ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Scientific conclusions

Overall summary of the scientific evaluation of Kytril and associated names (see Annex I)

Granisetron, the active ingredient of Kytril is a highly selective antagonist of 5-hydroxytryptamine (5-HT3) receptors and displays potent antiemetic activity.

Kytril was first approved in Europe in France, through the national procedure on 12 April 1991. Thereafter national approval was obtained in most of the EU countries.

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.

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.

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 to several days after administration of chemotherapy or radiotherapy

Postoperative nausea and vomiting (PONV), is defined as nausea and/or vomiting occurring within 24 hours after surgery.

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

Section 4.1 – Therapeutic Indications

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

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.

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 solution for injection is 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.'

Paediatric population:

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

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.'

Section 4.2 - Posology and method of administration

The harmonised proposed text proposed by the MAH was accepted by the CHMP for both the tablets and solution for injection.

Following a review of the available data, the MAH has concluded that the use of Kytril orally in PONV should not be recommended, which was supported by the CHMP. Based on data provided by MAH, the intramuscular route of administration was not considered to be acceptable by the CHMP.

There is insufficient clinical experience to recommend administration of Kytril tablets to children for CINV, RINV or PONV.

However as agreed by the CHMP, the administration of Kytril solution for injection is recommended 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.

The CHMP recommendation that Kytril should be used with a certain amount of caution in hepatically impaired patients was also included by the MAH.

Section 4.3 - Contraindications

According to the current European SmPC guideline (September 2009), the following contraindication was included: "hypersensitivity to the active substance or to any of the excipients".

The SmPC has not included cross-sensitivity reactions as a contraindication for Kytril , but instead included appropriate wording in the warnings and precautions section (section 4.4) of the EU harmonised SmPC. This is consistent with the recommendations and wording of the SmPC guideline.

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).

Section 4.4 - Special warnings and precautions for use

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.

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

Based on the theoretical possibility of cross-sensitivity reactions with granisetron, the MAH has proposed to include cautionary wording in this section of the SmPC.

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

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 Kytril. 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.

There is evidence that hepatic enzyme induction with phenobarbital in human volunteers resulted in an increase in total plasma clearance and intravenous Kytril of approximately 25 %. Therefore this interaction is included in section 4.5.

Section 4.6 - Pregnancy and lactation

There are no studies in pregnant women and it is not known whether Kytril is excreted in human milk. Based on the presented data the CHMP agreed that the use of Kytril should preferably be avoided during pregnancy.

Section 4.7 - Effects on ability to drive and use machines

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

Section 4.8 - Undesirable effects

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 terms hypersensitivity (e.g. anaphylaxis, urticaria) and constipation were included in the proposed SmPC as they are included in the majority of SmPCs, and are also supported by referenced texts and the CDS. The term 'headache' has been included as it is clearly described in the clinical studies and the literature as a very common adverse event. It was also endorsed by the CHMP 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. The MAH also proposed to include 'rash' as an adverse drug reaction with an uncommon frequency. Based solely on the hypersensitivity reaction, the CHMP agreed that rash should also be listed.

There was insufficient evidence for the adverse events agitation, anxiety, arrhythmias, chest pain, coma, dizziness, dysgeusia, hypotension/hypertension, syncope and/or drowsiness/ somnolence, anorexia, nausea, vomiting, abdominal pain, fever, fatigue and weakness/asthenia/tiredness, flu-like symptoms, oedema and pain in patients treated with Kytril and the CHMP therefore concurred that these terms could be excluded from the SmPC.

The SmPC wording regarding QT prolongation has been agreed 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 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.

The work-sharing PSUR covering period 19 Feb 2006 – 19 Dec 2008 (SK/H/PSUR/0004/001) refers 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.

In addition following further CHMP discussion, diarrhoea, (frequently reported adverse event in the pooled studies 276 and 278 and in the integrated summary of safety) and elevations in hepatic transaminases (observed in the CDS) were also included as adverse reactions.

Section 4.9 – Overdose

The MAH's proposal not to include hypothetical symptoms listed in a minority of SmPC, but to remain consistent with wording provided in the CDS was accepted by the CHMP.

Section 5.1 - Pharmacodynamic properties

Although there are some differences in wording, there are no significant discrepancies in this section. The clinical data have not been considered substantial enough to support the use of Kytril for RINV or PONV in paediatric patients.

Section 5.2 - Pharmacokinetic properties

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.

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.

Section 5.3 - Preclinical safety data

At the request of the CHMP the MAH re-submitted the reproductive data and an updated Non-clinical Overview. 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.

Taking into consideration the comments by the CHMP, the wording of section 5.3 has been amended by the MAH, taking into account the safety margins based on mg/kg basis and the appropriate study durations.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet
- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holders have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Kytril and associated names (see Annex I).