

**Rapporteur's
Public Assessment Report
for paediatric data in EU Worksharing procedure**

**KYTRIL
Granisetron**

UK/W/0014/pdWS/001

Marketing Authorisation Holder: Roche

Rapporteur:	UK
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Date of PAR:	

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Kytril
INN (or common name) of the active substance(s):	granisetron
MAH (s):	Roche Laboratories
Pharmaco-therapeutic group (ATC Code):	A04AA02
Pharmaceutical form(s) and strength(s):	Ampoules 1mg/1ml and 3mg/ml Tablets 1mg and 2mg

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I. EXECUTIVE SUMMARY AND RECOMMENDATION

In this article 46 procedure the MAH submitted the study report of a trial in the prophylaxis of postoperative nausea and vomiting (PONV) in children aged 2 to 16 years and a Drug Safety Report on QT interval prolongation.

Because of trial design issues the submitted efficacy data do not warrant inclusion in the product information.

The findings regarding QTc-interval prolongation should be reflected in the product information (SPC, PL) in sections 4.4, 4.5 and 4.8. The leaflet should be amended to reflect the changes made to the SPC. Variations to include information on QT-interval prolongation are ongoing in several European countries and have already been approved in some countries. So as not to cause confusion with these pending European variations, the changes should be implemented in the forthcoming harmonisation procedure under Article 30(2) of Directive 2001/83/EC.

II. INTRODUCTION

On 31st March 2009, the MAH submitted one completed paediatric study report (study ML16633 (Intravenous Granisetron (Kytril®) in the Prevention of Post-Operative Nausea and Vomiting (PONV) in Paediatric Subjects Undergoing Tonsillectomy or Adenotonsillectomy), in accordance with Article 46 EC Regulation No 1901/2006, as amended on medicinal products for paediatric use.

No clinical overview was provided and no proposals for reflecting the data in the product information were made as part of the submission under article 46. However, following a query from the Rapporteur, the MAH indicated that a report on QT-interval prolongation including paediatric data was available and had already been submitted in various European countries. This report was requested and relevant paediatric data are included in this assessment. Note that the Kytril product information in Austria, Hungary and Latvia already includes information regarding QT-interval prolongation.

Granisetron is authorised via the national procedure (in the UK in 1995). It is available as concentrate for solution for infusion or injection and as tablets.

In the UK, Kytril (granisetron) Ampoules are indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy (CINV) for adults and children of an unspecified age range) and for the prevention and treatment of post-operative nausea and vomiting (PONV) in adults only.

The recommended intravenous dose for both prevention and treatment of CINV in children is a single dose of 40 microgram/kg body weight (up to 3mg).

Kytril Tablets are indicated for the prevention of CINV in adults and children over the age of 12 years. The SmPC for tablets states in section 4.1: *There is insufficient evidence on which to base appropriate dosage regimens for children under 12 years old. Kytril Tablets are therefore not*

recommended in this age group. No specific dose recommendations are given in the SmPC for children aged ≥ 12 years. The dose recommendation for adults is 1mg twice a day or 2mg once a day, with the first dose of Kytril to be administered within one hour before the start of cytostatic therapy.

5HT3 antagonists and QT-interval prolongation

Granisetron belongs to the class of serotonin 5-HT₃ antagonists. 5HT₃-antagonists interact with human cardiac sodium and potassium channels (Kuryshv YA, 2003) and have been associated with changes in ECG parameters. The cardiotoxic potential of these agents has been widely discussed in literature. The SPCs for ondansetron and tropisetron contain relevant information in sections 4.4, 4.5 and 4.8. Because of evidence suggesting greater acute changes in QTc-interval in children than in adults and cases of sustained arrhythmias and cardiac arrest in children and adolescents dolasetron, another drug in the class, is contraindicated for the paediatric population in the UK.

The UK product information for Kytril currently does not contain any information regarding QT-interval prolongation. The US product information for Kytril states the following: *QT prolongation has been reported with KYTRIL (see PRECAUTIONS and Drug Interactions). PRECAUTIONS: An adequate QT assessment has not been conducted, but QT prolongation has been reported with KYTRIL. Therefore, Kytril should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders, as this might lead to clinical consequences. Patients with cardiac disease, on cardio-toxic chemotherapy, with concomitant electrolyte abnormalities and/or on concomitant medications that prolong the QT interval are particularly at risk. Drug Interactions: QT prolongation has been reported with KYTRIL. Use of Kytril in patients concurrently treated with drugs known to prolong the QT interval and/or are arrhythmogenic, this may result in to clinical consequences.*

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Study medication consisted of Kytril® (granisetron hydrochloride) 1 mg/mL Multidose Vials for injection.

III.2 Non-Clinical aspects

Not applicable.

III.3 Clinical aspects

1. Introduction

The MAH submitted one clinical study report (Research Report No. 1029920, dated 19th June 2008) and a Drug Safety Report on QT interval prolongation (No. 1031745, dated 25th November 2008). No clinical overview was provided.

No proposals were made for reflecting the results of the trial report submitted in accordance with article 46.

With the submission of Drug Safety Report on QT interval prolongation, the MAH proposed to include the following information in the SPC:

Section 4.4 “Special warning and special precautions for use”:

As for other 5-HT₃ antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. These changes were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, 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”.

Section 4.5 “Interaction with other medicinal products and other forms of interaction”:

“As for other 5-HT₃ antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. These changes were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, in patients concurrently treated with drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences”.

Section 4.8 “Undesirable effects”:

“As for other 5-HT₃ antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. These changes were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia”.

2. Clinical studies

➤ Study Title

Intravenous Granisetron (Kytril®) in the Prevention of Postoperative Nausea and Vomiting (PONV) in Pediatric Subjects Undergoing Tonsillectomy or Adenotonsillectomy, ML 16633

➤ Description

This study was conducted at 8 centres in the United States from April to December 2007.

➤ Methods

Study Design

Randomized, double-blind, fixed-dose study, with parallel groups. No placebo control.

Study Objectives

Primary - to estimate the effectiveness of two dose levels of intravenous granisetron (20 and 40 microgramm/kg) in preventing PONV.

Secondary - to estimate the effectiveness of the two dose levels of granisetron during the 24 h following extubation.

Exploratory - to describe pre- and postdose QT intervals and laboratory assessments

Safety - to examine the safety profile of the two treatment groups.

Study population

Children aged 2 to 16 years, ASA classification status of 1 - 3, undergoing elective surgery for tonsillectomy or adenotonsillectomy with a defined standard anaesthesia regimen and scheduled for hospital admission for ≤ 24 hours.

Children weighing ≥ 70 kg and/or > 95 th percentile for age were excluded, as were those scheduled to undergo additional concurrent medical/surgical procedures, with retching or vomiting in the 24 hours prior to anaesthesia or with a history of motion sickness or PONV.

Study Treatment

Granisetron 20 or 40 microgram/kg IV in 5 mL solution was administered as a single 30-second infusion approximately 15 minutes prior to extubation (end of surgery).

Assessor's comment

Dexamethasone 0.5 mg/kg IV (maximum of 20 mg) was to be administered immediately after induction and insertion of an IV line. Morphine and codeine were recommended for postoperative analgesia. These medications may have had an impact on efficacy assessment.

Endpoints:

The **primary** efficacy measurement was the proportion of study subjects with total control (no vomiting, no nausea, and no use of rescue medication) over the 2 hours following extubation.

Secondary efficacy endpoints were:

- Proportion of subjects with total control of PONV during the 24 hours following the time of extubation
- Proportion of subjects with no vomiting during the 2-hour interval following the time of extubation
- Proportion of subjects with vomiting from the time of extubation until PACU discharge
- Proportion of subjects with no vomiting during the 24 hours following the time of extubation
- Time to first vomiting episode following the time of extubation
- Proportion of subjects with no nausea during the 2-hour interval
- Proportion of subjects with complaints of nausea from the time of extubation until PACU discharge
- extubation until PACU discharge
- Proportion of subjects with complaints of nausea during the 24 hours interval
- Proportion of subjects requiring rescue medication from the time of extubation until PACU discharge

Assessor's comment

Several secondary endpoints referred to a 24-hour period, but patients could only be included if they were scheduled for hospital admission for ≤ 24 hours.

Safety Evaluations

ECG: preoperative and prior to discontinuation of IV access and anaesthesia reversal. Laboratory assessments pre- and postdose. Vital signs (systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature) at screening at the baseline assessment prior to surgery only. Adverse events.

Statistical Methods

Descriptive analysis to estimate response rates with an estimated precision of 0.12. There was no ITT analysis.

➤ Results

Recruitment/ Number analysed: Of the 171 randomised subjects, 14 did not receive treatment and another 14 were excluded from efficacy analysis.

ec11t37 Summary 37: Summary of Analysis Populations by Trial Treatment
 Protocol(s): ML16633
 Analysis: ALL PATIENTS Center: ALL CENTERS

	GRANISETRON 20 MCG/KG	GRANISETRON 40 MCG/KG	ALL PATIENTS
No. of Patients Randomized	87	84	171
No. Included in EVALUABLE	70	73	143
No. Excluded from EVALUABLE	17	11	28
Subject did not receive study medication	8	6	14
Subject received NSAIDS	1	5	6
Subject had planned secondary operative procedure	5	-	5
Subject's weight greater than 95th percentile for their age	2	-	2
Subject has history of migraines	1	-	1
No. Included in SAFETY	79	78	157
No. Excluded from SAFETY	8	6	14
Subject did not receive study medication	8	6	14

Baseline data

Baseline characteristics were similar in both treatment groups. The study report does not contain data on number of patients per age group (e.g. 2-6 yrs, ≥6 -12 yrs, ≥12 yrs).

Efficacy results

Total control of PONV during the first 2 hours was observed in 85.7% and 90.4% in the 20- and 40-microgram/kg dose groups, with a trend for a larger proportion with the higher granisetron dose (treatment difference of 4.7%, 95% CL − 0.09, 0.23; primary endpoint). Secondary endpoint results are summarised in the table below.

Endpoint	granisetron 20 microgram/kg	granisetron 40 microgramm/kg
Proportion of subjects with total control of PONV during the 24 hours following the time of extubation	65.7%	61.6%
Proportion of subjects with no vomiting during the 2-hour interval following the time of extubation	87.1%	94.4%
Proportion of subjects with vomiting from the time of extubation until PACU discharge	91.4%	95.9%
Proportion of subjects with no vomiting during the 24 hours	70.0%	68.5%

Endpoint	granisetron 20 microgram/kg	granisetron 40 microgramm/kg
following the time of extubation		
Time to first vomiting episode following the time of extubation	18.0 hours	17.8 hours
Proportion of subjects with no nausea during the 2-hour interval	88.6%	94.5%
Proportion of subjects with complaints of nausea from the time of extubation until PACU discharge	91.4%	97.3%
Proportion of subjects with complaints of nausea during the 24 hours interval	80.0%	84.9%
Proportion of subjects requiring rescue medication from the time of extubation until PACU discharge	94.2%	97.2%

Rapporteur's comments

As this trial included neither a placebo nor an active comparator, the results are not considered to provide adequate evidence of efficacy to justify inclusion in the product information. The efficacy results are from a completer's analysis and not an ITT analysis. It would have been preferable to present results of ITT analysis as well.

Safety Results

Adverse events

34 subjects (22%) reported an adverse event.

Serious adverse events (SAEs) were reported for six subjects on granisetron 20mcg/kg and two subjects on 40 microgram/kg. All SAEs were judged unrelated to study treatment.

There were no deaths and no withdrawals due to adverse events.

The incidence of adverse events was similar in the two treatment groups (23% and 21% in the 20- and 40-microgram/kg dose groups). Gastrointestinal disorders occurred most frequently, with vomiting the most frequent event (8% and 5%). Other more frequent adverse events included post-procedural haemorrhage and dehydration. No dose relationship was apparent for any of the adverse events reported.

Table 23 Overview of All Treatment-emergent Adverse Events, Safety Population

	Granisetron 20 µg/kg (n = 79) n (%)	Granisetron 40 µg/kg (n = 78) n (%)	All subjects (N = 157) n (%)
All treatment-emergent adverse events	18 (23)	16 (21)	34 (22)
Severe adverse events	2 (3)	0 (—)	2 (1)
Related adverse events	0 (—)	2 (3)	2 (1)
Serious adverse events	6 (8)	2 (3)	8 (5)
Deaths	0 (—)	0 (—)	0 (—)
Withdrawals due to an adverse event	0 (—)	0 (—)	0 (—)

Rapporteur's comments

No cases of arrhythmia, palpitation, hypotension, dizziness, syncope or seizure were reported. Although 2 subjects in each treatment group had clinically significant ECG abnormalities, these were not reported as adverse events.

ECG changes

ECGs were performed after the induction of anesthesia and insertion of IV access (predose) and at the end of surgery after the administration of study treatment and just prior to the reversal of anesthesia (postdose). Because ECG readings were not standardized across centres, an external cardiac electrophysiologist performed blinded reviews of all ECG tracings. For blinded review, tracings were identified by subject but were coded to blind sequence (pre- and postdose) and dose (20 or 40 microgram/kg). The original machine value for each interval was used in most cases and was changed only if the external cardiologist's measurement differed from the machine reading by more than 20 ms and the relevant investigator agreed to the change.

An abnormal postdose ECG was reported by the investigator prior to ECG review by the cardiac electrophysiologist for four subjects (borderline prolonged QT interval in three subjects and possible first-degree atrioventricular block in one subject.)

In the 20-microgram/kg group, an increase of heart rate of 8.0 bpm (95% CL 4.6, 11.3) was observed. The increase was lower in the 40-microgram/kg group (2.9 bpm, 95% CL -1.3, 7.2). The change in heart rate was highly variable in both treatment groups (ranges of -44 to +62 bpm and -57 to +63 bpm, respectively). These findings did not correlate with the granisetron dose and may have been due to baseline differences.

A small increase in PR interval was also observed in the 20-microgram/kg dose group (3.9 ms, 95% CL 0.6, 7.1), but not in the 40-microgram/kg group. No relevant changes were observed in QRS intervals.

QT-interval

Both Bazett's (QTcB) and Friderica's (QTcF) formula were used to calculate the QTc-interval.

All subjects had a normal predose ECG as judged by the investigator at the time of the ECG.

Mean increases for QTcB (21.9 and 19.9 ms in the 20- and 40-microgram/kg groups) and QTcF (15.0 and 16.0 ms) were observed in both treatment groups. Median changes in QT, QTcB, and QTcF were similar to the mean changes.

One subject in each dose group had a postdose QTcF that was > 500 ms and 5 subjects (3 and 2) had a QTcF increase of ≥ 60ms.

19 subjects (8 and 11) had a postdose QTcB > 500 ms and 10 subjects (6 and 4) had a QTcB increase of ≥ 60ms.

A summary of subjects with a QTc interval > 450, > 480, and > 500 ms pre- and postdose and those with a ≥ 30-ms and ≥ 60-ms increase from baseline is presented below.

Table 20 Proportions of Subjects with a QTc Interval > 450 ms and with an Increase in QTc Interval ≥ 30 ms by Time Category, Safety Population

Table tas_ecca_t12: ECG - QTc Interval Categorical Analysis
 Protocol: ML16833
 Analysis Population: Safety Subjects

Scheduled Time	Criteria	Granisetron 20 µg/kg N = 79	Granisetron 40 µg/kg N = 78	
Pre-dose	QTcB > 450 ms	44 (57.1)	42 (54.5)	
	QTcB > 480 ms	8 (10.4)	14 (18.2)	
	QTcB > 500 ms	2 (2.6)	5 (6.5)	
	n	77	77	
	QTcF > 450 ms	6 (7.8)	7 (9.1)	
	QTcF > 480 ms	0 (0.0)	1 (1.3)	
	QTcF > 500 ms	0 (0.0)	0 (0.0)	
	n	77	77	
	Post-dose	QTcB > 450 ms	65 (83.3)	65 (84.4)
		QTcB > 480 ms	26 (33.3)	26 (33.8)
QTcB > 500 ms		8 (10.3)	11 (14.3)	
n		78	77	
QTcF > 450 ms		15 (19.2)	12 (15.6)	
QTcF > 480 ms		1 (1.3)	1 (1.3)	
QTcF > 500 ms		1 (1.3)	1 (1.3)	
n		78	77	
QTcB increase ≥ 30ms		28 (36.4)	25 (32.9)	
QTcB increase ≥ 60ms		6 (7.8)	4 (5.3)	
n		77	76	
QTcF increase ≥ 30ms		20 (26.0)	18 (23.7)	
QTcF increase ≥ 60ms		3 (3.9)	2 (2.6)	
n		77	76	

n = number with QTc assessment at the relevant time point(s) and is the denominator for the percentages.
 QTcB = Bazett's correction, QTcF = Fridericia's correction.

Rapporteur's comments

The 'baseline' ECG was performed after administration of anaesthetics.

The study report does not state which lead was used to measure the QT interval, nor whether normal ECG standards for children were used. In the absence of such a statement it must be assumed that age-specific standards (such as Davignon's tables) were not used. This has a significant impact on the interpretability of the data. Shifts from normal (for age) to abnormal (upwards) would have been of interest.

It might have been preferable to have ECG readings performed by a paediatric cardiologist.

It has been proposed that the QT-interval should be measured at the time of peak plasma concentration of QT-prolonging drugs. The Kytril product information does not give information on Tmax and there is no relevant information in the study report, hence it is unclear whether the postdose ECG was performed at the time of Cmax.

The FDA label concisely summarises the data as follows: *An adequate QT assessment has not been conducted, but QT prolongation has been reported with KYTRIL.*

The incidence of QTc interval prolongation to >500ms or by ≥ 60 ms in children is not negligible, although it is noted that the ECG changes remained clinically asymptomatic in all reported cases.

For the MAH's own summary of the data, please see below.

Laboratory investigations

For most laboratory variables, mean changes were minimal and not clinically relevant, including AST and ALT concentrations.

Mean fasting blood glucose increased in both treatment groups (increases of 1.41 and 1.52 mmol/L in the 20- and 40-microgram/kg dose groups, respectively). This increase resulted in postdose values that were above the investigator's normal range in about 54% of subjects who had normal predose values in each dose group. No relationship between the increase in fasting blood glucose and the granisetron dose was observed.

Mean total plasma protein decreased in both treatment groups, also with no apparent relationship to dose (-13 and -5 g/L in the 20- and 40-microgram/kg dose groups). This decrease resulted in postdose values that were below the investigator's normal range in about 19% of subjects who had normal predose values in each dose group. Small mean decreases in albumin and globulin were also seen. The decrease in plasma albumin may have been related to the granisetron dose, as a shift in plasma albumin from normal to low was observed in about 16% and 25% of subjects in the 20- and 40-microgram/kg dose groups in addition to the small difference between dose groups in mean decrease (-2.9 and -3.2 g/L).

Rapporteur's comment

We do not consider that these changes merit reflection in the product information. Decrease in albumin might have resulted from intro/postoperative intravenous hydration.

3. Drug Safety Report

Drug Safety Report on QT interval prolongation (No. 1031745, dated 25th November 2008) contains the paediatric information from trial ML 16633 discussed above and from literature.

Information from clinical trials:

With respect to the ECG data summarised above, the MAH states the following:

'As this study was not a dedicated QT study several aspects make these findings difficult to interpret. There was no control nor placebo group to indicate whether the observed increase in QT was due to a period effect, an effect of concomitant medication or a real effect of granisetron treatment. No measurement of QT was done at baseline, before anesthesia and after the reversal of anesthesia. The ECG performed approximately 15 minutes prior to the end of surgery could have been done 1-2 hours post-dose. It has previously been shown that there is an increase of QT 1-2 hours following administration of the drug. Moreover, anesthesia was maintained with sevoflurane in all subjects and sevoflurane has been reported to cause a progressive prolongation of the QTcB interval (approximately 25 ms within 10 minutes). The prolongation of QT observed in this study could therefore be due to sevoflurane alone, but an additive effect of both sevoflurane and granisetron cannot be excluded. Given the many confounding variables, any contribution of granisetron to the observed increase in QT interval cannot be determined or excluded from this study.'

Rapporteur's comment

We agree that the trial design and methods were inadequate to provide robust data on QT-interval prolongation in children.

Spontaneous reports:

Two cases occurred in children (MCN 1993904865 and MCN 1997002423). These cases are outlined below. In 12 cases the age was not provided.

MCN 1993904865 (study 43694 A): A six years old male patient, with a medical history of neuroblastoma, experienced an anaphylactoid reaction after receiving granisetron and mesna, CFA. He recovered and received a bone marrow transplant 5 days later. The patient condition deteriorated and he experienced occlusion and sepsis. He died 29 days post therapy of cardiac arrest with secondary causes: multiorgan failure due to progression of neuroblastoma stage IV, cardiac arrhythmia, pulmonary hemorrhage, etc. Comment: The cardiac arrhythmia occurred 29 days after the use of granisetron and in the context of multiorgan failure due to progression of neuroblastoma. The role of granisetron is unlikely.

MCN 1997002423 (study 34694 A): A 7-year-old female patient with a medical history of leukaemia experienced diarrhoea and syncope during the forth cycle of chemotherapy. The reporter assessed the causality of Kytril as unrelated.

Assessor's comment

Causality for the 2 reported paediatric cases cannot be established.

Evidence from literature:

The following publications were identified:

1. Pinarli FG et al. Electrocardiographic findings after 5-HT₃ receptor antagonists and chemotherapy in children with cancer. *Pediatr Blood Cancer* 2006; 47: 567-71.
2. 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): 201-4.
3. Aapro M, Rabaeous M. Re: The effects of ondansetron and granisetron on electrocardiography in children receiving chemotherapy for acute leukemia. *Am J Clin oncol* 2005; 28(6): 634-5.
4. Lemerle J et al. Efficacy and safety of granisetron in the prevention of chemotherapy-induced emesis in paediatric patients. *Eur J Cancer* 1991; 27(9): 1081-3.
5. Fujii Y et al. Preoperative oral granisetron for the prevention of vomiting following paediatric surgery. *Paediatric Anaesthesia* 2002; 12: 267-71.
6. Fujii Y et al. Ramosetron compared with granisetron for the prevention of vomiting following strabismus surgery in children. *Br J Ophthalmol* 2001; 85:670-2.
7. Fujii Y et al. Comparison of granisetron, droperidol, and metoclopramide for prevention of postoperative vomiting in children with a history of motion sickness undergoing tonsillectomy. *J Pediatr Surg* 2001; 36(3): 460-2.

Assessor's comment

Search criteria and searched databases are not identified in the report.

Two studies investigated the effects of ondansetron and granisetron on electrocardiography in children with cancer and receiving concomitant chemotherapy.

Pinarli et al evaluate the ECG changes in 38 paediatric patients receiving chemotherapy for solid tumors and either ondansetron or granisetron (Pinarli FG et al. *Pediatr Blood Cancer* 2006; 47: 567-71). The 5-HT₃ receptor antagonist was received 30 min before antineoplastic agents in 83 chemotherapy days. Twelve lead ECGs were obtained four times on the first day of each chemotherapy: just before, 30, 90 min and 24 hrs after 5-HT₃ antagonist were given. Significant shortening of the PR interval and QRS complex durations were noted in the granisetron group at the 90 minute and at the 24 hour time points, respectively. Additionally, granisetron infusion caused a significant prolongation of the QTc interval at 90 minutes. The authors concluded that although minor ECG changes were observed after 5-HT₃ receptor antagonists and chemotherapy, neither dangerous rhythm disturbances nor serious ECG changes were seen.

Buyukaci et al.(*Am J Clin Oncol* 2005; 28(2): 201-4) investigated the effects of ondansetron (0.1 mg/kg) and granisetron (40microgram/kg) administrated intravenously over 30 sec on ECGs in 22 children receiving high-dose methotrexate therapy for acute lymphoblastic leukemia. ECG recordings were obtained before the administration of the anti-emetic, immediately after and at 1, 3,6 and 24 hours post-dose. Granisetron administration resulted in a statistically significant decrease of mean heart rate at 1 and 3 hours, and significant prolongation of mean QT and QTc dispersions following 1 hour of infusion. No meaningful change was observed with ondansetron and the effects of granisetron on ECG were transient and clinically asymptomatic.

In a published response to Buyukaci et al, Aapro M and Rabaeus [Am J Clin oncol 2005; 28(6): 634-5.] argued that there were some differences at baseline between the groups and given the small number of patients this can be significant. They conclude that the study only draws attention to the possibility that there might be a very temporary effect of granisetron.

In an open ascending dose study in 24 paediatric patients, single dose of 10, 20 and 40 microgram/kg of granisetron were administered IV, 1 hour before chemotherapy. There were no clinically important changes in pulse rate, blood pressure or Holter ECG and granisetron was well tolerated [Lemerle J et al. Eur J Cancer 1991; 27(9): 1081-3.].

Some studies investigated the efficacy and safety of granisetron in children in postoperative vomiting but no ECG data were reported. However no clinically adverse events were observed.

Rapporteur's comment

The data reported from literature support the introduction of relevant warning statements in the product information.

4. Discussion on clinical aspects

Granisetron has one paediatric indication – CINV. The submitted trial for the prophylaxis of PONV does not provide robust evidence of efficacy that would support an indication for PONV.

As the trial included neither placebo nor an active comparator control arm, we consider that the data do not merit being included in section 5.1 of the product information either.

The safety data are of some concern, in particular the not negligible incidence of QTc interval prolongation to >500ms or by ≥ 60 ms in children, although it is noted that the ECG changes remained clinically asymptomatic in all reported cases.

Ideally we would have liked to see a how QTc changes in children compare with those seen in adults.

We strongly support the introduction of warning statements regarding prolongation of the QTc-interval into the SmPC. These should be worded as follows:

Section 4.4 “Special warning and special precautions for use”:

As for other 5-HT₃ antagonists, cases of ECG modifications changes including QT interval prolongation have been reported with Kytril. These changes were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, 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)”.

Section 4.5 “Interaction with other medicinal products and other forms of interaction” :

“As for other 5-HT₃ antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. These changes were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, in patients concurrently treated with

~~drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences~~. **‘Use of granisetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias. (See section 4.4)’**

Section 4.8 “Undesirable effects” :

~~“As for other 5-HT₃ antagonists, cases of ECG modifications changes including QT prolongation have been reported with Kytril. These changes were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia”.~~ **(See sections 4.4 and 4.5)**

IV. MEMBER STATE COMMENTS FOLLOWING CIRCULATION OF THE PAR

Comments were received from 2 concerned member states (MSs).

These two MSs endorsed that the submitted efficacy data for the PONV indication in children aged 2 to 16 years do not warrant inclusion of any statement in the product information and agreed with the proposed additional information (regarding prolongation of the QTc-interval) for the product information.

There was some disagreement with respect to the wording proposed by the Rapporteur (see above):

Section 4.4

One MS was in favour of keeping the recently discussed and agreed statement during the renewal for another granisetron product: *“5-HT₃ antagonists such as granisetron may be associated with arrhythmias or ECG abnormalities. This potentially may have clinical significance in patients with pre-existing arrhythmias or cardiac conduction disorders or patients who are being treated with antiarrhythmic agents or beta-blockers.”*

Section

4.5

The other MS did not agree with the proposed wording as other medicinal products other than cardiotoxic drugs may affect the QT interval. Therefore they proposed a slight amendment to section 4.5: *“As for other 5-HT₃ antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. However, in patients concurrently treated with drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences”.*

In addition, the question was raised whether ECG changes including QT prolongation have been reported more frequently with the IV formulations, as it has been observed for ondansetron. If it is the case, this information should be reflected in the SmPC.

V. RESPONSES AND RESPONSE ASSESSMENT

Taking into consideration the Rapporteur’s and the MSs comments as outlined above, the MAH proposed the alternative wording as outlined below.

Section 4.4

“As for other 5-HT₃ antagonists, ECG changes including QT interval prolongation have been reported with Kytril. 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).”

Rapporteur’s comment

The proposed text is accepted. *Issue resolved.*

Section 4.5

“As for other 5-HT₃ antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. In patients concurrently treated with drugs known to prolong QT interval and/or which are arrhythmogenic, this may lead to clinical consequences”.

Rapporteur’s comment

Granisetron may be co-administered with cardiotoxic chemotherapy and we would therefore prefer specific mentioning of potential interactions with cardiotoxic chemotherapies in section 4.5. However, as the relevant information will be contained in section 4.4. and the early cardiotoxic effects of anthracyclines that are of concern when concurrently used with granisetron are electrophysiologic abnormalities, we can accept the proposed text provided that a cross-reference to section 4.4 is added.

Issue resolved provided a cross-reference to section 4.4 is added.

Regarding relative frequency of ECG changes in respect to different formulations of granisetron, the MAH stated the following:

It is irrelevant and possibly misleading to point to the relative frequency of ECG changes with respect to different granisetron formulations in the absence of any data in this area for the following reasons:

1. The submitted report is based on study No. ML 16’333 of 170 children that had been conducted to establish the efficacy and safety of granisetron in children aged 2-16 years in the context of tonsillectomy or adenotonsillectomy requiring general anaesthesia. Study design was for a multicentre, double-blind, parallel, randomised comparison between two dosing regimens, i.e. 20 and 40 µg•kg⁻¹.
2. The same formulation of granisetron was used in all trial patients, i.e. 1 mg/mL Multidose Vials for Injection.
3. The total number of evaluable patients in terms of QTc prolongation was 153, i.e. 77 and 76 in the 20 and 40 µg•kg⁻¹ groups respectively. Of those, a mere 3 (4 %) and 2 (3 %) had a >60 ms prolongation (following Fredericia’s correction to account for accelerated heart rate).
4. Whereas such ECG modification is indeed statistically significant as compared to baseline, there is no significant difference between the treatment groups. Furthermore, the group with the most significant deviation was actually receiving the lower dose regimen (20 µg•kg⁻¹).

The company proposes the following text for section 4.8:

“As for other 5-HT₃ antagonists, ECG changes including QT prolongation have been reported with Kytril. (See sections 4.4 and 4.5).”

Rapporteur’s comment

We maintain that the incidence rate for >60 ms QTc prolongation of 3-4% is not negligible. It is however reassuring that all reported cases of ECG changes in the submitted clinical trial remained clinically asymptomatic

As the trial design and methods of the submitted trial were inadequate to provide robust data on QT-interval prolongation in children, further comparisons based of these data are also unlikely to provide robust data. For the purposes of this procedure and on the basis of the data submitted for this procedure, the Rapporteur considers that the addition of proposed statement is adequate.

Nevertheless, the company should consider such analysis as part of the forthcoming harmonisation procedure in accordance with Article 30(2) of Directive 2001/83/EC, as amended.

The company proposed to incorporate the above changes into the proposed Kytril® EU SmPC harmonisation application, foreseen to be submitted in May 2010.

Rapporteur’s comment

Variations to include information on QT-interval prolongation are ongoing in several European countries and have already been approved in some countries. So as not to cause confusion with these pending European variations, the Rapporteur considers the applicant’s proposal to incorporate the above changes in the forthcoming harmonisation procedure acceptable.

VI. OVERALL CONCLUSION AND RECOMMENDATION

The submitted efficacy data do not warrant inclusion in the product information.

The product information (SPC, PL) should be updated to include warning statements regarding QTc interval prolongation in sections 4.4, 4.5 and 4.8. The changes should be implemented in the forthcoming harmonisation procedure under Article 30(2) of Directive 2001/83/EC. The leaflet will need to be amended to reflect the changes made to the SPC.