a pharmacokinetic (PK) study that failed to show equivalence of the i.m. with the i.v. route for AUC or Cmax. The second was a crossover study to assess prevention of CINV in 117 chemotherapy naïve patients with i.m. and i.v. treatments. Although the two routes demonstrated comparable efficacy, the design of the study precludes robust conclusions, as only chemotherapy naïve patients were used, and there was no adjustment for confounding from sustained activity in the crossover design. The third study compared i.m. granisetron alone against i.m. granisetron with dexamethasone in the prevention of delayed CINV, after initial administration of i.v. granisetron. Again only chemotherapy naïve patients were used, and the lack of a suitable control group does not allow a conclusion of efficacy.

Since no further data was provided by the MAH on the intramuscular administration of granisetron, the CHMP agreed that there is insufficient data to support the possible benefit of intramuscular administration of granisetron.

Paediatric population: Application in children is generally advised from the age of 2 years. In some countries (Iceland, Netherlands, Portugal), the RINV indication is specifically mentioned while in the others both the CINV and the RINV indications are meant to apply.

However as agreed by the CHMP, Kytril solution for injection maybe administered in children aged 2 years and above, only for the prevention and treatment of acute CINV.

There is insufficient clinical evidence to recommend administration of Kytril solution for injection to children in the prevention and treatment of RINV and PONV.

- **Film-coated tablets**

CINV & RINV

There is some disharmony among member states regarding the posology. In Germany, Lithuania, Spain and Slovenia the 1 mg dose is indicated or mentioned whilst in the other countries a range of 1-3 mg is refered to. The maximum recommended dose is usually 9 mg, and the total duration 5-14 days and 7 chemotherapy cycles. Combination with corticosteroids is suggested in several countries and information in relation to recommended doses of corticosteroids varies.

The MAH states that due to its high therapeutic index, daily doses up to 9 mg can be administered in the chemo- and radiotherapy-induced indications. In addition, dexamethasone has been administered in parallel, at doses of 8-20 mg once a day, either i.v. or p.o. Such association is considered classical practice for the CINV indication in the literature.

Paediatric population: There is insufficient clinical experience to recommend administration of granisetron tablets to children.

PONV

There is a lack of published data supporting the registration of Kytril film-coated tablets in the treatment of PONV. In response to the LoOI, the MAH performed a review of the available data, and has concluded that the use of granisetron orally in PONV should not be recommended.

CHMP conclusion

As there is insufficient data to support the intramuscular administration of granisetron, this route of administration was not considered to be acceptable by the CHMP.

Taking the CHMP discussion into account, the following wording was proposed by the MAH:

Tablets

'Posology

1 mg twice a day or 2 mg once a day for up to one week following radiotherapy or chemotherapy. The first dose of Kytril should be administered within 1 hour before the start of therapy. Dexamethasone has been used concomitantly at doses up to 20 mg once a day orally.

Paediatric population

The safety and efficacy of granisetron tablets in children have not yet been established.
No data are available.

Elderly and renal impairment

There are no special precautions required for its use in either elderly patients or those patients with renal or hepatic impairment.

Hepatic impairment

There is no evidence to date for an increased incidence of adverse events in patients with hepatic disorders. On the basis of its kinetics, whilst no dosage adjustment is necessary, granisetron should be used with a certain amount of caution in this patient group (see section 5.2).

Method of administration

The tablets should be swallowed whole with water.'

Solution for injection

Posology

Chemo- and radiotherapy-induced nausea and vomiting (CINV and RINV)

Prevention (acute and delayed nausea)

A dose of 1-3 mg (10-40 μg/kg) of Kytril solution for injection should be administered either as a slow intravenous injection or as a diluted intravenous infusion 5 minutes prior to the start of chemotherapy. The solution should be diluted to 5ml per mg.
Treatment (acute nausea)

A dose of 1-3 mg (10-40 μg/kg) of Kytril solution for injection should be administered either as a slow intravenous injection or as a diluted intravenous infusion and administered over 5 minutes. The solution should be diluted to 5ml per mg. Further maintenance doses of Kytril solution for injection may be administered at least 10 minutes apart. The maximum dose to be administered over 24 hours should not exceed 9 mg.

Combination with adrenocortical steroid

The efficacy of parenteral granisetron may be enhanced by an additional intravenous dose of an adrenocortical steroid e.g. by 8-20 mg dexamethasone administered before the start of the cytostatic therapy or by 250 mg methyl-prednisolone administered prior to the start and shortly after the end of the chemotherapy.

Paediatric population

The safety and efficacy of Kytril solution for injection in children aged 2 years and above has been well established for the prevention and treatment (control) of acute nausea and vomiting associated with chemotherapy and the prevention of delayed nausea and vomiting associated with chemotherapy. A dose of 10-40 μg/kg body weight (up to 3 mg) should be administered as an i.v. infusion, diluted in 10-30 ml infusion fluid and administered over 5 minutes prior to the start of chemotherapy. One

additional dose may be administered within a 24 hour-period if required. This additional dose should not be administered until at least 10 minutes after the initial infusion.

Post-operative nausea and vomiting (PONV)

A dose of 1 mg (10 μg/kg) of Kytril solution for injection should be administered by slow intravenous injection. The maximum dose of Kytril to be administered over 24 hours should not exceed 3 mg.

For the prevention of PONV, administration should be completed prior to induction of anaesthesia.

Paediatric population

Currently available data are described in section 5.1. but no recommendation on a posology can be made. There is insufficient clinical evidence to recommend administration of the solution for injection to children in prevention and treatment of Post-operative nausea and vomiting (PONV).

Special populations
Elderly and renal impairment

There are no special precautions required for its use in either elderly patients or those patients with renal or hepatic impairment.

Hepatic impairment

There is no evidence to date for an increased incidence of adverse events in patients with hepatic disorders. On the basis of its kinetics, whilst no dosage adjustment is necessary, granisetron should be used with a certain amount of caution in this patient group (see section 5.2).

Method of administration

Administration may be as either a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes.'

Section 4.3 - Contra-indications

Hypersensitivity reactions are included as contraindications in the SmPCs of 4 countries. The current European SmPC guideline (September 2009) recommends that the contraindications section of the SmPC should include "hypersensitivity to the active substance or to any of the excipients or residues from the manufacturing process, as well as any contraindication arising from the presence of certain excipients. The proposed text is based on the Roche Core Data Sheet (CDS) and includes hypersensitivity to the active substance or to any of the excipients.

The CHMP acknowledged that the adverse event profile for 5-HT3 receptor antagonists broadly overlap, and that hypersensitivity reactions for granisetron and overall for 5-HT3 receptor antagonists, have been reported very rarely.

The MAH has not included cross-sensitivity reactions as contraindications for granisetron in section 4.3, but instead included appropriate wording in the warnings and precautions section (section 4.4) of the proposed harmonised SmPC. This is consistent with the recommendations and wording of the SmPC guideline.

The SmPC for Italy contraindicates the use of granisetron in pregnancy and lactation. The Guideline on Summary of Product Characteristics states that pregnancy or breastfeeding should be mentioned in section 4.3 (contraindications) only if it is contraindicated. As there are no studies in pregnant women, it is not known whether granisetron is excreted in milk. It is therefore endorsed by the CHMP not to have pregnancy/lactation as a contraindication in section 4.3 but as information in section 4.6 (pregnancy and lactation).

CHMP conclusion

The MAH's proposed wording for this section of the SmPC has taken into account the SmPC guideline requirements.

The CHMP endorsed the MAH's proposal for the harmonised section 4.3:

'Hypersensitivity to the active substance or (to) any of the excipients.'

Section 4.4 - Special warnings and precautions for use

Sub-acute Intestinal Obstruction

All local SmPCs except Iceland include wording regarding Kytril's potential to lower bowel motility and all local SmPCs include wording regarding the need to monitor patients with signs of sub-acute intestinal obstruction following its administration. The Kytril CDS refers to its ability to reduce lower bowel motility in patients and warns of the need to monitor carefully any patients who receive it and show signs of sub-acute intestinal obstruction.

For other 5-HT3 antagonists such as ondansetron, caution is also advised when used in patients with signs of sub-acute intestinal obstruction or ileus (Martindale 2009). In common with ondansetron, the proposed wording in this section of the SmPC takes into account the effect of 5-HT3 antagonists in lowering bowel motility, and incorporates the CDS wording.

As it is well-known that 5-HT3 antagonists lower bowel motility, which is reflected in the literature, the CHMP endorsed the MAH's proposal that patients with signs of sub-acute intestinal obstruction should be monitored following administration of Kytril.

QT Prolongation

The CDS includes specific wording on QT prolongation. Some EU countries have already included the statement regarding QT prolongation in their local SmPC, while others are currently in the process of implementing this statement or will do so after completion of the Article 30 referral procedure. The same applies for the other affected SmPC sections (sections 4.5 and 4.8).

While some studies of high-dose intravenous granisetron (Carmichael et al. 2003[1], Carmichael et al. 2004[2]), found no significant adverse effects on pulse, blood pressure, or ECG measurements, ECG changes have been reported with granisetron by other researchers (Buyukavci et al. 2005[3], Pinarli et al. 2006[4]).

Buyukavci et al. evaluated the effects of ECG changes in children following administration of either granisetron or ondansetron. They concluded that intravenous granisetron causes clinically asymptomatic and transient changes on ECG measurements in children who received high-dose methotrexate therapy. Minor ECG changes were observed by Pinarli et al., however, the authors concluded that no serious ECG changes or dangerous rhythm disturbances were observed.

[1] Carmichael J and Harris AL. High-dose i.v. granisetronfor the prevention of chemotherapy-induced emesis:cardiac safety and tolerability. Anticancer Drugs 2003;14:739-744
[2] Carmichael J and Harris AL. The cardiovascular safety of high-dose intravenous granisetron in cancer patients receiving highly emetogenic chemotherapy. Cancer Chemother Pharmacol 2004;53:123-128
[3] Buyukavci M et al. The effects of ondansetron and granisetron on electrocardiography in children receiving chemotherapy for acute leukemia. Am J Clin Oncol 2005;28(2):201-204.
[4] Pinarli FG et al. Electrocardiographic findings after 5-HT3 receptor antagonists and chemotherapy in children with cancer. Pediatr Blood Cancer 2006;47:567-571.

A review (Navari et al. 2003[5]) of the electrocardiographic and cardiovascular effects of the 5-HT3 antagonists concluded that although this class of drugs may cause small, transient ECG changes, the clinical benefits of the drugs outweighed the small theoretical risk of any clinically significant cardiovascular events.

Overall, clinical data have demonstrated ECG interval changes - among these QT-prolongations, which are a class effect of the 5-HT3 receptor antagonists. These changes are seen in children as well.

Although no evidence of proarryhthmia has been noted following granisetron use, it is important that caution is exercised when prescribing it to any patients with pre-existing arrhythmias or cardiac conduction disorders, as there is a potential that these changes may lead to clinical consequences. Patients at greater risk include those with cardiac comorbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities.

Therefore the CHMP also endorsed the MAH's proposal that caution should be exercised in patients with cardiac co-morbidities or cardiotoxic chemotherapy and/or concomitant electrolyte abnormalities.

Cross-sensitivity with other 5-HT3 Antagonists

Currently only the SmPC for France and Belgium/Luxembourg includes specific wording regarding cross hypersensitivity for the injectable formulation of Kytril in section 4.4 of the SmPC. This wording reflects the need to ensure that prescribers and patients are aware of the theoretical risk of cross-sensitivity reactions with granisetron in patients who have previously reported hypersensitivity reactions to other 5-HT3 antagonists.

Cross-sensitivity between the two 5-HT3 antagonists tropisetron and ondansetron has been reported in the literature by Kataja et al. 1996 [6]. The report concerns two patients who experienced hypersensitivity reaction to one 5-HT3 antagonist and then developed a more severe reaction when exposed to another drug in the class. Close monitoring of these patients and cautionary use of other 5-HT3 antagonists has been recommended (Martindale, 2009, Meyler 2006).

However, a search of the literature did not reveal any reports of cross-sensitivity reactions associated with the use of granisetron specifically. Conversely there are reports of the successful use of granisetron in patients who were sensitive to ondansetron and vice-versa (Martindale 2009).

Based on the theoretical possibility of cross-sensitivity reactions with granisetron, the MAH has nevertheless proposed to include cautionary wording in the warnings and precautions section (section 4.4) of the EU harmonised SmPC.

Additional warnings and precautions in selected EU SmPCs that will not be included in Section 4.4 of the proposed SmPC

<u>Sodium content</u>

Currently the local SmPCs for Austria, Denmark, Germany, Iceland and Spain include an additional variable and conflicting warning regarding the sodium component of granisetron.

According to the CDS and local SmPCs, granisetron is intended for dilution with intravenous fluids including 0.9% sodium chloride B.P., 0.18% sodium, and sodium lactate, therefore the amount of sodium within the granisetron ampoule is relatively small compared with the sodium content in these solutions. Hence the inclusion of additional wording in this section of the SmPC is not considered to be warranted.

[5] Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine3 receptor antagonists. Ann Pharmacother 2003;37:1276-1286.
[6] Kataja V and de Bruijn KM. Hypersensitivity reactions associated with 5- hydroxytryptamine(3) –receptor antagonists: a class effect? Lancet 1996;347:584-85

Concerning sodium content and caution for patients undergoing low sodium diet, no published evidence to clarify the rationale for this warning has been found. Therefore the CHMP agreed not to include the warning.

Other glucocorticoids

One of the local SmPCs (Denmark) mentions the co-administration of dexamethasone within the warnings section of their SmPC, although this relates to a potential increase in efficacy rather than a safety concern per se.

Although there is published evidence which suggests that granisetron and dexamethasone in combination is more effective than granisetron alone for the prophylaxis of nausea and vomiting (Fujii et al. 2000[7]), the MAH agrees that this particular statement does not constitute a risk and that its inclusion in section 4.4 of the harmonised SmPC is not consistent with the SmPC guideline. The CHMP agreed with the MAH's proposal.

Rapid intravenous administration

Within section 4.4 of the SmPC for Greece and Cyprus, there is a statement regarding the possibility of adverse reactions following rapid intravenous administration. This event is not commonly reported for either ondansetron or granisetron. Therefore additional wording in section 4.4 regarding rapid intravenous administration was not considered to be warranted for inclusion in the harmonised SmPC.

Hepatocellular carcinoma warnings

The local German & Greek SmPCs include non-clinical carcinogenicity data that state that long- term administration (data from two-year carcinogenicity studies) show an increased incidence of hepatocellular carcinoma and/or adenoma in rats and mice of both sexes at 50 mg/kg body weight (rat dose reduced to 25 mg/kg body weight per day at week 59). An increased incidence of hepatocellular neoplasia was also detected in rats and mice at 5 mg/kg body weight. In both species no pharmaceutical effects (hepatocellular neoplasia) have been observed with low doses (1 mg/kg). In various in vitro and in vivo studies Kytril showed no genotoxic effects on mammalian cells.

Since the animal data was based on much higher doses and much longer (lifelong) treatment than indicated in clinical practice, it was not considered necessary by the MAH to include a special warning or precaution. Additionally, as this particular perceived risk does not lead to a precaution as such, inclusion of wording here would not be consistent with the SmPC guideline.

The CHMP agreed that the inclusion of animal results in section 4.4 is not consistent with the SmPC guideline and that implications that Kytril may cause cancer in humans are not well substantiated.

Children

Although the CDS states that there is insufficient information to recommend the use of Kytril in the prevention and treatment of PONV in children, according to the Roche clinical data, Integrated Safety Summary (ISS), the safety profile of granisetron in the pediatric population (based on post marketing data), did not differ from that of the adult population, and is consistent with the known safety profile of granisetron (ISS 2001, Section 7.5.4). Hence as per the SmPC guideline, no additional warnings or precautions are considered necessary.

Elderly patients and patients with hepatic and renal impairment

Wording of a similar nature is also included in several national SmPCs, making reference to no special precautions or dose adjustments to Kytril being required in ether the elderly, hepatically or renally

[7] Fujii Y, Saitoh, Y, Tanaka, H, et al. 2000. In: Aronson JK (editor). Meyler's side effects of drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions 2006 Elsevier B.V

impaired patients e.g. Belgium, Bulgaria, Czech Republic, Greece, Ireland, Italy, Lithuania, Portugal, Slovenia, UK.

However a number of national SmPCs (eg. Denmark, Iceland, Netherlands, Sweden), do stipulate the need for caution when granisetron is used in patients with hepatic impairment. In addition, caution when using granisetron in this particular group of patients is also mentioned in section 4.4 of some of the SmPCs for granisetron containing generics according to the comments made by some EU member states in the Final Assessment Report for Kytril PSUR work sharing procedure.

Open label, comparative studies of efficacy, safety and pharmacokinetics have been made in patients with hepatic impairment as a result of hepatic metastasis (compared to cancer patients with normal hepatic function). Overall around 50% reduction was seen in total clearance in hepatically impaired patients compared to cancer patients with normal hepatic function. Although hepatically impaired patients had higher mean AUC values, they were in the ranges similar to those observed in healthy volunteers who had received higher doses of granisetron in other studies. Although there are no data suggesting higher incidence of adverse effects in this population, there are significant pharmacokinetic differences that should induce appropriate degree of awareness. Considering that the primary route of elimination of granisetron is hepatic, the CHMP was of the view that Kytril should be used with a certain amount of caution in hepatically impaired patients and is mentioned as such in section 4.2 of the SmPC.

The current wording within the CDS stipulates that no dosage adjustment is necessary in renally impaired patients. According to the CDS, data indicate that pharmacokinetic parameters after a single intravenous dose in patients with severe renal failure are generally similar to those in normal subjects. The CDS also states that in patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement and that despite these changes, no dosage adjustment is necessary.

The CDS also does not advise any particular warning for elderly patients.

CHMP conclusion

It was agreed that additional information advising caution when used in hepatically impaired patients would be included in section 4.2 instead of section 4.4 of the SmPC.

Taking into account the CHMP recommendation, the following wording proposed by the MAH was agreed:

'As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following its administration.

As for other 5-HT_3 antagonists, ECG changes including QT interval prolongation have been reported with granisetron. In patients with pre-existing arrhythmias or cardiac conduction disorders this might lead to clinical consequences. Therefore caution should be exercised in patients with cardiac co-morbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities (see section 4.5).

Cross-sensitivity between 5-HT_3 antagonists (e.g. dolasteron, ondansetron) has been reported.'

Additionally for the tablets, the following text was also included:

'Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

There is insufficient clinical evidence to recommend administration of these tablets to children.'

Section 4.5- Interaction with other medicinal products and other forms of interaction

The wording in the majority of the SmPCs refers to the safe administration of granisetron with either anti-ulcer medication (with some SmPCs specifically referring to cimetidine), benzodiazepines, neuroleptic agents or anaesthetic agents.

No drug interactions were noted in patients receiving emetogenic cancer chemotherapy.

A number of the SmPCs also referred to the data on hepatic enzyme induction with phenobarbitol.

Several SmPC include extensive lists of drugs suspected of interfering with cytochrome P 450. Their role is considered hypothetical and it is not clear whether they are likely to increase or decrease the action of granisetron.

Reports of ECG changes in patients receiving 5-HT3 antagonists, including reports of QT prolongation that have led to clinical consequences, have already been discussed in the supporting evidence for SmPC wording in section 4.4. There is a need to apply caution when giving medication, which is known to prolong the QT interval, concurrently with 5-HT3 antagonists such as granisetron. The wording concerning QT prolongation and 5-HT3 antagonists has been reviewed as part of the Article 46 procedure, and has been approved as wording which accurately reflects the position regarding QTc prolongation.

The potential interaction between phenobarbitol and granisetron is referenced in review articles and published medical textbooks (Lang, Martindale 2009). There is evidence that hepatic enzyme induction with phenobarbital in human volunteers resulted in an increase in total plasma clearance of approximately 25 % of intravenous granisetron. Therefore it was agreed that this interaction remains in section 4.5.

There are in vitro studies that confirm the involvement of cytochrome P450 3A in the ring oxidation of Kytril. However, given the absence of a clinical consequence, the MAH proposes that this is not mentioned in this section but rather in section 5.2. Similarly studies have demonstrated that the activity of isoenzymes such as CYP3A4 are not modified by granisetron (Bloomer 1994[8], Gregory 1998[9]]).

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. In patients concurrently treated with medicinal products known to prolong QT interval and/or which are arrhythmogenic, this may lead to clinical consequences (see section 4.4).

In studies in healthy subjects, no evidence of any interaction has been indicated between granisetron and benzodiazepines (lorazepam), neuroleptics (haloperidol) or anti-ulcer medicinal products (cimetidine). Additionally, granisetron has not shown any apparent medicinal product interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients.'

Section 4.6 - Pregnancy and lactation

There are no studies in pregnant women and it is not known whether granisetron is excreted in human milk. The local SmPC for Italy is the only one to include a contraindication for pregnancy (see section 4.3).

[8] Bloomer JC, Baldwin SJ, Smith GJ et al. Characterisation of the cytochrome P450 enzymes involved in the in vitro metabolism of granisetron. Br J Clin.1994;38:557-566

[9] Gregory RE and Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55:173-189S

Data on the use of granisetron during pregnancy is very limited: there have been a small number of post-marketing case reports of patients becoming pregnant whilst receiving granisetron. The most recent PSUR, dated February 2010, confirmed that the cumulative total number of case reports received and entered on the Drug Safety database up to and including 19th December 2009 was 14 medically confirmed, and 3 non-medically confirmed case reports. In 6 of these case reports, the pregnancies were ongoing at the time of the report and a further 5 reports were lost to follow-up. Of the remaining 6 reports, the outcome was unknown in three case reports; two confirmed a healthy normal delivery and one concerned a therapeutic abortion. Based on the presented data the CHMP agreed that the use of granisetron should preferably be avoided during pregnancy.

CHMP conclusion

Taking into account the information provided, the following wording proposed by the MAH was agreed by the CHMP:

'Pregnancy
There is limited amount of data from the use of granisetron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of granisetron during pregnancy.

Breastfeeding
It is unknown whether granisetron or its metabolites are excreted in human milk. As a precautionary measure, breast-feeding should not be advised during treatment with Kytril.

Fertility
In rats, granisetron had no harmful effects on reproductive performance or fertility.'

Section 4.7 - Effects on ability to drive and use machines

According to the Roche clinical data, Integrated Safety Summary (ISS), a review of the safety profile of granisetron from clinical trials found no difference in frequency between placebo and granisetron treatment groups for the events of dizziness, vertigo and somnolence (ISS 2001). Investigation in healthy subjects showed no clinically relevant effect on resting EEG or on the performance of psychometric test of doses up to 200µ/kg.

Additionally, a review of the literature found no evidence that either granisetron or other 5-HT3 antagonists, such as ondansetron, affects driving or use of machinery (Meyler's 2006, Martindale 2009). The UK SmPCs for ondansetron are consistent with this.

The proposed SmPC text reflects the recommendations regarding section 4.7 in the European SmPC guideline.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'Kytril has no or negligible influence on the ability to drive and use machines.'

Section 4.8 - Undesirable effects

All adverse drug reactions (ADRs) listed in the company reference safety information, the Core Data Sheet (CDS) have been included. Additional ADRs listed in local SmPCs have been included if appropriate references could be identified. Where events have been reported in the clinical trials, the frequency category has been defined by calculating the total frequency in the granisetron arms (if there was more than one granisetron arm) of the specific study and comparing it to the frequency in the placebo arm. Events that were reported at an overall frequency of greater than or equal to 2% compared to the placebo arm were defined as adverse drug reactions. If the frequency differed between studies, the study with the highest reported frequency was used to determine frequency category.

The MedDRA System Organ Class (SOC) and preferred terms (PTs) were used appropriately.

In the development programme four double-blind randomised placebo controlled clinical studies were conducted (Studies 276, 278, 285 and 503). A pooled analysis for studies 276 and 278 was performed. The safety population for these four studies is described below:

• The pooled analysis of studies 276 and 278 involved 266 patients in the placebo arm, and a total of 780 in the combined granisetron arms (0. 1 mg, 1.0 mg and 3.0 mg respectively).

• For study 285, 162 patients received placebo and 163 received granisetron 0.1 mg after the onset of moderate or severe nausea/vomiting within 4 hours post surgery.

• Study 503 included 117 patients in the placebo arm and a total of 224 patients in the combined granisetron arms (1 mg and 3 mg) who received treatment immediately before reversal of anaesthesia.

In reviewing the adverse reactions presented in the different country SmPCs, information in standard textbooks such as Meyler's Side Effects of Drugs and Martindale were taken into consideration when determining the inclusion of ADRs in the proposed SmPC. The adverse event profile of another 5-HT3 antagonist, ondansetron that is considered to be similar to that of granisetron was also taken into consideration (Martindale 2009). The SmPCs from the following Member States attributed to the frequencies: Austria, Belgium/Luxembourg, Denmark, France, Germany, Iceland, Ireland, Italy, Netherlands, Sweden and Slovenia.

Immune system disorders

The term hypersensitivity e.g. anaphylaxis included in the proposed SmPC is included in the majority of SmPCs and is supported by referenced texts and the CDS. The Italian SmPC is the only one to include the event of 'urticaria'.

Case reports of hypersensitivity reactions have been received for 5-HT3 antagonists such as ondansetron; this includes reports of immediate hypersensitivity reactions, including anaphylaxis (Martindale 2009). Case reports of hypersensitivity have also been received for granisetron and are presented in the most recent PSUR, dated February 2010.

A literature search found one recent case report of urticaria associated with granisetron use, by Bursztejn et al. 2008[10], where the allergy to granisetron was confirmed with skin prick tests. While the event of hypersensitivity was not reported in the Roche clinical data within the Integrated Safety Summary, isolated events of urticaria were reported though not at a frequency consistent with an ADR. Based on the above it is proposed to apply the rule of three (as described in the SmPC guideline) to the events of 'hypersensitivity' and 'urticaria' and to include both as ADRs in the SmPC occurring at an uncommon frequency i.e 3/1167 where 1167 is the number of patients who received granisetron in the Roche clinical trials presented in the Integrated Safety Summary.

Metabolism and nutrition disorders

The Belgium and Spain SmPCs report anorexia as rarely being associated with Kytril. The term anorexia, is also reported in the SmPC for Denmark.

Anorexia is not described as an adverse event associated with 5-HT3 antagonists in reference textbooks (Meyler 2006) or Martindale 2009). A literature search for case reports of anorexia and decreased appetite was conducted and did not retrieve any cases.

[10] Bursztejn AC, Tréchot Ph, Cuny JF, Schmutz JL, Barbaud A. Cutaneous adverse drug reactions duringchemotherapy: consider non-antineoplastic drugs. ContactDermatitis 2008;58:365-368

While the event 'anorexia' has been reported in the Roche clinical data, within the Integrated Safety Summary, it does not meet the pre-defined criteria for an adverse drug reaction. Hence, it is considered that there is insufficient evidence to include the 'anorexia' as an ADR in the proposed SmPC. The CHMP agreed that there is insufficient evidence to include anorexia an adverse drug reaction.

Psychiatric disorders

The event terms of agitation, anxiety, sleeplessness/insomnia, drowsiness/somnolence are included as listed terms in some of the local SmPCs (Belgium and Hungary).

According to Roche clinical data, Integrated Safety Summary, it was reported in one study (study 285), that insomnia was reported at a frequency of 3.7% in the granisetron arm, compared to 1.2% in the placebo arm. In the pooled analysis for studies 276 and 278, insomnia was reported at 6.0% compared to a total of 5.3% in the 3 granisetron arms.

Based on a review of the available evidence the MAH argues that no data supporting a causal association between granisetron and agitation, anxiety, drowsiness/somnolence, hence these terms have been excluded from the proposed SmPC. However, according to the Roche clinical data, the term 'insomnia' did occur at a frequency of greater than 2% in the granisetron arms compared to the placebo control arm in study 285, it is proposed to include the event of 'insomnia' in the SmPC, as an ADR with the frequency of common.

The CHMP agreed that insomnia should be included in the SmPC as an adverse event, since it occurs with a frequency greater than 2 % compared with placebo, in the clinical study 285. However as there is no clear evidence of the adverse events agitation, anxiety and/or drowsiness/ somnolence in patients treated with Kytril, the CHMP concur that these terms could be excluded from the SmPC.

Nervous system disorders

Headache

The term 'headache' is included in all local SmPCs and is supported by referenced texts and the CDS. According to standard reference textbooks such as Martindale 2009 and Meyler 2006, ondansetron and other 5-HT3 antagonists may cause headache. A review of the literature supports this; Gregory 1998[11], Leslie 2006[12]and Tramer 1998[13] have reported headaches occur commonly in association with granisetron use. Indeed according to Gregory, headache is the only adverse event that occurred more frequently in patients receiving 5-HT3 antagonists than in those receiving a comparator.

According to Roche clinical data within the Integrated Safety Summary, in the pooled analysis for study 276 and 278, headache was reported with a combined frequency of 9.4% compared to 7.1% in the granisetron and placebo arms respectively. In study 285 headache was reported at a frequency of 14.8% compared to 11.7% in the granisetron and placebo arms respectively. However, in study 503 headache was reported in 13.7% of patients in the placebo arm and only 4.0% of patients in the granisetron arms. Based on the overall evidence, 'headache' is included as an ADR with an assigned frequency of very common. This was endorsed by the CHMP as headache is clearly described in the clinical studies and the literature as a very common adverse event.

[11] Gregory RE and Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55:173-189S
[12] Leslie JB and Gan TJ. Meta-analysis of the safety of 5-HT3 antagonists with dexamethasone or droperidol for prevention of PONV. Ann Pharmacother 2006;40:856-72
[13] Tramèr MR et al. Effcacy of 5-HT3 receptor antagonists in radiotherapy-induced nausea and vomiting: A Quantitative Systematic Review. Eur J Cancer 1998;34(12):1836-1844

Extrapyramidal reactions

The SmPCs for the countries of Belgium/Luxembourg, Denmark and Spain list extrapyramidal symptoms as an undesirable effect. Additionally, the SmPC for the UK states 'Dystonias and dyskinesias have been reported with medicines in the 5-HT3 antagonist class. Such events have been reported rarely with Kytril.'

Extrapyramidal events are not included within the CDS for Kytril. According to standard reference textbooks Martindale 2009 and Meyler 2006, extrapyramidal reactions have been reported in association with the use of ondansetron for post operative nausea and vomiting. However they do not report extrapyramidal reactions in association with granisetron. Extrapyramidal reactions were not reported by Gregory 1998[14] in his review of 5-HT3 antagonists.

A search of the published literature did not reveal any reports of extrapyramidal reactions specifically associated with the use of granisetron. In addition, a further search on the compound class of 5-HT3 anatagonists and extrapyramidal reactions provided published evidence in support of 5-HT3 antagonists being devoid of extrapyramidal side effects (Locatelli 1993[15]).

Extrapyramidal reactions, dystonias and dyskinesias did not occur as ADRs according to Roche clinical data within the Integrated Safety Summary. However the work-sharing PSUR covering period 19 Feb 2006 – 19 Dec 2008 (SK/H/PSUR/0004/001) referred to a case report of an extrapyramidal reaction following administration of granisetron. PSUR 1028611 also details an episode of dystonia following granisetron. In response to the LoOI the MAH discussed their own safety data as well as data in published trials and well known databases, and it was agreed that extrapyramidal reactions would be included as an adverse event in section 4.8 of the SmPC. Considering the lack of data for dystonia, the CHMP agreed with MAH not to include this undesirable effect in the proposed SmPC at this point in time.

Other events:

Dizziness, anxiety and coma

Dizziness is listed as an undesirable effect in a few SmPCs, although this event is not listed in the CDS. Both Meyler 2006 and Martindale 2009 list dizziness as an adverse event that occurs in association with ondansetron, and the other 5-HT3 antagonists, but did not specify any cases of dizziness associated with granisetron per se.

A search of the literature found no evidence of dizziness as an ADR associated with granisetron. Indeed there were no significant differences among treatment groups in studies where 'dizziness' was reported as an event (Gregory 1998).

According to Roche clinical data within the Integrated Safety Summary, dizziness while reported as an event, did not meet the criteria for ADRs. It was also noted that dizziness is reported as an adverse event in the clinical study 276 and 278. However the difference in frequency between the two treatment groups was less than 2 % for dizziness, in the pooled studies 276 and 278. Furthermore as there is no other clear evidence of dizziness in the literature, the CHMP therefore concurred that there is no need to include "dizziness" in section 4.8.

Some SmPCs include other events such as 'anxiety', 'syncope' and 'coma' . The events of anxiety, coma and syncope have not been reported as ADRs in standard reference textbooks of Martindale and

[14] Gregory RE and Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55:173-189S

[15] Locatelli MC, D'Antona A, Luporini G. Cisplatinum based chemotherapy: role of the antiserotoninergic ondansetron in prevention of emesis. J Chemother. 1993;5(3):197-206

Meyler. A search of the literature found no supporting evidence for these events of either 'anxiety', ' syncope' or'coma' as ADRs. Additionally, according to Roche clinical data within the Integrated Safety Summary, these events did not meet the criteria for ADRs. Based on the above review it is proposed to exclude the event terms 'anxiety', 'syncope' 'coma' and 'dizziness' from the list of ADRs in the proposed SmPC.

Cardiac disorders

There were only a few local SmPCs e.g. Belgium, Germany and Denmark that made reference to the event of 'arrhythmias' or more specifically QT prolongation. Only the SmPC for Italy lists additional arrhythmias such as: sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopia including unsustained tachycardia, ECG abnormalities.

The SmPC wording regarding QT prolongation has been mandated through the Article 46 procedure as follows "As for other 5-HT3 antagonists, ECG changes including QT prolongation have been reported with Kytril. (See sections 4.4 and 4.5). "The exact wording proposed for the SmPC is slightly different from that contained within the current CDS. The CHMP endorsed the MAH's proposal to place QT-prolongations as a description of selected adverse events, because the ECG modifications including the QT-prolongation seen were minor and generally not of clinical significance. However they may potentially become significant in increased risk subpopulations such as patients with cardiac co-morbidities, patients receiving cardiotoxic chemotherapy or patients having concomitant electrolyte abnormalities as described in section 4.4.

With respect to other arrhythmias, Martindale 2009 states that studies of high-dose intravenous granisetron were found to have no significant adverse effects on pulse, blood pressure, or ECG measurements (Carmichael 2003 [16], and Carmichael 2004 [17]). Carmichael 2003 also states that granisetron administered at four times the upper recommended dose demonstrated good efficacy and tolerability, with no clinically important cardiac effects.

A search of the literature did not retrieve any published case studies for granisetron and cardiac arrhythmias.

Whilst arrhythmias were reported during the clinical trial programme, they did not occur at a greater than 2% frequency in the granisetron arms compared to placebo. Specifically in the pooled analysis of studies 276 and 278, heart and rhythm disorders occurred in a total of 6.5% of patients who received placebo compared to 6.2% of patients who received granisetron. Specific rhythm disturbances that were reported were 'bradycardia' 'palpitation', tachycardia' and 'extrasystoles. In study 285 arrhythmias were not reported in either study arm. In study 503 arrhythmias occurred in 1.7% of patients who received placebo compared to a total of 2.2% of patients who received granisetron.

Specific arrhythmias reported were 'bradycardia', 'palpitation' and 'extrasystoles'. It is worth noting that arrhythmias associated with chemotherapy have been documented in the literature (Guglin 2009).

Taking into consideration the evidence presented above, the event of arrhythmia has been excluded as an ADR in the proposed SmPC.

The SmPC for Hungary alone lists chest pain as an undesirable effect. It is not included in the CDS. Chest pain has not been reported as ADRs in standard reference textbooks such as Martindale and

[16] Carmichael J and Harris AL. High-dose i.v. granisetronfor the prevention of chemotherapy-induced emesis:cardiac safety and tolerability. Anticancer Drugs 2003;14:739-744

[17] Carmichael J and Harris AL. The cardiovascular safety of high-dose intravenous granisetron in cancer patients receiving highly emetogenic chemotherapy. Cancer Chemother Pharmacol 2004;53:123-128

Meyler. A search of the literature found no supporting evidence for the event of 'chest pain' as an ADR. Additionally, according to the Roche clinical data within the Integrated Safety Summary, whilst the event of 'chest pain' was reported, it did not meet the criteria for an ADR. Therefore the event 'chest pain' has been excluded as an ADR in the proposed SmPC. The CHMP supported the exclusion of 'chest pain' as an ADR as there is currently insufficient evidence to support this adverse event was found.

Vascular disorders

Hypotension/drop in blood pressure has been reported as an adverse event for Kytril in some SmPCs e.g. Belgium/Luxembourg, France and Italy. Hypertension has been reported as an undesirable event in the Italian SmPC only.

Neither 'hypotension' nor 'hypertension' are listed in the CDS for Kytril.

Neither the event of 'hypotension' nor the event of 'hypertension' is listed in standard reference textbooks such as Martindale or Meyler as adverse events associated with granisetron. Indeed according to Martindale (2009), studies of high-dose intravenous granisetron found no significant adverse effects on pulse, blood pressure or ECG measurements.

A search of the literature did not reveal any case reports of either hypotension/decreased blood pressure or hypertension/raised blood pressure associated with granisetron use.

According to Roche clinical data within the Integrated Safety Summary, the events of 'hypotension' and 'hypertension' did not meet the criteria for ADRs.

On the basis of the above, it is proposed to exclude the events of 'hypotension' and 'hypertension' as ADRs in the proposed SmPC. The CHMP concurred with the MAH to exclude hypotension and hypertension as adverse drug reactions in the proposed SmPC as there are no convincing data supporting hypertension and hypotension as ADRs.

Gastrointestinal disorders

Constipation, ileus

The term 'constipation' or 'obstipation' is included in all local SmPCs. Additional wording is provided in the local French SmPC: 'constipation rarely complicated with ileus or intestinal obstruction in particular for patients with risk factors associated (Loir bowel motility, history of digestive operation). The local Dutch SmPC also mentions 'ileus'.

The event of constipation is listed in the CDS and is supported by referenced texts such as Martindale and Meyler. Constipation is consistent with the known effect of granisetron on gut motility.

A search of the literature found several supporting references for the event of constipation e.g. (Tramer 1998 [18], Gregory 1998 [19]), but none for the event of 'ileus'.

According to Roche clinical data within the Integrated Safety Summary, in the pooled analysis of studies 276 and 278, constipation was reported in 12% of patients in the placebo arm compared to a total of 13.2% of patients on the granisetron arms. In study 285, 'constipation' was reported in 2.5% of the placebo arm compared to 11.7% of patients in the granisetron arm. In study 503, constipation was reported in 0% of patients in the placebo arm compared to 0.4% of patients in the granisetron arm. Ileus was reported as an event but did not meet the predefined criteria for an ADR.

[18] Tramèr MR et al. Efficacy of 5-HT3 receptor antagonists in radiotherapy-induced nausea and vomiting: A Quantitative Systematic Review. Eur J Cancer 1998;34(12):1836-1844

[19] Gregory RE and Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55:173-189S

On the basis of the above it is proposed to include the event of 'constipation' as an ADR associated with granisetron use.

Based on the information provided by the MAH the CHMP agreed to maintain "constipation" and to exclude 'ileus'.

Diarrhoea

Diarrhoea is listed as an adverse event in a number of local SmPCs including Austria, Belgium/Luxembourg, Denmark, Spain, Iceland, Italy and Sweden, but not in the CDS. Neither Meylers, nor Martindale list diarrhoea as an adverse drug reaction.

A search of the literature found no supporting references for the event of diarrhoea, associated with granisetron, although there were some reports of diarrhoea associated with other 5-HT3 antagonists.

However 'diarrhoea' is mentioned as a frequently reported adverse event in the pooled studies 276 and 278 and in the integrated summary of safety, with frequencies of 1.1 % in the placebo group and 3.4 % in the Kytril group. Therefore following the recommendation of the CHMP, the MAH agreed to include diarrhoea as an adverse event.

Dysgeusia

The reported adverse event of taste disturbance (dysgeusia) is only included in the SmPC for Italy. No additional case reports of dysgeusia associated with granisetron are presented in the standard medical textbooks, such as Martindale and Meyler.

Additionally, a literature search found no other reports of dysgeusia associated with granisetron and this term has therefore been excluded.

As no evidence has been found to support dysgeusia as an adverse event, the CHMP endorsed the MAH's proposal to exclude it.

Nausea, vomiting and abdominal pain

Events of nausea, vomiting and abdominal pain have been reported for granisetron in several local SmPCs, although none of these events are listed in the CDS.

Similarly, none of these events are listed as ADRs in standard reference textbooks such as Meyler, Martindale. Gregory 1998 [20] makes the point that where abdominal pain has been reported as an event it was not reported at a significant difference from comparators.

According to Roche clinical data within the Integrated Safety Summary, the events of nausea, vomiting and abdominal pain did not occur with a greater difference of more than 2% frequency in the granisetron arms compared to the placebo arm in the clinical studies. Arguably nausea and vomiting may represent a lack of efficacy rather than an adverse drug reaction.

Based on the reviewed evidence, it is proposed to exclude the events of nausea, vomiting and abdominal pain as ADRs in the proposed SmPC.

The CHMP noted that nausea, vomiting and abdominal pain did not occur with greater difference of more than 2 % compared to placebo. Furthermore it was also noted that it may very well represent lack of efficacy rather than an ADR. Based on this the CHMP endorse the exclusion of "nausea, vomiting and abdominal pain" from the proposed SmPC.

Skin and subcutaneous tissue disorders

[20] Gregory RE and Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55:173-189S

Reports of skin rashes are included in most of the local SmPCs, additionally in one SmPC benign skin reactions are also listed while in another the event 'itching' is listed.

In the CDS rash is reported as a manifestation of hypersensitivity reactions.

The events of 'rash', 'itching' and 'benign skin reactions' are not reported in standard reference textbooks such as Meyler or Martindale as adverse drug reactions. Nor are these events mentioned by reviewers such as Gregory 1998[21], Tramer 1998 [22] as ADRs.

However a literature search found a randomized controlled study conducted by Sigsgaard et al. 1999 [23] in breast cancer patients undergoing chemotherapy, where rash was reported significantly more frequently in the granisetron arm (11.6%) than in the control chemotherapy arm (3.6%). However the frequency of rash reported in this study is confounded by the patients' concomitant chemotherapy regimen which varied between cyclophosphamide, methotrexate and fluorouracil, and cyclophosphamide, epirubicin and fluorouracil.

According to Roche clinical data within the Integrated Safety Summary there was no difference in reported frequency of events such as 'rash', 'pruritus', 'rash erythematous' between granisetron and the placebo arms in the clinical trials.

On balance as the reports of rash seen by Sigsgaard et al. 1999 are confounded by concomitant chemotherapy, and in the clinical trials reported in the Roche Safety Summary, the events of 'rash', ' pruritus' and 'rash erythematous' did not meet the predefined criteria for an ADR, it was proposed therefore to include 'rash' as an ADR and to allocate the frequency for its occurrence using the rule of three. On this basis it is proposed to include rash as an ADR with an uncommon frequency. The CHMP agreed that based solely on the hypersensitivity reaction, rash should be listed as such.

General disorders and administration site conditions

A number of general terms such as fever, fatigue and weakness/asthenia/tiredness, flulike symptoms, oedema and pain have been listed in some SmPCs, although these are not included in the CDS.

None of these events described are listed as ADRs for 5-HT3 antagonists in standard reference textbooks such as Meyler or Martindale. Additionally a search of the literature did not find any convincing references to support the existence of these events as ADRs.

According to Roche clinical data within the Integrated Safety Summary, whilst these events were reported as events in the clinical trials, none of them occurred with a greater difference of more than 2% frequency in the granisetron arms compared to the placebo arm in the clinical studies.

It was therefore proposed by the MAH to exclude the events of fever, fatigue and weakness/asthenia/ tiredness, flu-like symptoms, oedema and pain as ADRs in the proposed SmPC. The CHMP concurred with the MAH's proposal, as the frequency reported in clinical trials did not occur with a greater difference of more than 2% in the granisetron arm compared to the placebo arm, and no further evidence was available to support these ADRs.

Investigations

[21] Gregory RE and Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55:173-189S

[22] Tramèr MR et al. Effcacy of 5-HT3 receptor antagonists in radiotherapy-induced nausea and vomiting: A Quantitative Systematic Review. Eur J Cancer 1998;34(12):1836-1844

[23] T Sigsgaard, J Herrstedt, L J Andersen, H Havsteen, S W Langer, A-G Kjærbøl, H Lund, M Kjær, P Dombernowsky. Granisetron compared with prednisolone plus metopimazine as anti-emetic prophylaxis during multiple cycles of moderately emetogenic chemotherapy. BMJ 1999; 80 (3/4), p 412-418

Several local SmPCs list elevated liver transaminases as an adverse event. According to the CDS, elevations in hepatic transaminases have been observed and at similar frequency in patients receiving comparator therapy.

Standard reference textbooks such as Meyler and Martindale mention disturbances in liver enzyme in patients who received ondansetron, but provide no evidence of this event for granisetron specifically.

A search of the literature found no references to elevated liver transaminases specific to granisetron. In clinical trials there was no difference in frequency in elevated hepatic transaminases between the granisetron and placebo arms. Furthermore, according to one author, although elevations in hepatic transaminases have been seen in patients receiving 5-HT3 antagonists, similar elevations were not seen in human volunteers, which suggest that the chemotherapy was responsible for the elevations rather than the 5-HT3 antagonists (Gregory 1998[24]).

As elevations in hepatic transaminases have been observed in the CDS, the MAH agreed with the CHMP's view to include it in section 4.8 for both tablets and solution for injection.

Description of Selected Adverse Events

The potential of granisetron to reduce bowel motility and the implications for those patients with sub-acute intestinal obstruction has been included as a warning and is presented in section 4.4 of the SmPC.

ECG changes including QT prolongation, diarrhoea, extrapyramidal reactions and elevations in hepatic transaminases have been included in this section.

CHMP conclusion

Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

'Summary of the safety profile

The most frequently reported adverse reactions for Kytril are headache and constipation, which may be transient. ECG changes including QT prolongation have been reported with Kytril (see sections 4.4 and 4.5).

Tabulated list of adverse reactions

The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with Kytril and other 5-HT$_3$ antagonists.

Frequency categories are as follows:
Very common: ≥1/10;
Common ≥1/100 to <1/10;
Uncommon ≥1/1,000 to <1/100
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

Immune system disorders	
Uncommon	*Hypersensitivity reactions e.g. anaphylaxis, urticaria*
Psychiatric disorders	

[24] Gregory RE and Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55:173-189S

Common	*Insomnia*
Nervous system disorders	
Very common	*Headache*
Uncommon	*Extrapyramidal Reactions*
Cardiac disorders	
Uncommon	*QT prolongation*
Gastrointestinal disorders	
Very common	*Constipation*
Common	*Diarrhoea*
Hepatobiliary disorders	
Common	*Elevated hepatic transaminases**
Skin and subcutaneous tissue disorders	
Uncommon	*Rash*

**Occurred at a at similar frequency in patients receiving comparator therapy*

Description of selected adverse reactions

As for other 5-HT_3 antagonists, ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).'

Section 4.9 – Overdose

Although the SmPC for Denmark SmPC includes symptoms in addition to headache, and the SmPC for Sweden lists 'conceivable' symptoms, no other evidence is provided in support of the symptoms. Standard medical textbooks such as Meyler's and Martindale make no reference to symptoms in overdose. Furthermore, a search of the literature found no references to cases of granisetron overdose.

The proposed wording is based on the cumulative experience regarding overdose in the post marketing arena, and takes into consideration the varying differences in overdose for individual patients and their different circumstances. It is proposed not to include these hypothetical symptoms listed in a minority of SmPCs, but to remain consistent with wording provided in the CDS.

The CHMP endorsed the MAH's proposal not to mention conceivable symptoms in this section and as no other evidence has been provided, and the proposed wording is therefore considered to be acceptable.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

'There is no specific antidote for Kytril. In the case of overdose with the tablets/injection, symptomatic treatment should be given. Doses of up to 38.5 mg of Kytril as a single injection have been reported, with symptoms of mild headache but no other reported sequelae.'

5. PHARMACOLOGICAL PROPERTIES

Section 5.1 - Pharmacodynamic properties

Although there are some differences in wording, there are no significant discrepancies in this section.

– Reference to the i.v. route for the prevention and treatment of chemotherapy- and or radiotherapy-related nausea and vomiting (Czech Republic, Greece, Ireland, Malta, Netherlands, Portugal, Romania, Slovakia, Slovenia, UK).

– Extensive discussion of serotonin, β-adrenergic, dopaminergic, histaminergic and opioid receptors in the Italian SmPC, to point out that these are not affected by granisetron.

The pathophysiology of nausea and vomiting in relation to serotonin being released by mucosal enterochromaffin cells in the small intestine is well established. The role of 5-HT3 receptors and their specific antagonisation by granisetron has been extensively studied and reported.

Granisetron is a potent and highly selective 5-HT3-receptor antagonist that has little or no affinity for other receptors, a characteristic that is thought to underlie the favorable side effect and safety profiles of this agent. Extensive clinical trial data have shown granisetron to be an effective and well-tolerated agent for the treatment of nausea and vomiting in the oncology and surgical settings (Pellier 1992[25], Plosker 1991[26], Cunningham 1997[27], Jordan 2007[28]).

Granisetron has also been shown to be effective and well tolerated in special populations, such as patients refractory to antiemetic treatment, patients with hepatic or renal impairment, and children. Data also suggest that its safety profile and minimal potential for drug-drug interactions would make it an antiemetic agent of choice for elderly cancer patients (Aapro 2004[29]).

Paediatric population

The clinical data have not been considered substantial enough to support the use of granisetron for RINV or PONV in paediatric patients. The CHMP agreed that the reference to clinical study of granistron for PONV in children by Candiotti et al should be removed from section 5.1 as this would only encourage off-label use.

CHMP conclusion

The CHMP agreed with the following wording proposed by the MAH:

[25] Pellier P. A double blind dose-ranging study comparing the efficacy and safety of two oral doses of granisetron solution 20 µg/kg b.d. and 40 µg/kg b.d. for prophylaxis of cytotoxic-induced emesis in paediatric patients with malignant disease. Beecham Study 028, 1992
[26] Plosker G L, Goa K L. Granisetron. A review of its pharmacological properties and therapeutic use as anantiemetic. Drugs 1991;42(5):805-824
[27] Cunningham R S. 5-HT3-receptor antagonists: A review of pharmacology and clinical efficacy. Oncol Nurs Forum 1997;24 (7 Suppl):33-40
[28] Jordan K, Schmoll HJ, Aapro MS. Comparative activity ofantiemetic drugs. Crit Rev Oncol Hemat 2007;61:162-175
[29] Aapro M. Granisetron: An update on its clinical use in the management of nausea and vomiting. Oncologist 2004;9(6):673-686

'Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists.
ATC code: A04AA02.

Neurological mechanisms, serotonin-mediated nausea and vomiting

Serotonin is the main neurotransmitter responsible for emesis after chemo- or radio-therapy. The 5-HT_3 receptors are located in three sites: vagal nerve terminals in the gastrointestinal tract and chemoreceptor trigger zones located in the area postrema and the nucleus tractus solidarius of the vomiting center in the brainstem. The chemoreceptor trigger zones are located at the caudal end of the fourth ventricle (area postrema). This structure lacks an effective blood-brain barrier, and will detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The vomiting centre is located in the brainstem medullary structures. It receives major inputs from the chemoreceptor trigger zones, and a vagal and sympathetic input from the gut.

Following exposure to radiation or catotoxic substances, serotonin (5-HT) is released from enterochromaffine cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-HT_3 receptors are located. The released serotonin activates vagal neurons via the 5-HT_3 receptors which lead ultimately to a severe emetic response mediated via the chemoreceptor trigger zone within the area postrema.

Mechanism of action

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT_3) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D_2 binding sites.

Chemotherapy- and radiotherapy-induced nausea and vomiting
Granisetron administered orally has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults. (Tablets).

Granisetron administered intravenously has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults and children 2 to 16 years of age. (Solution for injection).

Post-operative nausea and vomiting

Granisetron administered orally/ intravenously has been shown to be effective for prevention and treatment of post-operative nausea and vomiting in adults.

Pharmacological properties of granisetron

Interaction with neurotropic and other active substances through its activity on P 450-cytochrome has been reported (see section 4.5).

In vitro studies have shown that the cytochrome P450 sub-family 3A4 (involved in the metabolism of some of the main narcotic agents) is not modified by granisetron. Although ketaconazole was shown to inhibit the ring oxidation of granisetron in vitro, this action is not considered clinically relevant.

Although QT-prolongation has been observed with 5-HT_3 receptor antagonists (see section 4.4), this effect is of such occurrence and magnitude that it does not bear clinical significance in normal subjects. Nonetheless it is advisable to monitor both ECG and clinical abnormalities when treating patients concurrently with drugs known to prolong the QT (see section 4.5).

Paediatric use (solution for injection only)

Clinical application of granisetron was reported by Candiotti et al. A prospective, multicentre, randomized, double-blind, parallel-group study evaluated 157 children 2 to 16 years of age undergoing elective surgery. Total control of postoperative nausea and vomiting during the first 2 hours after surgery was observed in most patients. '

Section 5.2 - Pharmacokinetic properties

Although there are some differences in wording, there are no significant discrepancies in this section. In a few cases (Finland, Hungary, Ireland, Romania, Slovenia), no reference is made to the paediatric population. In Iceland and Romania, mention is made that clinical efficacy is not clearly related to plasma concentration.

Absorption

After rapid intravenous administration of granisetron 20 or 40 µg/kg to healthy volunteers, mean peak plasma concentrations were 13.7 and 42.8 µg/L, respectively. Peak plasma concentrations and area under the plasma concentration-time curve (AUC) increased roughly in proportion to dose, while half-life, volume of distribution and clearance values remained essentially unchanged, indicating linear kinetics over a wide range of dosages (10 to 300 µg/kg).

The CHMP considered the MAH's proposed wording in section 5.2 to be acceptable with the addition that the pharmacokinetics of oral administration is linear up to 2.5-fold of the recommended dose in adults and also that the plasma concentration does not correlate unequivocally with the antiemetic efficacy of the substance for both the tablets and solution for injection formulations.

Distribution

The volume of distribution of granisetron is 2.2 to 3.3 L/kg in cancer patients. Mean plasma half-life is longer in cancer patients (about 10 to 12 hours) than in healthy volunteers (3.1 to 5.9 hours).

Furthermore, total body clearance values are lower and AUC values are higher in cancer patients, and together, these findings may reflect differences in drug elimination due to underlying disease processes, increased age of cancer patients relative to healthy volunteers or other factors.

Metabolism

Several authors have reviewed the role of dytochrome P-450 in connection with granisetron and other active principles known to interact with this enzymatic complex. It has been reported that such interactions, either stimulating or inhibiting metabolic pathways, did not reach clinical significance.

Excretion

It has been reported that elimination of granisetron is primarily by non-renal mechanisms, with only 8 to 15% of the parent compound recovered in the urine.

Other information

Interaction studies have been reported to document that the concomitant administration of granisetron with psychotropic drugs such as lorazepam did not cause significant disturbances.

Several authors have mentioned that clinical efficacy is minimally related to serum concentration and to dosage.

In addition, studies conducted in populations presenting with kidney damage as well as in the elderly have provided evidence that dose adaptations were not warranted in such patients. However it has been noted that in patients with hepatic impairment due to neoplasic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement. No dosage adjustment has been recommended.

Pharmacokinetics in the paediatric population with i.v administration was explored and reported to be similar to that in adult patients. Considering the few clinical trials performed in children, the CHMP agreed that an age range need not be mentioned.

CHMP conclusion

Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

'Pharmacokinetics of the oral administration is linear up to 2.5-fold of the recommended dose in adults. It is clear from the extensive dose-finding programme that the antiemetic efficacy is not unequivocally correlated with either administered doses or plasma concentrations of granisetron.

A fourfold increase in the initial prophylactic dose of granisetron made no difference in terms of either the proportion of patient responding to treatment or in the duration of symptoms control.

Absorption (Tablets only)

Absorption of granisetron is rapid and complete, though oral bioavailability is reduced to about 60% as a result of first pass metabolism. Oral bioavailability is generally not influenced by food.

Distribution

Granisetron is extensively distributed, with a mean volume of distribution of approximately 3 l/kg. Plasma protein binding is approximately 65%.

Biotransformation

Granisetron is metabolized primarily in the liver by oxidation followed by conjugation. The major compounds are 7-OH-granisetron and its sulphate and glycuronide conjugates. Although antiemetic properties have been observed for 7-OH-granisetron and indazoline N-desmethyl granisetron, it is unlikely that these contribute significantly to the pharmacological activity of granisetron in man.
In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily (see section 4.5).

Elimination

Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged granisetron averages 12% of dose while that of metabolites amounts to about 47% of dose. The remainder is excreted in faeces as metabolites. Mean plasma half-life in patients by the oral and intravenous route is approximately 9 hours, with a wide inter-subject variability.

Pharmacokinetics in special populations

Renal failure

In patients with severe renal failure, data indicate that pharmacokinetic parameters after a single intravenous dose are generally similar to those in normal subjects.

Hepatic impairment

In patients with hepatic impairment due to neoplasic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement. Despite these changes, no dosage adjustment is necessary (see section 4.2).

Elderly patients

In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

For the paediatric population:

Tablets:
'These tablets are not recommended in children.'

Solution for injection:

'In children, after single intravenous doses, pharmacokinetics are similar to those in adults when appropriate parameters (volume of distribution, total plasma clearance) are normalized for body weight.'

Section 5.3 - Preclinical safety data

The Kytril CDS does not provide information about acute toxicity and acute CNS-related adverse effects. The liver is not mentioned as the primary target organ of systemic toxicity in chronically treated rats and dogs. In different countries the current SmPC deviates from the proposed wording mainly by specific wording.

At the request of the CHMP the MAH re-submitted the reproductive data and an updated Non-clinical Overview. Animal based (rodents) carcinogenicity studies have shown an increased incidence of hepatocellular carcinoma. However it is acknowledged that the animals received lifelong treatment and at much higher doses. The hepatocellular neoplasia has not been observed when giving lower doses (1 mg/kg). Several in vitro and in vivo studies did not show that Kytril had a genotoxic effect on mammalian cells. Implications that Kytril may cause cancer is in humans are currently considered to be unfounded.

The wording of section 5.3 has been amended by the MAH taking into consideration the following CHMP comments:

- Safety margins are based on mg/kg basis
- The terms acute, subchronic and chronic have been replaced by the appropriate study durations
- Genotoxicity data is mentioned before carcinogenicity data.

CHMP conclusion

Taking into account the recommendation of the CHMP, the following wording proposed by the MAH was agreed:

'Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity. Carcinogenicity studies revealed no special hazard for humans when used in the recommended human dose. However, when administered in higher doses and over a prolonged period of time the risk of carcinogenicity cannot be ruled out.

A study in cloned human cardiac ion channels has shown that granisetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. Granisetron has been shown to block both sodium and potassium channels, which potentially affects both depolarization and repolarization through prolongation of PR, QRS, and QT intervals. This data helps to clarify the molecular mechanisms by which some of the ECG changes (particularly QT and QRS prolongation) associated with this class of agents occur. However, there is no modification of the cardiac frequency, blood pressure or the ECG trace. If changes do occur, they are generally without clinical significance.'

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Conclusions

The data provided by the MAH support the use of Kytril in the prevention and treatment of CINV and RINV, for both formulations - tablets and solution for injection (i.v. only). The evidence provided by the MAH was considered to be insufficient to support the i.m. route of administration.

The data presented are sufficient to support the use of Kytril only in the prevention of delayed CINV and RINV but not in the treatment of delayed CINV and RINV, for both formulations - tablets and solution for injection (i.v. only).

Based on the evidence provided, the use of Kytril in PONV was restricted to the solution for injection formulation only. The use of granisetron orally in PONV is not recommended.

In children aged 2 years and above, the indication for Kytril solution for injection for the prevention and treatment of acute CINV was accepted by the CHMP. The indication for Kytril solution for injection in the paediatric population for the treatment and prevention of delayed CINV was not agreed by the CHMP. The MAH does not recommend administration of Kytril solution for injection for paediatric use in RINV and PONV.

The wording concerning QT prolongation and 5-HT3 antagonists has been reviewed and approved as part of the Article 46 procedure, and the approved wording regarding QTc prolongation has been included in section 4.5 as well as in sections 4.4 and 4.8. In addition following the CHMP discussion, the adverse events diarrhoea, elevations in hepatic transaminases and extrapyramidal reactions were also added to section 4.8.

Based on the published and unpublished updated documentation, as well as the ensuing CHMP discussions, the proposal for the harmonized SmPC including the amendments provided by the MAH was considered to be acceptable by the CHMP.

2.5. Recommendation

The basis for this referral procedure was a harmonisation of the SmPC, labelling and package leaflet.

The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,
- comments from the marketing authorisation holders,

was of the opinion that the benefit/risk ratio of Kytril and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SmPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for Kytril and associated names (see Annex I).