

**Rapporteur's
Public Paediatric Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended**

**Primperan (and others)
Metoclopramide**

DE/W/007/pdWS/001

Rapporteur:	Germany
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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Various
INN (or common name) of the active substance(s):	Metoclopramide
MAH (s):	Sanofi-Aventis
Pharmaco-therapeutic group (ATC Code):	A03FA01 (prokinetics)
Pharmaceutical form(s) and strength(s):	Tablets 10 mg 2.6 mg/ml oral solution 10% oral solution Suppositories 10 mg and 20 mg Injectable Solution 20 mg/2 ml ampoules Injectable Solution 100 mg/5ml ampoules
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I. EXECUTIVE SUMMARY

In November 2009, one MAH submitted data regarding the paediatric use of metoclopramide (MTC), in accordance with article 45 of the regulation EC No. 1901/2006 as amended on medical products for paediatric use.

The MAH provided an extensive documentation of available data for MTC, guided by a newly drawn up clinical overview, and partly referring to an earlier risk-benefit assessment of the compound in children dated 25th October 2005, which was prepared for answering a request from the French National Authority (AFSSAPS).

The content of both reports mainly refers to a multitude of published literature regarding the documentation of efficacy and safety (including pharmacoepidemiological studies) and the evaluation of the safety database of the MAH with regard to spontaneous adverse events reporting in children.

After having received the MAH answers on the request for supplementary information, it now became clear that the MAH's intention is to harmonise the core safety information (chapters 4.4., 4.8. and 4.9 of the SPC) related to children only, but not to harmonise the indication and posology sections related to children.

This is intended to reflect the current diverging licensing status of the compound within Europe.

After the scientific evaluation of the data and the responses received to the request for supplementary information, this AR provides a conclusion as regards the treatment of children with subsequent wording of the SPC which is given as a recommendation to the Member States. However, MSs are reminded to consider that the Paediatric Regulation does not foresee a compulsory update of the SmPC and PL, and that CMDh is clearly preferring the update of SmPC and PL through cooperation with the MAH.

Moreover, as the conclusion of this AR is removing most of the previously approved indications for children, it obviously is contradicting the intention of the article 45 procedure, as also expressed in the CMDh "Recommendations on submission and assessment in paediatric worksharing" (CMDh/141/2009), which states that "it is not the aim of Article 45 or 46 procedures to remove existing paediatric indications for products which are already in clinical use in particular member states. Removal of indications, for example if there is new evidence regarding safety, should be considered by individual member states unless there has been prior agreement by CMDh or through another regulatory procedure". This would also have to be considered by the NCAs.

The proposal given is not in accordance with the proposal of the MAH, and it may as well not fit into the individual regulatory framework of individual MSs and may therefore have to be adapted to the national requirements.

The proposals for sections 4.1. and 4.2. are therefore given for consideration only.

II. RECOMMENDATION

Based on the review of efficacy and safety of the compound metoclopramide, the Rapporteur considers that the only pharmaceutical form to be used for the compound in children should be the i.v. form.

For the **i.v. form**, the following wording should be included in the SPC/PIL.

Section 4.1 Therapeutic indication:

[The existing indications should include a header such as "Adult population":]

Paediatric population including adolescents:

Metoclopramide is indicated for the treatment of postoperative nausea and vomiting for children from 1 year of age.

For other indications, the use in the paediatric population is not recommended.

Section 4.2 Posology:

Paediatric population:

For the treatment of postoperative nausea and vomiting, metoclopramide should be administered after the termination of the surgical procedure.

The recommended dose is 0.15 mg/kg b.w. given as a slow injection (at least 3 minutes).

The maximum dose in 24 hours is 0.5 mg/kg b.w. If additional doses are needed, these should be separated by at least 6 hours.

Metoclopramide should not be used in children younger than 1 year as there are insufficient data regarding efficacy and safety of the product in this patient population.

The following warnings/safety information related to the use in the paediatric population should be included in the SPC (of the i.v. form):

Section 4.3 Contraindications:

Metoclopramide is contraindicated in neonates.

Section 4.4.: Warnings/Precautions:

Extrapyramidal disorders may occur, particularly in children and young adults and/or when high doses are used (see 4.8. undesirable effects).

Respect the time interval (at least 6 hours) specified for children in the dosage section between each metoclopramide administration, even in case of vomiting, in order to avoid overdose.

Section 4.8 undesirable effects:

Nervous system and psychiatric disorders:

Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even following administration of a single dose of the drug, particularly in children and young adults (see Section 4.4.).

Blood and Lymphatic system disorders:

Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency particularly in neonates.

Section 4.9 Overdose:

Treatment for extrapyramidal disorders is only symptomatic (benzodiazepines in children).

For all **rectal and oral forms**, the following is recommended to be included in the SPC:

Section 4.1:

[No pediatric indication; the existing indications should include a header such as “Adult population”:]

Section 4.2:

Paediatric population including adolescents:

Use in the paediatric population is not recommended.

Section 4.3 Contraindications:

Metoclopramide is contraindicated in neonates.

Sections 4.4, 4.8 and 4.9. Should be similar to the one for the i.v. forms with the exception of the advice on proper dosing, as follows:

Section 4.4: Warnings/Precautions:

Extrapyramidal disorders may occur, particularly in children and young adults and/or when high doses are used (see 4.8. undesirable effects).

Section 4.8 undesirable effects:

Nervous system and psychiatric disorders:

Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even following administration of a single dose of the drug, particularly in children and young adults (see Section 4.4.).

Blood and Lymphatic system disorders:

Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency particularly in neonates.

Section 4.9 Overdose:

Treatment for extrapyramidal disorders is only symptomatic (benzodiazepines in children).

III. INTRODUCTION

Only one MAH submitted a multitude of completed paediatric study(ies) and literature reports for metoclopramide, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

An elaborate expert overview has been provided summarising the multitude of paediatric data available.

In their initial submission, the MAH did not clearly state whether the submitted paediatric study(ies) do influence the benefit risk for metoclopramide and an explicit proposal for the harmonisation of the sections 4.1 and 4.2 of the SPC has not been made.

The MAH, however, was submitting sections of the SPC, including contraindications, warnings and precautions, interactions, pregnancy (only partly) and lactation, driving information, adverse reactions, and overdose, for which a harmonisation is out of the scope of an article 45 procedure, as this mainly concerns the treatment of adults (at least not exclusively the treatment of children).

The evaluation of the MAH was based on the current assessment of the compound in the Member State FR, and the currently approved status of the compound in this MS. This includes the following indications:

- Nausea and vomiting:
 - o Chemotherapy- and radiotherapy-induced nausea and vomiting
 - o Postoperative nausea and vomiting
- Gastrointestinal motility disorders
 - o Gastroesophageal reflux disease
 - o Other gastrointestinal motility disorders
- Digestive tract explorations

The approved dose range in the paediatric population is, regardless of the indication, 0.1 mg/kg/day to 0.5 mg/kg/day (maximum daily dose).

The MAH did not clearly present for which pharmaceutical forms the treatment of children is proposed, but only lists all formulations available:

- 10 mg tablets
- 2.6 mg/ml oral solution
- 1% oral solution
- Suppositories of 10 mg and 20 mg
- Injectable solution of 10 mg/2 ml and 100 mg/5ml

The MAH further referred to the restrictions for the compound implemented in the MS FR, e.g. the contraindication of certain formulations (e.g. 1% oral solution for children in general, the contraindication of the 20 mg suppository for children of less than 40 kg of weight, and the contraindication of the 10 mg strengths (all formulations of 10 mg) out of the chemotherapy indications) for children weighing less than 20 kg (and further restrictions including reinforcement of warning section, and change of prescription classification)..

However, the status of the compound regarding the treatment of children is very different from MS to MS, and the company/MAH stated that in IT, metoclopramide (MTC) has been generally contraindicated in children (below 16 years of age).

Moreover, in the MS NL, the indication for metoclopramide has been restricted by the National Authority to the following indication in children:

“MTC is only indicated for severe nausea and vomiting of known origin, for which treatment with other drugs has shown insufficient effect or is not possible”.

Furthermore, the MAH is submitting the material on behalf of its national subsidiaries comprising only 12 Member States. Therefore, a multitude of MSs and MAHs have not been considered in the material submitted by the applicant, including the one of the Rapporteur (where a different MAH acts as the “originator”).

In Germany, to be given for completeness and as an example for further divergence, the compound is generally licensed for use in children older than 2 years of age, contraindicated in the younger age groups, and certain dosage forms and strengths are restricted to children older than 14 years of age. Treatment of chemotherapy-induced nausea and vomiting is also restricted to children older than 14 years of age. Digestive tract explorations are only licensed for the i.v. form.

No complete overview has been provided as regards the licensing status and the restrictions of use of the compound in the different European countries.

Assessor’s former comment

It appears that the divergent licensing status of the compound within Europe, has prevented the MAH from presenting a clear and outspoken proposal for harmonisation of the paediatric information to be contained in the SPC as regards the indications and dosage. From a regulatory point of view, it appears at the moment uncertain whether any compromise could at all be regarded to be feasible, considering the divergent opinions of the MSs in the past, ranging from a multitude of indications without age restriction to a general contraindication for the paediatric population (up to the age of 16). Therefore, the attitude of the MAH to request the harmonisation of safety information only, may be acceptable. However, it has to be clearly stated that it is outside the scope of an article 45 procedure to achieve a complete safety harmonisation.

The MAH should provide the following:

- *Provide a full overview on the licensing status for children across Europe*
- *Make a clear statement whether a harmonisation of indications and posology is indeed not intended with this article 45 procedure.*
- *Declare whether the proposals made in the core safety document should be a proposal for harmonisation of paediatric information across Europe. If this is the case, the company should check whether all items are indeed suitable for such an article 45 procedure (=whether the information contained does indeed refer to specific paediatric needs only).*

After the receipt of the response to the Request for Supplementary Information, it has now become clear that:

- The MAH does not intend a full harmonisation of the paediatric information for the substance
- The MAH insists in the expression of the full range of indications, posologies, pharmaceutical forms
- The MAH recommends the 2.6 mg/ml oral solution to be the recommended pharmaceutical form in the paediatric population.

For further overview on the response: See Chapter VIII of this AR.

IV. PREVIOUS SCIENTIFIC DISCUSSION

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

No specific information is given on the pharmaceutical formulations used in the clinical studies presented. Almost all studies presented are old studies presented as literature reports that do not include specific information on the pharmaceutical form used.

As already mentioned, the MAH does not clearly present for which pharmaceutical forms the treatment of children is proposed, but only lists all formulations available:

- 10 mg tablets
- 2.6 mg/ml oral solution
- 1% oral solution
- Suppositories of 10 mg and 20 mg
- Injectable solution of 10 mg/2 ml and 100 mg/5ml

It is furthermore stated that for the treatment of children, the 1% oral solutions have been attributed to overdoses, and the 2.6 mg/ml oral solution appears more appropriate. Dosing with 10 mg tablets, and both strengths of suppositories may be difficult in the younger age groups with the missing possibility of weight based dosing adjustments.

The company clearly states that the 2.6 mg/ml oral solution “would be recommended as the most appropriate form in children”.

Assessor’s comment

As presented later, if any recommendation is made, the recommendation would include the injectable solution only to be used in children (see below). Therefore, a specific discussion of the pharmaceutical formulations appears not to be necessary.

IV.2 Non-clinical aspects

1. Introduction

The Applicant states that in a pharmaco-toxicological report on metoclopramide dated 1995 no studies on juvenile animals were reported. The title Part IC: Expert report on the pharmaco-toxicological documentation” suggests that this document was once prepared for regulatory purposes, most likely an application for market authorisation.

The Applicant submitted two non-clinical studies and two published articles which in the opinion of the Applicant do not contain any non-clinical information relevant for the paediatric assessment in the context of this EU work-sharing procedure, but which in one way or the other touch the topic “juvenile animal” or the topic “preparation intended for use in children”.

The MAH submitted two non-clinical study report(s) for metoclopramide

- Etude de la tolérance chez le lapin, Primperan, suppositoires enfants
- Evaluation of the antiemetic potential of intragastrically administered (R)-Zacopride and Metoclopramide: Preliminary study of cisplatin-induced vomiting in the piglet.

and two published articles on non-clinical studies in juvenile animals using metoclopramide:

- Hillemeier C, McCallum R, Oertel R, Gryboski J. Effect of Bethanechol and Metoclopramide on Upper Gastrointestinal mMotility in the Kitten (1986) J Pediatr Gastroenterol Nutr. 5, 134-137

- Gonzales GF, Ortega JG, Salazar M. Effect of neonatal administration of an antidopaminergic drug (metoclopramide) on sexual behaviour of male rats (2000) Archives of andrology 45, 137-142

2. Non clinical studies

Etude de la tolérance chez le lapin, Primperan, suppositoires enfants.

The study is provided in French without English translation. The study is a non-GLP local tolerance study in rabbits dated 1969 using a suppository preparation once intended to be used in children. 6 rabbits, strain "Fauve de Bourgogne" of unknown sex and age (bodyweight 2.5 to 3 kg) were either administered one suppository (containing 10 mg metoclopramide) or vehicle 5 days per week for one month. Three days prior to sacrifice the treatment was stopped. All animals were investigated macroscopically and of three animals of each group histological preparations of the mucosa of the ano-rectal junction were investigated. No histological alterations could be identified in either group.

Evaluation of the antiemetic potential of intragastrically administered (R)-Zacopride and Metoclopramide: Preliminary study of cisplatin-induced vomiting in the piglet.

The study is a non-GLP pharmacodynamic study investigating the antiemetic effect of (R)-zacopride in response to cisplatin in female piglets (4 [controls] to 8 [verum] per treatment group, strain Piétrain or Piétrain–Hampshire [no information provided on the assignment of the different strains to the different treatment groups], mean age 60 days, body weight 5.88 to 9.54 kg), in which metoclopramide was used as a reference substance. Cisplatin (5.5 mg/kg bodyweight intravenously) was injected 45 min prior to intragastric (R)-zacopride (5 mg/kg bodyweight/5 hours) or metoclopramide (15 mg/kg bodyweight/5 hours) administration. Animals were observed for 60 hours. The parameters measured were latency to the first vomiting episode, number of vomiting episodes and nausea episodes during acute phase (during the first 15 hours), during late phase (from start of 16th hour to end of 60th hour) and cumulative vomiting episodes and nausea episodes during acute and late phase.

Whereas (R)-zacopride highly significantly increased the latency to the first vomiting episode and highly significantly reduced the number of vomiting and nausea episodes during acute phase or cumulatively during acute and late phase. Metoclopramide did not alter the latency of the first vomiting episode significantly (2.58 ± 2.36 hours vs. 1.18 ± 0.28 hours for control). Whereas metoclopramide reduced acute (15.75 ± 7.70 vs. 22.13 ± 4.39 for control) and late phase vomiting episodes (4.00 ± 2.62 vs. 6.25 ± 2.71 for control) by large but non-significantly, the cumulative number of vomiting episodes during acute and late phase were reduced significantly (19.75 ± 7.25) compared to control (28.38 ± 4.03). Similar findings were observed for the number of nausea episodes.

Abnormal behaviour (abundant production of fluid saliva and institution of motor activity during which the piglets rubbed their snout against the walls of the observation stalls) was observed in 6 out of 8 piglets treated with metoclopramide, but in none of the (R)-zacopride treated animals.

Hillemeier C, McCallum R, Oertel R, Gryboski J. Effect of Bethanechol and Metoclopramide on Upper Gastrointestinal mMotility in the Kitten (1986) J Pediatr Gastroenterol Nutr. 5, 134-137

The study is a published non-GLP study, comparing the effect of the muscarinic agonist bethanechol (80 µg/kg bodyweight i.m.) and the dopamine antagonist metoclopramide (300 µg/kg bodyweight i.m.) on lower esophageal sphincter pressure, amplitude of esophageal peristalsis, and gastric emptying in kittens aged 5-7 weeks (8-9 animals/group). Both substances did not reveal an effect on esophageal peristalsis. Whereas bethanechol increased the basal lower esophageal sphincter pressure to a large extent (about 13.6 mm Hg), metoclopramid showed only a small and non-significant increase (about 3.1 mm Hg). Whereas bethanechol did not accelerate gastric emptying, metoclopramide caused significantly more rapid gastric emptying (retaining of gastric contents after 10 min of 43%, 49%, and 28.2% for control, bethanechol, and metoclopramide, respectively).

Gonzales GF, Ortega JG, Salazar M. Effect of neonatal administration of an antidopaminergic drug (metoclopramide) on sexual behaviour of male rats (2000) Archives of andrology 45, 137-142

This published non-GLP study investigated the effect of 100 µg of subcutaneously injected metoclopramide in 3 day old male neonatal Holtzman rats on male sexual behaviour (determination of intromission and ejaculation) towards sexually receptive, age-matched female rats at day 90 post injection. Whereas 10 out of 10 control rats exhibited a normal male sexual behaviour pattern (100% intromission, 100% ejaculation), only 4 out of 10 male rats treated neonatally with metoclopramide showed intromission (40%), and for 3 out of 10 (30%) ejaculation could be determined.

3. Discussion on non clinical aspects

The rectal tolerance study in adult rabbits using a suppository formulation once developed for paediatric use is of very limited value for the paediatric assessment of this article 45 procedure.

The Applicant states that the pharmacodynamic studies conducted on metoclopramide to investigate the antiemetic effect in adults after cytotoxic treatment were performed in ferrets and dogs. Therefore, no comparison can be made to the studies in piglets and kittens. Furthermore, the studies did not focus on safety aspects. Abnormal motor behaviour is a known adverse effect of metoclopramide. Therefore, the abnormal behaviour described in the piglet study is not raising new concerns.

In the discussion section of the publication on the effect of treatment of neonatal male rats on sexual behaviour in the adult rat, the authors cite another publication [Le Vay S (1995) A difference in hypothalamus structure between heterosexual and homosexual men. Science 253, 1034-1037] demonstrating that in humans 4 interstitial nuclei of the anterior hypothalamus and in the rat a sexually dimorphic nucleus of the preoptic area are highly interrelated with the typically male sexual behaviour and that its development is dependent on androgenic action during a critical period of brain maturation. In the introduction section of the publication, Gonzales et al. state that the critical period for sexual differentiation of the brain is occurring in humans during prenatal life and in the rat during perinatal development.

Assessor's comments

The position of the Applicant, that the submitted studies and the retrieved published papers do not provide any relevant information for the paediatric assessment in the context of this EU work-sharing procedure is endorsed. Nevertheless, the Applicant is asked to comment, whether the impairment of sexual behaviour seen after administration of metoclopramide to the perinatal rats might be relevant for consideration of therapeutic use of metoclopramide in pregnant women, and whether the current recommendations for use during pregnancy and lactation might need modifications.

IV.3 Clinical aspects

IV.3.1 Introduction

The MAH has divided the clinical overview regarding efficacy in two parts:

The first part introduces into the diseases to be treated and existing treatment guidelines in general and especially for children.

This comprises the following indications and fields of use for MTC:

Nausea and vomiting:

- Chemotherapy induced nausea and vomiting (CIVM)
- Radiotherapy-induced nausea and vomiting (RIVM)
- Postoperative nausea and vomiting (POVM)
- Other situations with nausea and vomiting

Gastrointestinal motility disorders:

- Gastroesophageal reflux disease (GERD)
- Other G.I. motility disorders

Digestive Tract explorations.

In the same order, the single studies, as well as the meta-analyses available are described. The overview makes partly reference to a previously drawn-up overview, which was in fact the “Risk-benefit assessment in children” filed for the AFSSAPS in France, which, does, however, also contain a full description of efficacy.

In this Assessment Report, a brief description of all studies, the ones included in the new overview, and the ones in the Risk-Benefit Assessment (of 2005) will be included.

IV.3.2 Pharmacokinetics

The company altogether presents 4 studies (published reports) for the study of pharmacokinetics of MTC in children, two of which have already been included in the earlier safety review.

The four studies are the following:

1. Study Kearns (Kearns GL et al, J Pediatr Gastroenterol Nutr 1988):

This was a combined PD and PK study in 6 infants (range 0.9 to 5.4 months; mean age 2.59 months) suffering from suspected GERD. MTC was administered as oral solution at a dose of 0.15 mg/kg on the first day, followed by 0.15 mg/kg every six hours for a total of 10 administrations. Blood samples were taken at 0.5, 1.0, 2.0, 4.0, 6.0, 12, 18, and 24 hours after the first dose and again at 0.5, 1, 2, 4, and 6 hours after the last dose.

The results of the study regarding PK are shown in the following table:

Table 1 PK parameters observed in 6 infants at first and 10th oral administration

First administration	Tmax (h)	Cmax (ng/mL)	Kel (h ⁻¹)	T1/2 (h)	AUC (ng.h/mL)	Vd area/F (L/kg)	Cl/F (L/h/kg)
Mean	2.0	29.0	0.14	5.13	357	4.94	0.66
SD	0.5	2.3	0.03		132	0.44	0.16
Tenth administration	Tmax (h)	Cmax (ng/mL)	Kel (h ⁻¹)	T1/2 (h)	AUC (ng.h/mL)	Vd area/F (L/kg)	Cl/F (L/h/kg)
Mean	2.2	56.8	0.17	4.15	260	4.42	0.67
SD	0.4	10.5	0.04		40	0.65	0.14

Of note, the youngest infant (0.9 months) had a marked prolongation in half-life (23.1h), and the authors draw attention to the risk of overdosing in young infants (aged less than 1 month).

The mean values in this study approximately correspond to the ones observed in adults.

2. Study Bateman (Bateman DN et al R. J Clin Phramcol 1983):

In this study, the PK of MTC has been studied in nine children aged 9-14 years. The children received MTC at an i.v. dose of 0.15-0.46 mg/kg b.w. as anti-emetic medication for the prevention of CINV. Plasma sampling was done at 1, 2, 4, and 6 hours post dose. The following results of this study were reported:

Table 2: PK parameters of i.v. dosing of MTC in children aged 7-14:

	Age (years)	Dose (mg/kg)	Half-life (h)	C(0) (ng/ml)	V (l/kg)	CL (l h ⁻¹ kg ⁻¹)
Mean	11.7	0.35	4.4	152	3.0	0.56
± s.e. mean	0.67	0.025	0.56	31	0.38	0.10
Range	7–14	0.22–0.46	1.7–8.3	65–395	1.0–4.8	0.12–1.22

As can be seen, the results achieved appear to correspond quite well with the results of the Kearns study above.

3. Study Pons (Pons G et al Fund Clin Pharmacol 1993)

In this study, 24 infants from 1 to 18 months of age and suffering from GERD were randomly assigned to 3 doses of MTC (0.1, 0.2, or 0.4 mg/kg, and placebo) as oral solution. The study was a PK-PD study.

Plasma concentrations were determined at 1 hour post-dose only. There was a clear dose-dependant increase of plasma concentrations ranging from 2.17, 35.4, to 78.1 ng/ml for the three active treatment groups. The results were found to be in good concordance with the previous results of Kearns et al.

4. Study Kearns (2) (Kearns GL et al; J Clin Pharmacol 1998):

This study was conducted in 10 premature infants with GERD ranging from 31 to 40 weeks of postconceptional age. In this study a single oral (solution) dose of 0.1 or 0.145 mg/kg as given. Blood samples were taken at 0.5, 1., 2, 4, 6, 12, 18, and 24 hours after dosing.

The mean PK parameters for the mean dose of 1.2 mg/kg in this study were 17.72 ng/ml for C_{max}, 2.45 for t_{max}, 0.795 l/hr/kg for Cl/F and 9.78 l/kg for Vd/F.

A prolonged clearance was observed in 30% of the infants studied, and the volume of distribution appeared to be 1.4- to 2.1-fold higher than values reported in previous studies in adults. It was therefore concluded that MTC PK may exhibit a developmental dependency, and the recommendation of the authors was to give 0.15 mg/kg bw to be given every 6 hours for infants older than 31 weeks of postconceptional age.

Assessor's comments

The PK data presented are rather scarce considering the duration of market presence of the product. However, it seems that two things may be concluded from the material presented: PK of MTC in children generally resembles the values observed in adults. However, there seems to be a tendency for reduced clearance of the compound in the very young and premature infants.

Therefore, as a preliminary conclusion, administration of MTC in premature infants and infants younger than 1 month of age cannot be recommended from a PK point of view.

The MAH is therefore requested to justify the use of MTC in young and preterm infants more adequately from a PK point of view. Newer results of studies on the PK and metabolism of the compound and the known facts on the development of metabolic capacities in newborns should be taken into account.

The MAH is also requested to declare whether any harmonised proposal is made regarding the inclusion of PK information for children in the SPC.

IV.3.3 Clinical study(ies) (Efficacy)

The studies in support of efficacy are presented by indication. As the total number of references/studies is so high, no detailed description of the studies will be presented in this AR.

IV.3.3.1 Nausea and Vomiting indications

IV.3.3.1.1 Chemotherapy and Radiotherapy induced nausea and vomiting

For this indication, 9 studies are presented all together.

5 of these studies have been presented in the 2005-safety review and are therefore not included in detail in the new overview. However, in this AR, the studies from the 2005 safety review and the studies presented in the new overview will be presented in the same level of details:

1. Study Köseoglu (Köseoglu V et al; Eur J Pediatr 1998)

This study was a randomised comparative study on the efficacy and safety of ondansetron compared to MTC administered to control nausea and vomiting in 15 children treated with antineoplastic chemotherapy (variety of substances and doses). The mean age of the children was 7.6 years. MTC was administered with a 1 mg/kg i.v. “loading dose” and for a total of 5 days given four times daily orally (pharmaceutical form not stated). The MTC regimen also included the administration of diphenhydramine in order to prevent extrapyramidal side effects. The “continuous dose” remains a little bit unclear as it is given as 0.15 mg/kg per day, with the statement that this has been given four times a day, which would make a total daily dose of 1.45 mg/kg on the first day, and 0.6 mg/kg on the following days. The overall results of the study are shown in the following table:

Table 3: Comparison of anti-emetic efficacy in Study Köseoglu:

Control of emesis	Cisplatin		Non-cisplatin	
	Ondansetron n:9	Metoclopramide¶ n:9	Ondansetron n:23	Metoclopramide¶ n:23
Early period#				
Complete	5*	1	21*	17
Major	3	1	2	1
Minor	1	3	–	1
None	–	4	–	4
Nausea grading				
None	7*	–	22	19
Mild	1	2	1	1
Moderate	1	2	–	2
Severe	–	5	5	1
Late period‡	4*	8	2	6

No serious side effects were seen in the study, however, the overall number of side-effects was 9 in the metoclopramide, and 3 in the ondansetron groups, with 0/5 events referring to extrapyramidal reactions in the ondansetron and MTC groups, respectively.

Assessor’s comment

MTC is clearly inferior to ondansetron. Of note is the high number of extrapyramidal reactions despite prophylactic treatment.

2. Study Dick et al: (Dick GAS Arch Dis Child 1995):

This randomised study was comparing ondansetron and metoclopramide plus dexamethasone (unblinded trial).

30 patients aged 18 months to 15 years were included. All of them received UKALL IV intensification chemotherapy consisting of vincristine, daunorubicin, etoposide, cytarabine, and prednisolone.

MTC was administered as a 10 mg/m² starting dose and the same continuing dose administered every six hours (all administered as i.v. dosing). Procyclidine 2.5 mg was administered to prevent extrapyramidal reactions. Dexamethasone was given as a 5 mg/m² i.v.-starting dose and half the dose administered three times daily p.o.

During the first 24 hours, 93% of the children treated with ondansetron achieved complete or major response, compared to 33% who received the MTC/dexamethasone regimen. Of the 15 children receiving MTC, 10 were changed to ondansetron (as planned escape procedure in case of failure). Adverse event reporting is not included in the literature report.

Assessor's comment

Again, MTC is inferior to ondansetron, despite combination treatment with dexamethasone.

3. Study Allen (Allen JC et al; J Clin Oncol 1985):

This study was a dose-escalation study to establish the safe dose range of MTC and study the efficacy of MTC as antiemetic in children receiving cancer chemotherapy.

45 patients age 7 to 22 years (mean 16 years) were included. All patients received either cisplatin, and/or cyclophosphamide.

In phase I of the trial, the dose was increased in 9 steps from 0.2 mg/kg to 3 mg/kg given intravenously in 35 patients. In part of the patients, diphenhydramine was given additionally to prevent extrapyramidal effects. The results of this part of the study were not reported in detail; however, a "safe dose" of 2 mg/kg was established. The second part of the study was conducted in 10 patients receiving chemotherapy (and the MTC regimen) for the first time.

The efficacy results of the study are given in the following table:

Table 4. Antiemetic Efficacy of Metoclopramide (2 mg/kg) Plus Diphenhydramine (0.5 mg/kg) on Day 1

Chemotherapy Experience	No. of Patient Trials	Antiemetic Response (Vomiting Episode/24 h)			
		Major (0-2)	Minor (3-5)	Equivocal (6-8)	Failure (>8)
Previously treated	21	3 (14%)	6 (29%)	5 (24%)	7 (33%)
New	10	4	3	2	1

The overall results regarding safety are shown in the following table:

Table 5: MTC dose-related toxicity during first 24 hours

Table 3. Metoclopramide Dose-Related Toxicity During First 24 Hours

MCP Dose	No. of Patient Trials	Sedation*		Hiccoughs	Diarrhea		Akathisia	Extrapyramidal Reactions
		+1	+2		+1	+2		
0.2	2	2†						
0.5	3	1		1				
0.75	3	1		2			1	
1.0	3		1		3			
1.33	5	1		2	1			
1.67	5	3		1	1			
2.0	21	14	1	3	1	1	5	3
2.5	3	2					1	
3.0	3	2		1	1		3	1
Total	48	26	2	10	7	1	10	4

No clear conclusions were drawn from the study apart from the one that randomised trials should be conducted in children, because CINV had the same negative implications as in adults.

Assessor's comments

Only limited conclusions can be drawn from this study because of the missing control group and special study design. Of note are the total of sedation and extrapyramidal reactions observed (despite widespread use of prophylaxis).

4. Study Graham-Pole (Graham-Pole J et al: J Clin Oncol 1986):

This study was a randomised comparative, double-blind study comparing MTC with chlorpromazine. It was conducted in 50 cancer patients aged 6 to 18 years receiving a variety of chemotherapies. MTC was administered i.v. (30 minutes infusion) at a dose of 0.5 mg/kg up to 5 times daily (every 3 hours). Extrapyramidal effects were treated with diphenhydramine, if occurring.

Chlorpromazine was significantly better than MTC in reducing both the frequency and the duration of nausea and vomiting. Also extrapyramidal reactions were more common in MCT-treated patients.

Assessor's comments

The study does not speak in favour of the use of MTC in CINV. Despite a relatively high dose (up to 2.5 mg/kg b.w. per day), which is higher than the one postulated to be safe by the MAH, MTC was inferior to chlorpromazine. Of note, this trial was a decisive successor trial of the one by Allen mentioned above, and therefore failed to prove usefulness of MTC in CINV with an increased rate of adverse effects compared to chlorpromazine.

5. Study Howrie (Howrie DL et al: Drug Intell Clin Phram 1986):

This is a case-collection study with 11 paediatric oncology patients only. Data were collected during 22 courses of chemotherapy. The dosage used was 1 mg/kg 2-3 times daily up to 2 mg 5 times within 8.5 hours.

In these series, 7 of 11 children reported subjective benefit compared with the previous antiemetic response. MTC effectively reduced the volume of emesis per 24 hour period compared to the historical control. Acute dystonic reactions developed in 5/11 patients, mostly in the high dose regimens.

Assessor's comments

Again the study is to be regarded to be of limited value. No control group is included, as well as the doses are higher than the ones proposed by the MAH.

6. Study Benz-Lemoine (Study report by MAH 1988):

This study is submitted in French original language only, without translation. Therefore, the main features of the study are taken from the description in the clinical overview only.

This was a randomised, controlled double-blind study that compared MTC to alizapride, both administered as oral solution during one cycle of chemotherapy. The daily dose of MTC was 0.5 mg/kg. 92 patients from 8 centres with a mean age of 7.5 years were included. Despite requiring a haematological malignancy as inclusion criterion, 2 case of osteosarcoma, 3 cases of neuroblastoma, 1 case of renal adenocarcinoma, and 1 neuroblastoma were included. Of the haematological neoplasias, most were lymphoblastic leukaemia, NHL- and Hodgkin lymphomas. A variety of antineoplastic substances was administered.

Study drop-outs prior to finalisation of the study were 2 in the alizapride and 4 in the MTC groups.

The primary efficacy criterion was the global assessment by the investigator, which was given on a VAS scale. This was 67.5 for alizapride, and 64.4 for MTC (non-significant). The global assessment on a 4-part categorical scale was "excellent" or "good" for 80.9% of the cases for MTC and 77.2% for alizapride (n.s.). All other criteria were also not significantly different, with no clear tendency for one or the other treatment.

Adverse events were reported in 6.8% and 10.4% in the alizapride and MTC groups, respectively.

Assessor's comment

Regardless of the fact that this study has deficiencies regarding the design (no non-inferiority hypothesis tested etc), the problem with any conclusion is that the comparator is largely undefined for efficacy. In the MS Germany, the substance is licensed for the prevention of nausea and vomiting related to chemotherapy, radiotherapy and postoperatively. However, the compound has been contraindicated for children younger than 14 years of age.

7. Study Labar (Labar B et al. Libri Oncol 1995)

This was a randomised double-blind clinical trial comparing ondansetron with metoclopramide for the prophylaxis of vomiting and nausea induced by conditioning regimen before bone marrow transplantation (various cytotoxic substances and radiation).

The antiemetic prophylaxis started 8 days prior to marrow infusion and lasted until day 6 after BMT.

MTC was given as a 1 mg/kg per day infusion regimen (for the whole 15 days). 24 and 28 patients in the two groups were included and their age was in the range of 15 to 51 with an unknown number of patients younger than 18 years.

The mean grade of vomiting and nausea was significantly less severe in the ondansetron group compared with the mean grade in the MTC group. Patients who received ondansetron experienced also less severe stomach discomfort.

Regarding adverse effects, 4 and 0 events with extrapyramidal adverse effects and 5 and 2 with headache occurred in the MTC and ondansetron groups, respectively, with 1 event of bone pain each.

Assessor's comment

Known superiority of ondansetron over MTC has been confirmed in this study. Also, adverse event profile appears to be better for ondansetron. Treatment regimen (1 mg/kg daily dose) and age range of the included patients appear not to be relevant for the current assessment.

8. Study Basade (Basade M et al Indian Pediatr 1996):

This was a randomised, single-blind cross-over study in patients >15 years of age with malignancies receiving cyclophosphamide based chemotherapy.

Treatment regimes were either dexamethasone or MTC at a dose of 1.5 mg/kg i.v. 15 minutes prior to chemotherapy. Cross-over took place before the next chemotherapy cycle.

27 children were included in this study. The age range was 3 to 14 years (median: 7). Complete response for vomiting and nausea were significantly greater with dexamethasone (16 vs. 8 and 15 vs. 8 patients).

Adverse events were altogether occurring in 11 patients in the MTC and 3 in the dexamethasone group. Most frequent adverse events in the MTC group were lack of appetite (4), depression (3), and abdominal discomfort (2).

Assessor's comment

Inferiority of MTC vs. dexamethasone has to be concluded from this study. Furthermore, the treatment regimen uses a relatively high (single) dose of MTC. Adverse event profile also seems worse than with dexamethasone. However, the patient population appears to be relatively irrelevant for the overall assessment of the safety and efficacy in children.

9. Study Luisi (Luisi FA et al: Sao Paolo Med J 2006):

This was a randomised open trial comparing efficacy and safety of MTC (administered with dimenhydrat) with granisetron. A total of 26 patients suffering from osteosarcoma and receiving chemotherapy with a regimen containing iphosphamide, epirubicin and/or carboplatin. 80 chemotherapy treatment cycles were included. Patients were a mean 14 years of age with an age range of 7-19. The dose of MTC was 2 mg/kg.

The following table shows the main study results:

Table 6: Overall antiemetic efficacy of MTC and granisetron in children:

Response	Points	Drug	
		Metoclopramide	Granisetron
Complete	0	(4/40) 10.0%	(25/40) 62.5%*
Partial	0 to 10	(14/40) 35.0%	(13/40) 32.5%
Minimum	11 to 20	(17/40) 42.5%	(2/40) 5.0%
Absence	More than 20	(5/40) 12.5%	(0/40) 0%
Total		(40/40) 100%	(40/40) 100%

*p < 0.0001.

Only the incidence of somnolence was reported, which was 0 in the granisetron group, and 7.5% in the MTC group.

Assessor's comments

Again, inferiority to a serotonin antagonist is described, and again, a relatively high dose has been used in this study, which is generally not recommended by the MAH.

In their introductory part to the description of the single studies for CINV, the company also refers to several guidelines for the treatment of this disorder. These guidelines all clearly recommend the use of a 5-HT3 receptor antagonist and dexamethasone in combination in children receiving highly or moderately emetogenic chemotherapy.

From the studies documenting inferior efficacy to ondansetron and considering the extrapyramidal side-effects, the company concludes that MTC should not be used as first-line treatment in children, but advocates that those children not adequately responding to standard treatment might benefit from the substitution of a 5-HT3 antagonist and/or the addition of another antiemetic agent.

Two reviews are presented in support of this conclusion, which recommend a dose of 0.1-0.2 mg/kg/dose every 6 hours with a maximum dose of 15 mg q6h.

Assessor's comment/Overall conclusion on CINV indication

Efficacy of MTC in the treatment of CINV appears to be doubtful. There are several studies documenting inferiority to the established substances dexamethasone and 5-HT antagonists. Also, in most of the studies presented, treatment regimens and doses have been used that are beyond the 0.5 mg/kg dose that is recommended and regarded to be safe in the paediatric population by the MAH.

The proposal regarding a "second line" treatment with MTC is not supported by data, as no data on those patients not sufficiently treated or with tolerability problems regarding established medicines are available. Regarding these patients, it is completely unclear which dose would have to be used, and how tolerability would turn out, when e.g. intolerance to other compounds is already present and a combination treatment is then administered. It appears unclear on which data the recommendation of the two reviews referenced are based upon. The applicant should clarify this.

Almost all studies used i.v. route of administration. Therefore, it appears also unclear whether an oral treatment is at all suitable for the treatment of CINV.

At the moment, the treatment of CINV in children cannot be recommended and should not be included in any harmonised recommendation for the treatment of children with MTC unless further material in support of this indication can be presented.

IV.3.3.1.2 Postoperative Nausea and Vomiting

For this indication, 24 studies are presented altogether.

16 of these studies have been presented in the 2005-safety review and are therefore not included in detail in the new overview. 8 new studies are also presented. In this AR, all 24 references are briefly described and assessed.

Study Ferrari (Ferrari LR et al: Anesth Analg 1992):

This study was a randomised, double-blind, placebo controlled study comparing MTC with placebo. The dose administered was 0.15 mg/kg as an IV injection after the transfer to post-anaesthesia unit. 102 children with a mean age of 6.5 and 6.1 years of age (placebo and MTC groups, respectively) that underwent tonsillectomy were included. Vomiting occurred in 47% of the patients in the MTC group, and 70% in the placebo group (p=0.026). Frequency of vomiting was 1.1 in the MTC group, and 3.1 in the placebo group. Time to vomiting was also significantly longer with MTC than with placebo (6.4 hours vs. 5.6 hours; p<0.001). No side effects are reported in this publication.

Study Broadman: (Broadman LM et al: Anesthesiology 1990):

This study was also a randomised, double-blind, placebo controlled study, conducted in strabismus patients with an age range of 2 to 18 years. MTC was administered at a dose of 0.15 mg/kg intravenously after postoperative transfer to the postanesthesia recovery room. 126 children were included. The incidence of postoperative vomiting was 35% in the MTC vs. 59% in the placebo group. The mean discharge time was 207.5 min and 248.8 min in the MTC and placebo groups, respectively (differences all statistically significant). Again, adverse reactions were not observed in this study.

Assessor's comment

Clear efficacy against placebo has been shown in these two studies.

Study Lin (Lin DM et al: Anesthesiology 1992)

This was a randomised double blind study comparing MTC at two dose levels (0.15 mg/kg and 0.25 mg/kg) with droperidol 0.075 mg/kg i.v. and placebo. MTC was administered i.v. as a single injection after the induction of anaesthesia and before the start of surgery. 110 patients (mean age 43-62 months) undergoing strabismus surgery were included.

The incidence of POV was 88% in the placebo group, and 29% and 33% in the high MTC dose group (difference statistically significant), whereas it was 68% in the low dose MTC group (not significant). Hospital stay in the droperidol and high dose MTC group were significantly shorter than with control. Again, no side effects were reported.

Assessor's comment

The dose showing efficacy in the first two studies was not efficacious in this study. However, the administration in this study was different, as the study medication was given preoperatively. Therefore, preoperative medication with MTC obviously needs higher doses.

Study Liu (Liu YC et al: Acta Anaesthesiol 1992)

This was a randomised double-blind study comparing MTC 0.15 mg/kg i.v. with placebo, ephedrine 0.5 mg/kg i.m., ephedrine 1.0 mg/kg o.m., and droperidol 50µg/kg i.v. 100 patients undergoing inguinal hernioplasty were included. The mean age of the patients was between 6.5 and 7.0 years.

In this study, ephedrine turned out to be completely ineffective, whereas droperidol, as well as MTC had clearly decreased rates of POVN. Duration of somnolence, time to discharge and time to orientation was shorter with MTC than with droperidol. The authors concluded that MTC was a more suitable agent than droperidol for paediatric outpatient surgery. Further adverse events were again not reported.

Assessor's comment

The 0.15 mg/kg i.v. dose is again superior to placebo when administered after surgery.

Study Fuji (Fuji Y et al: J Pediatr Surgery 2001):

This study was a randomised, double-blind trial comparing granisetron 40 µg/kg, droperidol 50µg/kg, and metoclopramide 0.25 mg/kg given intravenously after induction of anaesthesia. 90 patients undergoing tonsillectomy were included with an age range of 4-10 years (mean age: 6.5 years). All patients were required to have a history of motion sickness (as marker of increased risk for POVN).

The rate of emesis free patients in the three groups were 73%, 23%, and 20% in the granisetron, droperidol, and MTC groups (granisetron statistically significantly superior to the other two groups. The level of sedation was not different between the groups. There were not differences regarding adverse events, with headache and constipation being the only events reported.

Assessor's comment

Again, MTC was administered before surgery, and turned out to be inferior to granisetron.

Study Bach-Syles (Bach-Styles T et al: The Clinical Forum for Nurse Anesthetists 1997):

This was a randomised double-blind placebo and ondansetron-controlled study for metoclopramide (0.25 mg/kg i.v.) in patients undergoing elective ophthalmic surgery. Study drug administration was done after induction of anaesthesia, before start of surgical manipulation. 101 children aged between 1 and 17 years were included.

The overall incidence of vomiting was 36% in the placebo group, 45% in the metoclopramide group, and 17% in the granisetron group, patient satisfaction was also not different between MTC and placebo, whereas it was significantly different with granisetron.

Adverse event reporting was not included in the study.

Assessor's comment

Again, administration before surgery did not result in superiority over placebo.

Study Stene (Stene EN et al: J Clin Anesth 1996):

This was a randomised, placebo controlled study comparing metoclopramide 0.25 mg/kg i.v. to ondansetron 0.15 mg/kg and placebo. 132 children aged 2-12 years of age undergoing tonsillectomy were

included. Study medication was administered after induction of anaesthesia, before surgical procedure started.

The rate of postoperative vomiting was 54% with MTC, 26% with ondansetron, and 69% with placebo. Statistically, ondansetron was superior to placebo and MTC, whereas the difference between MTC and placebo was not significant. The rate for early vomiting, however, was 50% for placebo, 12% for ondansetron, and 17% for MTC.

Assessor's comment

Again, MTC was inferior to a serotonin-antagonist, and not significantly different from placebo. Again MTC was administered before surgery started.

Study Scuderi (Scuderi PE et al: J Clin Anaesthesia 1997):

This was a randomised 4-treatment group study comparing MTC (0.25 mg/kg i.v.) to ondansetron, droperidol, and placebo. 160 patients aged 1 to 16 (mean 3.5 to 4.6 years) undergoing strabismus surgery were included. Administration of study drugs was before start of surgical procedures, after induction of anaesthesia. Incidence of vomiting was 32% and 25% in the MTC and placebo groups, whereas the incidence was 5% in the droperidol and ondansetron groups (both statistically significantly superior to placebo and MTC).

Assessor's comment

Again, no superiority vs. placebo, and inferiority of MTC to 5-HT antagonist with administration before surgery.

Study Shende (Shende D et al: Anaesthesia 1997):

This was a double blind study comparing metoclopramide (0.25 mg/kg i.v.) with ondansetron, and placebo. 176 patients aged 9 months to 12 years of age undergoing strabismus surgery were included (exclusion of those with motion sickness). Also in this study, study medication was given before surgical procedures.

Emesis was observed in 71.7% of the children in the placebo, 34.4% in the ondansetron, and 61.4% in the MTC group. Ondansetron was statistically significantly superior to both groups. Statistical evaluation regarding the comparison of MTC and placebo is not provided by this study. Adverse events were reported for ondansetron (2 each for headache and abdominal cramps) and for MTC (four patients with headache).

Assessor's comment

Again inferiority to the 5-HT antagonist is shown, with uncertain result regarding the comparison to placebo. However, no clear difference can be seen from a clinical point of view. Again, study medication was administered before surgery.

Study Furst (Furst SR et al: Anesthesiology 1994):

This study was double-blind and compared MTC (0.5 mg/kg i.v.) with ondansetron and droperidol, as well as with placebo. 256 patients undergoing tonsillectomy were included. Patients were aged between 2 and 12 years of age, with a mean age of 5.6 years. Study drug administration was after induction of anaesthesia but before start of surgery. The "non-emesis-rate" was 84% for ondansetron, 52% for droperidol, and 46%, and 43% for MTC and placebo. Ondansetron was statistically significantly superior to all other treatments.

Extrapyramidal reactions were not observed in the study, although adverse event reporting appears to be incomplete.

Assessor's comment

Although, again, statistical evaluation comparing MTC and placebo is not included, it is again clear that MTC is inferior to the 5-HT antagonist and, again not relevantly different from placebo. Again administration was pre-surgery.

Study Kymer (Kymer PJ et al: J Clin Anesth 1995):

This study compared the oral administration of MTC (0.15/kg) with either droperidol (300 mg/kg), and the combination of both, as well as placebo, all given as oral medication. Study medication was given 1 to 1.5 hours prior to start of the operation. 145 children aged 1 to 15 years (mean 47 to 53 months) undergoing strabismus surgery were included.

The number of children vomiting during the first 24 hours was 27% in the droperidol, 22% in the combination treatment group, and 62% in the MTC, and 56% in the placebo groups. The difference between the droperidol and the combination group in comparison to the other two groups were statistically significant.

Adverse event reporting is not included in the literature report.

Assessor's comment

Again, no efficacy of MTC can be concluded. However, this was administration even before induction of anaesthesia, and oral administration.

Study Fujii 2002 (Fujii Y et al: Ophtahalmologica 2002):

This double blind study compared MTC (0.25 mg/kg i.v.) with granisetron, and droperidol.

120 children aged 4 to 10 (mean age 6.7 to 7.0 years) undergoing strabismus surgery were included in the trial. Study drug administration was done only after first vomiting (up to 3 hours postoperatively) occurred and patients then observed for a further 24 hours. The rate of emesis free patients was 88% with ondansetron, 63% with droperidol, and 58% with MTC. Granisetron was statistically significantly superior to both comparators, whereas the difference between droperidol and MTC was not statistically significant. Serious adverse events were not reported, but detailed adverse event reporting is not included in this literature report.

Assessor's comment

Known superiority of granisetron confirmed. No further conclusion possible due to missing placebo group.

Study Rose (Rose JB et al: Paediatric Anaesthesia 1996):

This was a randomised, double-blind, placebo controlled study comparing MTC 0.25 mg/kg i.v. per dose with ondansetron and placebo.

Study drug was administered with a first dose pre-anaesthesia (half of the patients), and a second dose was administered 1 hour after completion of the surgery (also half of the patients (thus a 5-group comparison was performed).

212 children undergoing tonsillectomy were included. The mean age of the patients was 78 to 92 months. The rate of vomiting patients was 50% for placebo, 40% for those receiving one dose of MTC, and 23% for those receiving one dose of ondansetron. The rate for the two-dose administration was 18% for MTC, and 8% for ondansetron. The comparison for the two-dose administration of MTC with placebo was statistically significant, whereas there was not significant difference for the two ondansetron groups to the twice-administration MTC group.

Adverse event reporting was not included in the literature report.

Assessor's comment

This study shows that administration before and after surgery results in superior efficacy for MTC compared to placebo. Again ondansetron is better, but MTC with twice administration has acceptable results regarding efficacy, whereas pre-operative administration alone does not relevantly influence occurrence of vomiting.

Study Fujii 1998 (Fujii Y et al: *Pediatr Anaesth* 1998):

This double-blind study compared droperidol, granisetron, and MTC with placebo. MTC dose was 0.25 mg/kg and study drug administration was before the start of the surgical procedure.

100 patients aged 4-10 (mean age approx. 6.5 years) undergoing surgery of the extremities, inguinal hernia repair or resection of phimosis were included. Patients with a history of motion sickness were excluded.

The rate of emesis free patients was 60% with placebo, 76% with droperidol, 68% with MTC, and 88% with granisetron.

Adverse events were generally mild and comprised mainly headache and drowsiness with incidences of 20% for placebo, 24% for droperidol, 20 for MTC, and 25% for granisetron).

The difference between MTC and placebo was not statistically significant.

Assessor's comment

Again, no evidence for efficacy for pre-operative administration of MTC in PONV can be provided.

Study Calamandrei 1994 (Calamandrei M et al: *Cehiers d' Anesthésiologie* 1994)

This literature report is provided with French original with English abstract only.

The study compared metoclopramide (0.12 mg/kg i.v.) with ondansetron and placebo. The study comprised 60 children aged 4-12 undergoing either hernia repair or orchidopexy. Patients with a history of motion sickness were excluded. Study drug administration was before surgery.

The incidence of vomiting was 0% with ondansetron, 10% with placebo, and 25% for MTC. The difference between ondansetron and MTC was statistically significant.

Adverse event reporting was not included in the literature report.

Assessor's comment

Again, results from studies above are confirmed. Pre-operative administration of MTC does not seem to be efficacious.

Study Mjehed (Mjehed K et al: *Ann Fr Anesth Reanim* 1996):

Again, this study has only been submitted in French language with English abstract.

The study compared oral ondansetron with oral MTC without placebo group.

30 patients undergoing strabismus surgery were included, mean age was 9 years.

Study drug administration was three times: 1 hour before induction of anaesthesia, and 8 and 16 hours after anaesthesia. Dose was 4 mg for ondansetron, and 5 mg for metoclopramide.

Rate of vomiting and nausea was 53% and 40% for ondansetron, and 60% and 33% for MTC.

The authors conclude that oral ondansetron was – contrary to i.v. ondansetron – not superior to MTC.

Adverse event reporting was not included in the study report.

Assessor's comment

The study is of course of limited size, and of limited value regarding the overall evaluation of (oral) MTC. Of note, the total dose administered (with the mean weight of the patients being approx. 30 kg) is 0.5 mg/kg. Overall, however, a conclusion of efficacy of MTC in the indication under discussion cannot be drawn.

8 additional, more recent studies are presented in the clinical overview of the article 45 procedure. These studies are the following:

Study Fujii (Fujii Y et al: Can J Anaesth 1996):

This study was a randomised, double-blind study comparing granisetron with placebo and MTC.

70 patients aged 4-10 years (mean approx. 6.5 years) were included that underwent strabismus surgery or tonsillectomy (with or without adenoidectomy). Patients with a history of motion sickness were excluded. Study medication was administered before surgery; MTC dose was 0.25 mg/kg i.v.

The rate of patients with vomiting was 4%, 9%, and 29% in the granisetron, MTC and placebo groups, respectively, and the rates of retching was 9%, 13%, and 33% in the first 3 hours, whereas in the hours 3-24 these rates were: 4%, 13%, and 17%, and 9%, 26%, and 33%.

The difference between MTC and placebo was only significant for the first time period.

The number of adverse events was 6, 5, and 5 in the placebo, MTC, and granisetron group respectively, with most events occurring as headache and drowsiness.

Assessor's comment

This study reports an interesting subgroup analysis for different time-points, whereby it can be concluded that the duration of action of MTC is not long enough to provide 24 hours efficacy, but only short-term efficacy (up to 3 hours) when given before surgery.

Study Ercelen (Ercelen O et al Acta Anesth Italica 1996):

This was a randomised, placebo-controlled study comparing droperidol, MTC, ondansetron, and placebo. Study drug administration was after induction of anaesthesia, before surgery. 100 children with an approx. mean age of 7 years undergoing strabismus surgery were included.

MTC was administered at a dose of 0.1 mg/kg.

The percentage of postoperative nausea and vomiting was 8% for ondansetron, 12 % for droperidol, 44% for MTC, and 48% for placebo. Droperidol and ondansetron were statistically significantly superior to MTC and placebo. Statistical evaluation is not reported for the comparison of MTC and placebo.

Adverse event reporting is not included in the literature report.

Assessor's comment

The results of the previous studies are more or less confirmed. Of note, the lower dose of 0.1 mg/kg was tested in the first study presented here, but did not appear to be efficacious.

Study Scuderi (Scuderi PE et al: J Clin Anesth 1997):

This double-blind randomised study compared ondansetron, droperidol, MTC and placebo.

160 patients aged 1 to 12 years of age (mean age about 4 years) undergoing strabismus surgery were included. MTC was administered at a dose of 0.25 mg/kg i.v. after induction of anaesthesia but before surgery.

The rate of emesis was 5% each for droperidol and ondansetron, whereas it was 33% for MTC and 25% for placebo.

However, there were no differences between the groups for post-discharge vomiting.

Adverse events reporting is not included in the study report.

Assessor's comment

Results of previous studies confirmed.

Study Daftary (Daftary S et al: J Anaesth Clin Phramcol 1998):

This double blind study compared ondansetron with MTC and placebo. 150 Patients aged 4 or above (mean age around 12 years) undergoing tonsillectomy were included.

Study drug was administered before induction of anaesthesia; MTC dose was 0.2 mg/kg i.v..

The incidence of nausea was 32% in the ondansetron group, and 60% and 50% in the placebo and MTC groups. The incidence of vomiting was 22%, 42%, and 38% in the three groups. The difference to ondansetron was statistically significant, whereas the difference between MTC and placebo was not.

Adverse events occurred as headache and dizziness, with two patients in the placebo, and 1 each in the ondansetron and MTC groups.

Assessor's comments

Results of previous studies confirmed. Of note, dose of MTC was slightly different.

Study Kathirvel (Kathirvel S et al: Europ J Anaesthesiol 1999):

This randomised double-blind study evaluated the combination of ondansetron and MTC (0.15 mg/kg) in comparison to MTC (0.25 mg/kg i.v.), placebo, ondansetron, and placebo.

100 children aged 1-15 years (mean age approx 6 years) undergoing strabismus surgery were included. Study medication was administered before induction of anaesthesia.

Emesis incidence was 72% for placebo, 40% for ondansetron, 60% for MTC, and 44% for the combination. The difference between ondansetron and the combination from placebo was statistically significant, whereas all other comparisons were not.

No separate adverse event reporting is included in the literature report. However, no excessive residual sedation is reported in any of the groups.

Assessor's comment

The results of the previous studies are again confirmed. However, it appears that no additional effect can be achieved with MTC administered together with a 5-HT antagonist.

Study Butkovic (Butkovic D et al: Paediatric Anaesthesia 2005):

This study compared laser acupuncture with MTC. 120 children undergoing hernia repair, circumcision, or oclidopexy with an aged 5-14 years (mean age approx 7.7 years) were included. Patients with a history of motion sickness were excluded.

The patients were assigned into one of three treatment groups: The first group received laser acupuncture 15 min before the induction of anaesthesia (and placebo), the second group received MTC 0.15 mg/kg i.v. (and sham laser), and the third group received placebo (and sham laser).

During the first two hours, the rates of vomiting and retching were 12.5%, 10%, and 40% for the acupuncture, MTC, and placebo/sham group, and for the hours 2-6 these rates were 7.5%, 7.5% and 15% for these two groups, and for 6-24 0%, 0%, and 4%.

Statistical significance could be shown for both groups against placebo/sham for the first two hours only.

Adverse event reporting was not included in the literature report.

Assessor's comment

This study is the first study that is able to show efficacy of MTC in the administration of the drug before the start of surgery. Of note, this result was achieved with the relatively low dose of 0.1 mg/kg only.

Study Gunter (Gunter JB et al: Paediatric Anaesthesia 2006):

This was a factorial study with a rather complicated design.

240 children scheduled for adenotonsillectomy were randomised to one of the following 15 combination groups including ondansetron 0-60 µg/kg, MTC (0-400 µg/kg, and/or dexamethasone 0-500 µg/kg.

Using multivariate logistic regression, models were generated for the probability of emesis before discharge, after discharge and overall for 24 hours.

The odds of emesis increased by a factor of 3 to 4 for children older than 7 years. Before discharge, a decrease of the odds for emesis was seen by factor 0.29 for each of 15 µg/kg dose of ondansetron, and by a factor of 0.37 for each of 100 µg/kg for MTC. After discharge, the decrease in odds was by factor 0.67 for each of 125 µg/kg dexamethasone. Over 24 hours, odds of emesis decreased with all three medications. A negative interaction was seen for the combination of ondansetron and MTC, reducing the efficacy of the combination.

Assessor's comment

The results of this study are not easy to assess. However, contrary to the conclusion of the authors, the negative interaction seen between MTC and ondansetron for the combination of the two only confirms the results of the previous study seen above, and would therefore not be regarded to be surprising. The study does not report at what time-point study drugs were administered, and is therefore to be regarded to be of limited value regarding this question. As results for the single dose groups are not reported, only the dose-response relationship for the included medications can be confirmed. As no adverse event reporting is included, also, no risk-benefit assessment for increasing doses is possible. Overall, the study is therefore considered to be of limited value.

Study Bolton (Bolton CM et al: Bri J Anaesthesia 2007)

This is the largest study included in the dataset, involving 557 children (aged approx. 5 years mean) undergoing tonsillectomy (with or without adenoidectomy). The study compared MTC (0.5 mg/kg) with ondansetron 0.2 mg/kg. All patients received a background medication of 0.1 mg/kg dexamethasone. The study drug was administered after induction of anaesthesia.

The primary outcome was any vomit before discharge from hospital.

The study was planned as a non-inferiority study where the expected and acceptable delta was set to 7.5% in the overall vomiting rate.

An unscheduled interim analysis was performed in this study after 2 years due to slow recruitment; however, the assumptions made were allegedly confirmed.

The vomiting rates were 37.3% with MTC, and 25.3% with ondansetron, showing an absolute difference of 12.0% and a significant superiority of ondansetron. This was confirmed with further investigations, like, e.g. time to first vomiting.

Adverse event reporting is not included in the literature report.

Assessor's comment

This is the first study investigating this relatively high dose of 0.5 mg/kg. The study was, however, only able to confirm the known inferiority of MTC compared to ondansetron. Therefore, it will remain unknown, whether this high dose will perform any better than the doses of the previously reported trials with pre-surgery administration that used lower doses (up to 0.25 mg/kg). A clear conclusion regarding the overall assessment of the indication is therefore not possible with this study, all the more – despite the high numbers of patients – adverse event reporting was obviously completely neglected by the authors.

The company further presents two Cochrane based reviews and meta-analyses, both published in 2006.

- Study Carlisle (Carlisle B et al: Cochrane Review 2006)

The applicant presents the 2006 version of this (meanwhile updated) review. This meta-analysis included 737 studies altogether, involving 103,237 people with approximately 76% of women, and 24% men; 78% adults and 22% children. Sixty drugs were studied. The review concludes that eight drugs are effective in preventing PONV: droperidol, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine, granisetron, and MTC.

Regarding MTC compared to placebo, the relative risk was 0.76 (0.70-0.81) for prevention of vomiting, and 0.76 (0.70 to 0.82) for prevention of PONV.

The comparison of MTC with dolasetron, domperidone, and tropisetron was not significantly different. There was also no evidence for a difference in the risk of side effects for MTC compared to placebo.

A difference in outcome was not detected in the included studies regarding the age of the patients, type of operation, gender, and timing of administration. The confidence intervals for all outcomes in children and adults overlapped.

The funnel plots did not indicate asymmetry for MTC.

Assessor's comment

This meta-analysis provides overwhelming evidence of overall efficacy of MTC in the prevention of PONV. However, there is not clear separate display of the data for children. Therefore, the data cannot be taken to disregard the conclusions from the 24 studies analysed above.

- Study Bolton (Bolton CM et al. BMJ 2007):

This meta-analysis analysed the data for the prevention of PONV in children after tonsillectomy (with or without adenoidectomy). It is therefore clearly more suitable for the assessment of the use of MTC in children, than the a.m. overall meta-analysis.

22 of the 92 identified studies met the inclusion criteria for the meta-analysis.

For MTC, only four studies were included, of which all have already been included in the 24 studies above (Studies Furst, Ferrari, Stene and Rose). One additional study was included; however, this study used only a 4-hour endpoint for the assessment of the prevention of nausea and vomiting. The overall effect for MTC doses of 0.15 to 0.5 mg/kg b.w. yielded an OR for MTC of 0.51 (0.22-0.68). A sensitivity analysis was performed excluding the “weaker” trials, however, results were similar. There was also no evidence of heterogeneity and no evidence that the effect of MTC varied according to dose.

Assessor’s comments

With this meta-analysis, there is additional evidence for efficacy of the compound in general. Two of the included studies were not able to show a statistically significant effect on their own (Stene and Furst), which were those that administered the dose pre-surgery. The study by Rose and Ferrari were those that either had their dose given after surgery (Ferrari), or were able to show a non-significant effect with one dose given after surgery, and a significant effect with two doses (one before, and one after surgery) (Study Rose).

Overall conclusion on prevention of PONV

The efficacy of MTC in the prevention of PONV has been shown in several studies. However, obviously, the efficacy of MTC, and the magnitude of its effect, is dependent on the timing of dosing. Whereas many studies showed that when MTC is given before surgery, there is only an inconsistent, and clinically marginally relevant, and almost always not statistically significant treatment effect, the studies that administered the dose after surgery were more consistent and showed a clear effect of MTC. Although the pooled evaluation of data (whether for adults or for children) revealed superiority of MTC over placebo, it is considered that the recommendation for the administration of MTC in this indication should clearly also take the timing of dosing into account. Therefore, a proposal to be included in any SPC for MTC should recommend that the dose be administered after termination of the surgical procedure.

As regards the recommended dose, the single studies and the meta-analysis have shown that doses from 0.15 mg/kg b.w. are efficacious. Therefore, this should be recommended as the usual dose, to be repeated if needed, up to a daily dose of 0.5 mg/kg b.w. in 24 hours.

It is at the moment unclear whether there is a consistent evidence of efficacy in all age groups. It appears that most studies (at least those with documented efficacy) have been conducted in children older than 2 years of age, and smaller children have, if at all, only rarely been included.

Regarding the safety in this indication, most reports did not include a decisive recording of adverse events. However, the problems with the first 24 hours after general anaesthesia in the assessment of adverse events (especially with events like somnolence and sleepiness) are obvious. An increased incidence of extrapyramidal effects, however, cannot be concluded, probably also due to the sedative effects of general anaesthesia. However, it has also to be said that the indication PONV can be regarded to be less problematic, as the administration is usually restricted to one dose, or at least to a 24 hour interval only.

The treatment of PONV is therefore recommended to be included in a harmonised paediatric recommendation, however, with the restriction to the i.v. formulations only, with a dose of 0.15 mg/kg b.w. (to be repeated if needed up to a daily dose of 0.5 mg/kg b.w.) and to be given after the completion of the surgical procedure.

IV.3.3.1.3 Other situations with Nausea and Vomiting

Only two studies are submitted by the MAH for this indication, one of which was included in the previous safety review, and one of which is a new study.

Study Cubeddu 1997 (Cubeddu Aliment Pharmacol Ther 1997):

This was a very small study of 36 patients (aged 6 months to 8 years; mean age between 1.0 and 2.5 years in the three groups) randomised to ondansetron, MTC (0.3 mg/kg), or placebo given as single i.v. dose in children suffering from nausea and vomiting due to gastroenteritis. The number of patients without emesis in the first 24 hours was 58% with ondansetron, 33% with metoclopramide, and 17% with placebo. The rate for treatment failures was 17% for ondansetron, 42% for MTC, and 33% for placebo. The mean number of emetic episodes was 2 in the ondansetron group, and 2 each in the MTC and placebo groups. The difference between ondansetron and placebo was statistically significant, whereas all other comparisons were not. 90% of the patients experienced drowsiness as adverse events; however, the incidence was not different between the groups. One patient in the MTC group experienced tremor.

Study Van Eygen 1979 (Van Eygen M, Postgraduate Medical Journal 1979)

The study included 60 children suffering from nausea and vomiting due to gastroenteritis with an age range of 2 to 6 years (mean age 3.25 years).

The patients were randomised to receive either 30 mg domperidone, 10 mg metoclopramide, or placebo given as suppositories, one of which was given at the start of the observation period. Three further suppositories could be given within the 24 hours, if required.

The number of suppositories administered was 31 in the domperidone group, and 35 and 47 in the MTC and placebo groups, respectively, a result which was statistically significant for the difference between domperidone and placebo only.

The overall evaluation revealed a number of 16 excellent ratings for domperidone, 9 for MTC and only 2 for placebo, showing statistical significance for both active treatments over placebo. The symptom questionnaire revealed statistically significant superiority of domperidone over placebo for nausea, vomiting, anorexia, and abdominal pain, and superiority over MTC in the items nausea and vomiting. MTC was also more effective than placebo in nausea and vomiting.

The authors concluded that domperidone would be the drug of choice in the situation under investigation. Safety evaluation was not included in this study.

Assessor's comments

In the indication "nausea and vomiting due to gastroenteritis" only two studies are available, one conducted with i.v. administration, and one conducted with a suppository. Both trials are rather small trials, and were not able to clearly show statistically significant differences between MTC and placebo. Although in both studies some therapeutic effects can be regarded to be documented overall, a clear conclusion from the two studies cannot be drawn. Therefore, the treatment of nausea and vomiting due to gastroenteritis with MTC cannot be recommended from these data.

The MAH further presents two meta-analyses for the support of this indication:

Study Alhashimi (Alhashimi D et al: Cochrane collaboration 2006):

This review assessed the effectiveness of antiemetics on gastroenteritis-induced vomiting in children and adolescents. The study included 396 participants in three trials, one of which was the a.m. trial by Cubeddu. Therefore, results are not reported any further.

Assessor's comment

No further conclusions can be drawn from this study.

Study DeCamp (De-Camp LR et al: Arch Pediatr Adolesc Med 2008):

This study assessed and pooled altogether 11 articles on the treatment of vomiting due to gastroenteritis in children. 2 studies in MTC were included, which were again the same as reported above. No conclusions on MTC are drawn in this meta-analysis.

Assessor's comment

No further conclusions can be drawn from this study.

Overall conclusion on treatment of nausea and vomiting due to gastroenteritis

Only very little data on this indication is available with inconsistent results and different pharmaceutical forms. A clear superiority of MTC vs. placebo cannot be concluded from these studies. Therefore, the indication "Nausea and vomiting due to various reasons" or "Nausea and vomiting due to gastroenteritis" is not recommended to be included into any harmonised recommendation for children.

IV.3.3.2 Gastrointestinal Motility Disorders:

IV.3.3.2.1 Gastroesophageal Reflux Disease:

2 studies already included in the previous safety review, and 5 new studies are presented in support of this indication by the MAH. Furthermore, two systematic reviews/meta-analyses are presented.

Study Leung (Leung AKC et al: Curr Ther Res 1984):

This was a study in 41 patients with "radiologically" proven gastroesophageal reflux" with symptoms of persistent regurgitation and/or failure to thrive and apnoea. This was an unselected case series from one clinical centre. The mean age at the diagnosis is given to have been 160 days with a range of 21-1215 days). The patients were randomly assigned with 3:1 unequal randomisation to treatment with MTC (0.5 mg/kg b.w. per day in 4 divided doses with oral medication) or control treatment.

After 4 weeks of treatment there was a significant decrease in regurgitant episodes with MTC compared to control.

The total treatment duration (until subsidence of symptoms) and the results regarding weight gain were only reported for the MTC group, without results for the control group.

5 patients in this study encountered side effects, with two of them having drowsiness, 2 experiencing irritability and fussiness, and one with acute oculogyric crisis after incidental overdose (four times the prescribed dose).

Assessor's comment

This has to be regarded as a very weak evidence of efficacy, as no clear inclusion criteria are reported and outcome is only partially included. However, there seems to be some therapeutic activity of MTC in these children. However, safety seemed to be an issue.

Study Tolia (Tolia V et al: J Pediatr 1989):

This study included 30 infants diagnosed for GER with pH probe. The age range was 1 to 9 months, with a median age of 2 months. No secondary GERD patients were included. The study procedures included extended pH monitoring at baseline and after therapy, gastroesophageal scintigraphy (to assess gastric emptying). Study duration was 2 weeks, with a cross-over after the first week of treatment. Patients either received MTC at a dose of 0.1 mg/kg four times daily or placebo (pharmaceutical form not given). The results revealed a statistically significant difference in the percent time of $pH \leq 4$ for the pH probe results, however, symptom evaluation and gastric emptying times were not different between placebo and MTC groups. A higher weight gain was seen in a subgroup of older patients with MTC compared to placebo.

It is also stated that no side effects occurred during the study.

Assessor's comment

The study does not speak in favour of MTC treatment of GERD, as there was no effect on the clinically more relevant endpoints. Also, treatment duration in this study was very short, and therefore a conclusion on efficacy appears not be possible from these data.

Study De Loore (De Loore I et al Postgraduate Medical Journal 1979):

This study included 47 infants and children (aged 1 month to 8 years) suffering from pronounced vomiting after meals in which organic G.I. lesions had been excluded. The presence of decisive gastroesophageal reflux was not assessed during this study.

The patients were randomised to receive wither domperidone, placebo or MTC as oral 1% solutions. The MTC dose was 0.3 mg/kg b.w. three times daily.

The evaluation of efficacy was symptomatic and comprised nausea and vomiting, and the investigator overall rating. Treatment duration was 2 weeks.

Both active treatments were recorded to be superior to placebo, with domperidone being significantly superior to MTC in the nausea and vomiting evaluation.

No adverse events were reported.

Assessor's comment

Again a piece of weak evidence for efficacy with low numbers, short treatment duration and unclear inclusion criteria (not really requesting the presence of GERD).

Some pharmacologic activity in the children can, however, be concluded.

Study Rode (Rode H et al: J Pediatr Surg 1987):

The study included 18 infants (mean age 6.45 months) which were admitted to the hospital due to failure to respond to medical therapy (not stated) or due to complications of GER. Reflux was confirmed by barium meal and extended pH monitoring. Patients received either cisapride 0.33 mg/kg, or MTC 0.2 mg/kg both given every six hours. Two control pH-metries were performed with different posture. The total duration of the study is not clearly reported.

Both agents improved the parameters measured, but cisapride was found to be more effective in enhancing lower esophageal sphincter competence and esophageal motor function. MTC did improve the no. of reflux episodes, the % time of pH <4, and the no. of refluxes longer than 5 minutes. However, no clear effects were seen on the longest reflux, the esophageal clearance time, and the ambient pH of the lower oesophagus.

No adverse events were reported.

Assessor's comment

This is clearly a pharmacodynamic study by nature with very short duration only. No placebo comparison is included. No clear conclusion can be drawn regarding efficacy of MTC:

Study Machida (Machida HM et al: J Pediatr 1988):

This study investigated the use of MTC in 28 patients with a median age of 5.5 months in patients that were referred to the study centre due to regurgitation for the assessment of GER. Of the patients, 7 had failure to thrive, 5 had apnoea, and one had suspected oesophagitis. No secondary GERD patients were included. Barium contrast study, esophageal manometry, and pH monitoring were performed before and after the i.v. administration of MTC at a dose of 0.125 mg/kg (for esophageal manometry) of MTC 0.125 mg/kg four times daily (for pH monitoring).

The double-blind part of the trial randomised patients either to MTC 0.125 mg/kg four times daily, or placebo. Efficacy criteria were episodes and estimated amount of emesis per day.

MTC was able to reduce end-expiratory LES pressure significantly, however, no relevant effect on No. of 24 hour reflux episodes, % time of pH <4, the no. of episodes lasting longer than 5 minutes, and the duration of the longest episode was seen (in fact some of the results were statistically significantly better at baseline).

Only 8 patients were included in the double-blind part of the trial, 3 on MTC, and 5 on placebo.

3 of the 5 infants discontinued the medication before two weeks due to side-effects (increased vomiting and irritability). In the placebo group, symptoms improved in 4 patients, and did not change in one.

Assessor's comment

The study is again a very small study, and for the greater part, a pharmacodynamic study only. Furthermore, pharmacodynamic results do not speak in favour of MTC treatment compared to placebo or baseline. Moreover, safety related events were occurring at a considerable frequency preventing the evaluation of the double-blind phase of the trial.

Study Pons (Pons G et al: Fundam Clin Pharmacol 1993):

This study was already included in the PK section of this AR. The study was aimed to assess the clinical efficacy and optimal dose of MTC in GER in infancy.

24 infants age 1 to 18 months were included who were referred to the study centres for suspected GER and with diagnosed GERD according to pH metry.

Patients were randomised to receive placebo or MTC at doses of 0.1, 0.2, or 0.4 mg/kg 30 minutes before a formula meal, and pH metry was then repeated on day 1 and 2 of the treatment period.

However, no significant differences were seen in comparison to baseline and for the different doses, neither on day one nor on day 2 of the treatment period. No dose response effect was observed. This may have been attributable to the high variability observed.

Assessor's comment

This is again only a PD study. However, pharmacodynamic activity of the compound in the parameters of interest relating to GERD cannot be concluded and a dose response relationship could not be established.

Study Bellisant (Bellisant E et al: Clin Pharmacol Ther):

This was a randomised placebo-controlled, double-blind study aimed at assessing the efficacy of MTC (dose 0.2 mg/kg given thrice daily during 14 days as the 2.6 mg/ml oral solution).

The main endpoint was the variation of the percentage of time pH <4. 44 infants with a mean age of 105 days were included in the study. Repeated sequential analyses were performed during the study, and it was stopped after the seventh analysis without rejection of the inefficacy hypothesis. The median improvements for placebo and MTC after 14 days of treatment in the pH<4 endpoint was 22% and 39% (p=0.28). All other secondary endpoints were also not significant.

4 infants had tolerability problems that led to premature termination of the treatment, one in the placebo, and 3 in the MTC group. The effects were seen as not being related to study medication (in the MTC group these were repeated apnoea on one, vomiting in the second, and irritability, agitation, and bottle refusal in the third child).

Assessor's comment

Again, the study uses PD endpoints only, is of limited duration and size, and is not able to conclude a clear beneficial treatment effect of MTC (although some activity on the primary endpoint can be noted).

The MAH also presents 2 systematic reviews in support of this indication:

Study Craig: (Craig WR et al; Cochrane Collaboration 2004):

The review investigated the pooled effects of thickened feeds, positioning, and MTC as compare to placebo in improving the outcome of GER in the developmentally normal children aged one month to two years. 20 trials meeting the inclusion criteria were retrieved, which involved 771 children.

Whereas thickened feeds appear to be effective for reducing the regurgitation severity score, as well as the frequency of emesis, the reflux index was not reduced.

Positioning, however, could not be concluded to be effective in the treatment of childhood GER.

For MTC, seven studies were identified, of which 6 have already been included above (studies Leung, Tolia, DeLoore, Machida, Pons, and Bllisant (plus one additional study published as abstract only).

The pooling of the results concluded a reduction of daily symptoms (assessed after 1 week, based on two papers only), reduced reflux index (also based on the analysis of two studies only), however, also an increase of side effect (risk difference of 26%). The evaluation of “proportion of patients with perceived improvement”, the “number of refluxes >5 minutes during pH monitoring period”, and the “number of reflux episodes of pH <4.0 during monitoring period”, were not statistically significant. The authors concluded that MTC may have some benefit in comparison to placebo in the symptomatic treatment for GER, but that this effect must be weighed against possible side effects.

Study Hibbs (Hibbs MA et al: Pediatrics 2006):

The authors performed a systematic search for relevant review articles on the use of MTC for GERD in infants. Cohort, case-control, and intervention studies were included, case reports, case series, review articles and abstracts were excluded.

12 articles met the inclusion criteria, of which 11 were prospective trials, and five of these were randomised blinded clinical trials. Of these 5, 3 were included above already (Tolia, Pons, and Bellissant).

The study size ranged from 6 to 77 patients, and the MTC dose ranged from 0.1 to 1 mg/kg per dose. Eight studies were reported to show improvement with MTC in at least one measured outcome; one of the studies showed worsening symptoms with MTC.

Of the 5 randomised trials, 2 showed no effect on any outcome, and 2 showed a significant placebo effect. 4 of the studies commented on adverse effects, with irritability being the most frequently reported potential adverse effect. Other adverse effects included dystonic reactions, drowsiness, oculogyric crisis, emesis, and apnoea.

Marked heterogeneity regarding patients populations, dosing, and outcomes were stated, and for this reason, a meta-analysis was not performed.

The level of evidence for the use of MTC in GERD was rated as “poor”, leading to an “inconclusive” recommendation for the safety and efficacy of MTC in infants.

Assessor’s conclusion on treatment of GERD

The conclusions of the systematic review(s) regarding the treatment of GERD in infants with MTC can be fully supported: There is insufficient evidence to recommend such a treatment as the evidence is too weak, and the heterogeneity among the studies is too high. Furthermore, for this indication, only studies in infants were presented, and substantial safety issues seem to be unresolved for this age group.

The MAH is requested to present further material, also in older children for the support of GERD treatment with MTC.

IV.3.3.2.2 Other gastrointestinal motility disorders

Under this subheader, various studies for varying indications are presented. The presented studies comprise 2 studies included in the previous safety review, and 3 new studies.

Study Olsson (Olsson GL et al: Acta anaesth. Scand. 1982)

This placebo controlled study investigated the effects of MTC on reducing the risk of aspiration during emergency operations.

58 children aged 0-15 years were included to receive either placebo or 0.3 ml/kg b.w. at induction of anaesthesia. Anesthetic technique was standardised during operation.

Outcome measures were the mean aspirated volume of gastric content, and further responder categories made thereof.

There was a significant difference to the advantage of MTC for total volume of aspirated gastric content and the related categories (No. of pat. With aspirated volumes exceeding 0.25, 0.50, and 1.00 ml/kg b.w).

Adverse event reporting was not included in the literature report.

Assessor’s comment

The study appears to indicate that gastric emptying is accelerated under the influence of MTC. The “efficacy” is based on a PD parameter only, of which the clinical relevance regarding the prevention of acid aspiration remains unknown.

Study Hyman 1 (Hyman PE et al: Paediatric Research 1985):

This double-blind, placebo controlled study comparing MTC with betanechol and placebo was conducted in 10 infants with “upper gastrointestinal motor disorders” investigated also the influence of MTC on gastric emptying.

Infants were fed with a 5% glucose meal, with a phenol re-dye-dilution technique, which was combined with acid titration, measurements of gastric volume, and fractional emptying rate, fluid output, and acid output.

MTC increased the fractional emptying rate in 8 of 10 infants, but did not alter gastric acid secretion. MTC also increased gastric fluid output. No significant effects were seen for betanechol.

No side effects were seen during the trial. The authors concluded that further studies were warranted to assess the clinical efficacy of MTC in infants with “non-obstructive causes of delayed gastric emptying”.

Assessor’s comment

PD study indicating a pharmacodynamic effect on gastric emptying. Clinical efficacy cannot be assessed.

Study Hyman 2 (Hyman PE et al:

This was a double-blind, placebo-controlled, randomised study measuring the effect of MTC on gastric emptying. Three groups of infants were studied: The first group was composed of nine infants with episodes of regurgitation at least six times daily (mean age 6 months), the second group consisted of 7 preterm infants with gastroparesis not related to intercurrent illness (mean age 10 weeks), and the third group comprised 6 infants with prolonged gastroparesis following abdominal surgery (for duodenal atresia, NEC, jejunal atresia, and gastroschisis, with a mean age of 2 months.

Significant increase in the fractional emptying rate of the stomach was seen in the first two groups, but no in the postoperative group.

There were no adverse reactions during the study.

Assessor’s comment

Again, a PD study with single administration and inconsistent effects across different populations.

Study Zatman (Zatman TF et al: Br J Anaesth 2001):

This randomised study compared the effects of MTC with erythromycin on gastric emptying. 80 children aged 4-15 years undergoing tonsillectomy were evaluated for gastric residual volumes after the administration of either erythromycin dose 1 mg/kg or MTC 0.15 mg/kg i.v.. MTC and erythromycin produced similar gastric volumes, and there was no difference in post-operative vomiting (although retching was more common in the MTC group). In the erythromycin group there were more patients with negative aspirates (45.9%) than in the MTC group (35.1%) without reaching statistical significance. Equal efficacy as prokinetic agents was concluded by the authors.

Assessor’s comment

Erythromycin is a known motilin agonist which accelerates gastric emptying. The conclusions of the study are therefore unclear. The study investigated gastric volume on one side (which is a PD parameter only of unknown significance for acid aspiration), and nausea and vomiting on the other hand. The effects on PONV are detailed above, and efficacy has already been concluded. However, for the gastric emptying part of the study, any conclusion ob clinical efficacy appears to be doubtful.

Study Harley (Harley D et al: Acta Paediatrica 2007)

This was a pilot double-blind study aimed to compare MTC with placebo in the treatment of feeding intolerance in infants. 20 preterm very low birth-weight infants (500 g to 1500 g birth weight) with gastric residuals greater than 20% volume (of the previous feeding) were included. MTC was given i.v. at a dose of 0.05 mg/kg b.w. every 8 hours, until the patients received a total feeding volume of >100 ml/kg b.w./day, and thereafter, the medication was administered enterally for further 7 days.

The endpoints were time to reach full enteral feeds, the daily number of significant gastric residuals, and the incidence of NEC.

In this study, there were no significant differences between the groups in the major outcome variables of the study: The time to full enteral feeding was 13.2 days with MTC, and 13.0 days with placebo, and the daily number of significant gastric residuals was 0.7 and 1.0 for the MTC and placebo group, respectively. No NEC events occurred during the study.

The authors concluded that a large study of MTC therapy for feeding intolerance would not be feasible, because no conceivable benefit could be expected.

Assessor's comment

Clearly a "negative" study, questioning the PD effects seen in above studies for their clinical usefulness. However, this was a different patient population from age.

Assessor's conclusion on treatment of "Other gastrointestinal motility disorders"

There is great heterogeneity in the studies, patient populations, therapeutic settings (including possible indications) and outcomes in the studies presented. Most investigations have been performed in PD parameters only, and have found effects consistent with the acceleration of gastric emptying in infants and children. No effects could, however, be seen in premature infants.

However, despite the effects, it remains completely unclear whether a measurable clinical benefit for the patients can be concluded, as clinical parameters of therapeutic benefit have not been investigated.

An indication "other gastrointestinal motility disorders" cannot be supported from these studies.

IV.3.3.3 Digestive Tract Explorations

Only one clinical study, already described in the previous (1995) safety review is presented in support of this indication by the MAH.

Study Grunow (Grunow JE et al: Journal of Paediatric Gastroenterology and Nutrition 1988):

This randomised, placebo-controlled study investigated the effects of oral MTC on procedure times during small bowel biopsy in children.

18 children between 19 days and 12 years were included (of which 9 were younger than 2 years. The indications for biopsy were suspected carbohydrate malabsorption, one for exclusion of chronic giardiasis, and the remaining for suspected eosinophilic gastroenteritis.

The dose of MTC was 0.2 mg/kg b.w. administered as syrup. Promethazine and chlorpromazine were given as sedation. The procedure was started at a mean of 41-45 minutes after the administration of the study drug.

The mean total procedure time was half that for control (43.7 vs. 86.5 minutes) which was largely attributable to the time needed to cross the pylorus. Even more important, total fluoroscopy time was reduced from 84.4 seconds to 40.9 seconds.

Assessor's comment and overall comment on "Digestive Tract Explorations"

This study clearly shows the reduction of time needed for endoscopic instrumentation and, even more important, for radiation times. However, this is only a very small study of 18 children, and only one study is presented in support of this indication.

Therefore, at the moment, the indication cannot be supported to be part of a harmonised recommendation for children. The applicant should present additional data, not only in children, but also in adults, and discuss the transferability of the data.

In their introductory part, the company has included an overview on treatment recommendations/guidelines of informed societies for GI endoscopy, which, however, for adults did not find sufficient evidence for firm conclusions. For children, no specific data or recommendations have been identified.

Overall Discussion of efficacy

MTC has been used and is proposed to be used by the MAH in the following indications:

- Nausea and vomiting:
 - o Chemotherapy and radiotherapy-induced nausea and vomiting
 - o Postoperative nausea and vomiting
- Gastrointestinal Motility disorders:
 - o Gastroesophageal reflux disease
 - o Other gastrointestinal motility disorders
- Digestive Tract Explorations

The proposed dose range in the paediatric population was, regardless of the indication and mode of administration 0.1 mg/kg/day up to 0.5 mg/kg/day.

The evaluation of available data regarding the use of the compound in children, however, sheds considerable doubt on the clinical usefulness and proof of efficacy of the compound in this patient population. There is especially no clear evidence for efficacy in all gastrointestinal motility disorders, and there is no clear evidence for efficacy in chemotherapy- and radiotherapy induced nausea and vomiting. In these indications, sufficient and possibly safer medication are available for children (Serotonin antagonists and dexamethasone for CINV, H2-blockers and PPIs (at least ranitidine and omeprazole) for gastroesophageal reflux disease.

The evidence in the indication “digestive tract explorations” is restricted to one trial only, and would largely depend on further supporting material available.

There is sufficient evidence for efficacy of MTC in the treatment of PONV. However, this will have to be restricted to the treatment with i.v. administration only and when given after the termination of surgery. All oral preparations should therefore not include a recommendation for the treatment of children. As regards the recommended dose, doses from 0.15 mg/kg b.w. are recommended, to be repeated if needed, up to a daily dose of 0.5 mg/kg b.w. in 24 hours.

A restricted indication, only recommending the treatment with MTC in case of failure of other therapies cannot be recommended as MTC has been shown to provide no additional benefit if administered with a 5-HT antagonist.

As regards the documented age range for efficacy in children, the four studies with documented efficacy in the PONV indication included children from the age of 1 up to 14 years only. Therefore, the treatment of infants less than 1 year of age with proven efficacy is not documented and can therefore also not be recommended.

IV.3.4 Clinical Safety

The safety review given by the MAH is divided into two parts

- The Review of safety based on the MAH’s data
- The Review of safety based on Scientific Literature.

IV.3.4.1 Data of the MAH:

The MAH searched for all serious cases that occurred during clinical trials. However, this evaluation did not identify any single case.

Therefore, the report refers to spontaneous reporting only.

For this overview, the MAH concludes that the safety profile of MTC in children corresponds to the one described in their CCSI and is therefore not different from adults.

The overview provided from these data is given as follows:

The overall number of cases in children of less than 18 years registered until 30th September, 2009 was 1079, of which 923 were reported by Health Care Professionals, and 156 by consumers. Of the 156 cases from consumers, a total of 173 adverse reactions, and in the 923 cases from Health Care Professional, 1967 adverse reactions were included.

The most frequently mention SOC in the reports from Health Care Professionals were the following (data derived from the former Sanofi database, which is the bigger database and comprises 831 cases with 1875 events):

- 1074 events in the SOC “nervous system disorders” of which the most frequent single events were:
 - o 231 cases of “dyskinesia”
 - o 208 cases of extrapyramidal disorder
 - o 160 cases of “dystonia”
 - o 127 case of hypertonia
- 172 events in the SOC “eye disorders” of which the most frequent single events were:
 - o 98 cases of “oculogyric crisis
 - o 32 cases of gaze palsy
- 160 cases of “injury, poisoning and procedural complications” of which
 - o 75 cases were termed “overdose” and
 - o 63 case termed “accidental overdose”
- 131 cases of the SOC “musculoskeletal and connective tissue disorders”, of which the most frequent events were:
 - o 41 events of torticollis
 - o 27 events of trismus and
 - o 12 muscle rigidity.

Under addition of adverse events that are less frequently reported and can, however, nevertheless be identified to be extrapyramidal disturbances in nature, it appears that approximately nearly 1200 of the total of the 1875 events (more than 60%) are related to extrapyramidal disorders.

Other relevant adverse events mentioned by the MAH comprise the following:

- 79 ADRs of consciousness disorders with depressed level of consciousness, altered level of consciousness, somnolence, coma etc.
- 49 ADRs of convulsive disorders (sometimes associated with extrapyramidal disorders)
- 30 ADRs of respiratory disorders coded apnoea, dyspnoea, respiratory arrest, respiratory depression, etc. In some cases the MAH attributes the events to other adverse reactions mainly anaphylactic reactions or are linked to extrapyramidal disorders. The MAH refers to a former PSUR (PSUR_May05-Arp06_01) which concluded that “a few cases were reported as transient respiratory arrest with a favourable outcome after MTC i.v. injection. In some cases, the respiratory symptom could in fact be related to other disorders, such as extrapyramidal syndrome. From these cases no definite conclusion can be made”
- 25 ADRs of anaphylactic reactions, including 4 cases of coded anaphylactic shock.
- 12 ADRs of cyanosis, of which 2 were reported secondary to methaemoglobinaemia, 2 to anaphylactic shock, 2 to extrapyramidal disorders, 2 to respiratory failure, and 1 to shock.
- 10 cases of methaemoglobinaemia
- 7 reports of death, sudden death, sudden infant death syndrome and cardiac arrest, corresponding to 6 cases.

- 3 ADRs corresponding to 3 cases from former Sanofi originated from a Japanese partner. Regarding the review of these cases, the MAH also refers to a previous PSUR. This former PSUR included a cumulative review of shock, which suggested that in 14 out of 38 cumulative cases a causal involvement of MTC. 13 of these 14 cases were from a partner from Japan. In this country, the injectable formulation contains sulfites. Therefore, the MAH suggests that the occurrence of shock is largely attributable to the i.v. form available in Japan only.
- 2 ADRs of tardive dyskinesia.

For this overview, the MAH concludes that the safety profile of MTC in children corresponds to the one described in adults.

Cases of overdose and misuse:

The MAH states that out of the 923 cases reported by Health Care Professionals, about 45% are considered by the MAH as an overdose and/or misuse (this relates to about 37% of the consumer reports). This is based on an overdose definition of more than 0.5 mg/kg per intake, or 1.0 mg/kg per day. Of this total number of cases, 384 were recorded in the former Sanofi database which mostly originated from France (309 cases).

These numbers of overdose and misuse cases led to the former inquiries conducted by the French authorities.

The MAH refers to both inquiries conducted for the years 1986 to 1996, and the second conducted for the years 1997 to 2002 (in order to assess the impact of the measures taken after the first inquiry).

The MAH also refers to a review of further cases of extrapyramidal disorders in children conducted/drawn up in 2005, comprising the years 2002 to 2005.

However, within the documented safety review (as referred to previously in the efficacy part) from 2005, this cumulative review of the 2002 to 2005 cases is not included.

Assessor's comment

The missing of this appendix to the 2005 safety report is not acceptable and should therefore be provided. Also, it is considered that the statement that almost all extrapyramidal reactions are attributable to overdose cannot be accepted in the form presented. No evidence is given for this statement.

Furthermore, as different licensing status decisions have been taken in several Member States, which have obviously related the occurrence of extrapyramidal adverse effects to the age range of the patient populations, the MAH is requested to present an evaluation of the ADRs included in the above presentation according to age.

This may include relevant percentage of certain fields of adverse events (especially, of course, extrapyramidal events) in relation to the overall number of events etc.

Fatal cases

The MAH separately presents the 17 out of 923 cases where the outcome of the ADR was fatal.

Of the total of 17 cases, 5 had a quick occurrence of death after intravenous and/or intramuscular injection of MTC, and could be secondary to the adverse reaction of cardiac arrest (mentioned above and listed in the CCSI):

- This comprised the following cases:
 - o 1 case of "sudden death"
 - o 1 case of "extrapyramidal disorders"

- 1 case of “death, cardiac arrest, bradycardia, dyspnoea, pallor, respiratory arrest and convulsion
- 1 case of cardiac arrest and tonic convulsion, and
- 1 case of cardiac arrest, coma, overdose, respiratory arrest and convulsion.

Two of the cases were mostly attributed to MTC, whereas in the other cases underlying conditions could also be attributed.

Out of the total number of cases, 6 cases in which MTC was administered orally (or unknown route in 1), alternative explanations have been found:

- 1 case with recent vaccination, ibuprofen administration and episodes of pallor
- 1 case with suspected meningitis
- 1 case with administration of dextrometorphan
- 3 cases with underlying disease (gastroenteritis with fever; diarrhoea with dehydration, others)

3 of the total number of cases death was preceded by respiratory disorders (n=1), dyspnoea, bradycardia, and pallor (n=1), or malaise, convulsions and respiratory arrest (n=1)

6 cases occurred secondary to other adverse reactions, i.e. Reye syndrome (n=1), anaphylactic shock or angioedema (n=2), neuroleptic malignant syndrome (n=1) and shock (n=2). The cases of shock or angioedema originated from Japan.

The applicant concludes that death could occur shortly after MTC injection in children secondary to cardiac arrest. This issue is not specific to children. No other safety issue was identified from this review of cases with fatal outcome by the MAH.

Assessor’s comment

The description of fatal cases within the report is somehow misleading. The MAH is not accurately evaluating whether a causal relationship to MTC can be excluded or has to be concluded. Although it is true that the cases are not specific to children, it would be interesting if a differential number of cases (relative to exposure) is reported in comparison to adults, or whether other events eventually led to death in children as compared to adults.

IV.3.4.2 Review of the Scientific Literature

Review of the clinical trials:

This review includes the trials described above in the efficacy section. As has been seen, most of the trials referred do not include any section about adverse events, or do report that no adverse events have occurred during the trials. Therefore, in the following sections, the AR only reports data from trials presented by the applicant that were not described in the efficacy section.

The only literature reference that has not been described above is a study by Allen et al, which is briefly described in the following:

Study Allen (Allen, JC et al: J Clin Oncol 1985):

This study was conducted in children, adolescents and adults age 7-22 years. The aim of the study was to establish a safe dose range for the treatment of children. This was therefore a dose-increase toxicity study in children receiving highly emetogenic chemotherapy with cisplatin or cyclophosphamide. The dose was started with 0.2 mg/kg and increase was performed in nine steps up to 3 mg/kg. MTC was given every two hours for four doses, beginning on-half hour before start of chemotherapy. Diphenhydramine was added in order to reduce extrapyramidal side effects. With MTC doses > 2 mg/kg, 15% of the children experienced extrapyramidal reactions, and 33% had akathisia. Also children who received two consecutive days of MTC had a higher frequency of extrapyramidal reactions. However, the number of patients per dose group was small, and even in the 0.2 mg/kg dose group 2 out of 2 patients experienced sedation.

Review of published individual case reports and safety studies:

The MAH performed a literature review with a cut-off date of 13th October 2009.

Published cases that are included in MAH's database have been excluded from the literature review.

The following presentation focuses on publications from 1995 to 2009.

- Published individual Cases:

- 15 publications have been identified relating to extrapyramidal disorders. Of note, one publication reported an unusual extrapyramidal symptom, laryngeal dystonia, describes as difficulties in swallowing and associated with retrocollis.
- 1 publication described galactorrhea in a 3.5 month-old infant
- 1 publication described a neuroleptic malignant syndrome
- 1 publication described a case of tardive dyskinesia in a 1-year old girl.
- 1 publication described a case of methaemoglobinaemia
- 2 publications described accidental spinal or intra-arterial injection.
- 1 publication described the increase of serum aldosterone.

- Published safety studies:

During the period under evaluation, 5 studies were published. These were the following:

- **Study Menniti-Ippolito** (Menniti-Ippolito F et al: Ital J Pediatr 2004): This was a case-control study investigating whether in children hospitalised for neurological disorders (cases) or other acute conditions (controls), the use of MTC was a risk factor. 407 cases and 523 controls were included. Of the 930 children, 13 were hospitalised for extrapyramidal symptoms. The use of MTC was for 9 in the extrapyramidal symptoms group, and 3 in the control group. The odds ratio for use of metoclopramide in the population with extrapyramidal symptoms was therefore 390 with 95% CIs of 61-2807. The MAH reports that this publication was taken into account for the decision of the Italian authorities to contraindicated MTC in children less than 16 years. Of note, in the 9 cases with involvement of MTC, only 4 had received doses higher than the currently recommended 0.5 mg/kg per day, whereas the other 5 received doses between 0.3 and 0.5 mg/kg per day. Of these 5 children, two were 1 year or younger of age, whereas the other three were 6-8 years of age.
- **Study Crouch and Study Cheraghali** (Crouch BI et al: Am J Health-Syst Pharm 2009; Cheraghali F et al: Acta Medica Iranica 2006): These two publications concerned the safety analysis of drugs poisoning in children with the indication of the frequency of MTC poisoning. The American study evaluated the 10-fold dosing drugs errors reported between 2000 and 2004 in children less than 6 years old. The most common drugs mentioned were the H2-receptor antagonists and MTC in children younger than 12 months of age.
The Iranian publication evaluated cases diagnosed with poisoning from 1997 to 2002 in a paediatric hospital. MTC was the most frequently mentioned single drug, being related to 6.2% of all cases.
- **Study Cézard** (Cézard C et al: Thérapie 2003): This study concerned a retrospective analysis of cases of MTC poisoning collected at a French poisoning centre from 1995 to 2000 with a total of 184 cases of MTC related poisoning (i.e. phone calls to the poisoning centre), of which acute dystonia was present in 81 cases. Hospitalisation was needed in 9% of the cases. The majority of cases was related to liquid formulations of MTC. The age range of the cases showed that the proportion of children with an age <1 year was relatively high (22 <1 year; 19 between 1 and 5; 34 aged older than 5 years).
- **Study Lifshitz** (Lifshitz M et al: J Pharm Technol 2002): This was a retrospective analysis of the records of 52 children admitted for adverse reactions to metoclopramide to an

Assessor's comment

The literature provided shows that poisoning and occurrence of dystonic/extrapyramidal reactions in children has constantly been a topic in the scientific literature. However, most of the studies are only retrospective analyses, and cannot be used to really assess the frequency of MTC overdosing or poisoning, or the frequency of occurrence of extrapyramidal symptoms. However, what can be seen in these studies is the following:

- *The data indicate that symptomatic poisoning appears to be relatively common, especially in the youngest age group*
- *Poisoning does obviously also occur with formulations intended for use in the paediatric population (see French study)*
- *The occurrence of extrapyramidal symptoms is, contrary to what has been stated by the applicant obviously not confined to overdosing, but does occur in relevant numbers with doses within the proposed therapeutic dose range.*
- *Although the Italian study has obviously been used to contraindicate the use of MTC in the whole paediatric age range, the study alone does not indicate that the paediatric population is at increased risk regarding the occurrence of these events.*

4 further publications have also been mentioned by the MAH, which have been published before 1995. One of these is the study Allen 1985, which is already described above. The following additional studies are presented here:

- **Study Bouloche** (Bouloche J et al: *Helf paediat Acta* 1987).
This study is a retrospective analysis of 18 cases of extrapyramidal syndromes in children and a subsequent literature analysis. The authors find out that 60% of the cases correspond to doses in excess of the recommended daily dose of 0.5 mg/kg per day or 0.2 mg/kg for single doses. They further conclude that dystonic reactions in the absence of overdosing occur essentially in female subjects aged over 9 years.
- **Study Bateman** (Bateman DN et al: *BMJ* 1985)
This study examined the epidemiology of extrapyramidal reactions to MTC by relating the reports to the Adverse Reactions Register of the UK Committee on the Safety of Medicines with the prescribing figures by general practitioners in the UK. The period under review was 1967-82 with an estimated 15.9 million prescriptions and 479 reports of extrapyramidal reactions. Regarding the sub-population analysis, there was an overall increased risk in female patients, and in young adults, especially in girls and women aged 12-19. It was also found out that there was a high rate of overdosing in the lower age groups (more than 75% in those aged 0-11, and around 50% for those 12-19).
- **Study Galland** (Galland MC et al: *Thérapie* 1983):
This was a study on 87 cases of extrapyramidal disorder with MTC reported to a French pharmacovigilance and poisoning centre, of which 70 were due to an overdose, and 52 due to high-dose therapy (not defined in the report). The report (only included as short abstract in the Appendix C of the clinical overview) recommended to stick to the maximum daily dose of 0.5 mg/kg/day as preventative measure.

Assessor's comment

The studies appear to be of rather limited value, especially the study by Galland which is only reported as very short abstract. The study Bateman has obviously used questionable methodology as the adverse reactions reports could be displayed for age ranges, however, the prescription data were

not. Therefore, the frequencies calculated for the different age ranges do not relate the number of events to an age-range related prescription number. Nevertheless, it can be concluded that it appears that a high percentage of adverse reactions have indeed been related to relative or absolute overdosing, but not all.

IV.3.4.3 Addendum: Evaluation of the BfArM-Safety-Database

In order to fully evaluate the Rapporteurs available data, a request to the Pharmacovigilance Department has been made to evaluate all cases of AEs reported to the BfArM for the substance.

General evaluation:

Up to the data lock point of 17.03.2010, the database comprises 637 of ADRs to metoclopramide representing a total of 1932 symptoms, in which MTC was suspected to be the responsible agent. 4 cases (including 20 symptoms) include children who were exposed to MTC during pregnancy, 37 cases with 84 symptoms concern children up to the age of 12, and 69 reports concern adolescents. All other cases were reported in adults.

The percentage for children was therefore 5.8%, and the common rate for children and adolescents was 16.6%.

Profile of the ADRs:

The most common reported terms were the following (all ages):

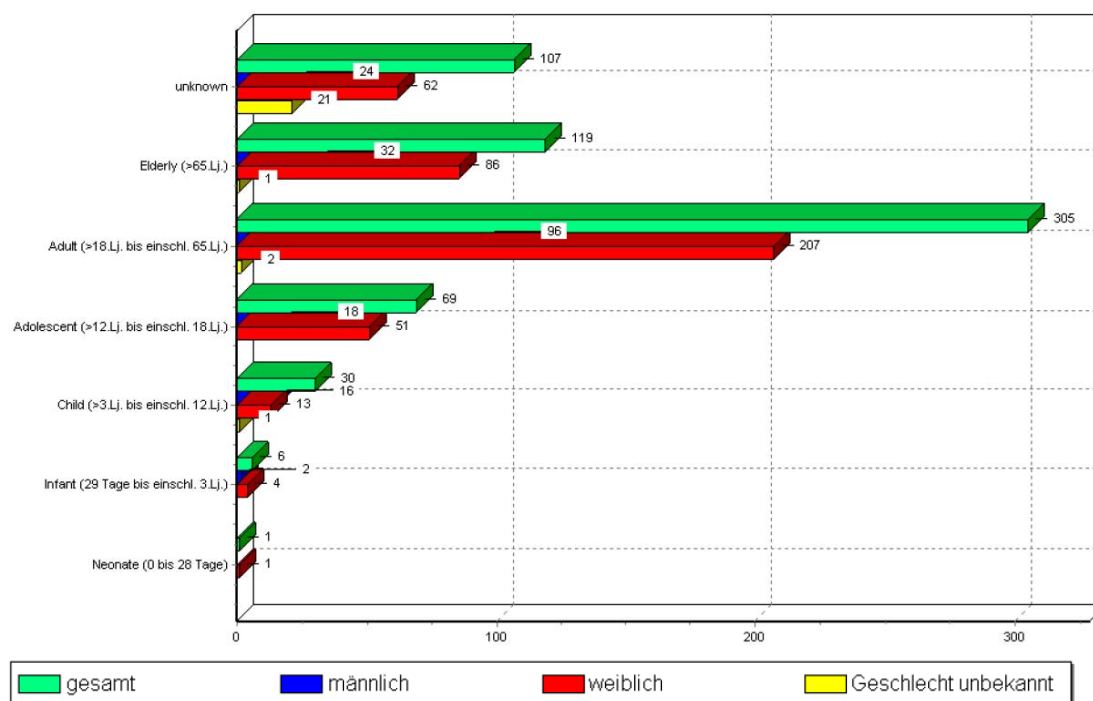
Dyskinesia (100), Stevens-Johnson-Syndrome (74), extrapyramidal disorder (51), Suicide attempt (36), nausea (26), pruritus (26), rash (25), fatigue (24), tremor (24), somnolence (23), convulsion (23), blister (22), pyrexia (21), tachycardia (21), vomiting (20), tortocollis (21), drug abuse (20).

The most common reports in children up to 12 years were:

Dyskinesia (11), extrapyramidal disorder (7), torticollis (4) visual impairment (3), convulsion (3). Therefore, 31 of 37 cases were concerning extrapyramidal symptoms.

Age distribution:

The following graph shows the distribution of cases according to age:



Apart from the children aged 3-12 years old, where this has not been observed, generally, female gender is associated with an increased number of reports.

The age distribution in children is reported in the following table:

Age (years)	Number of cases
1	3
2	3
3	0
4	2
5	2
6	1
7	2
8	3
9	4
10	2
11	6
12	8
unknown	1

It is generally considered that a remarkable higher occurrence of ADRs in children or of CNS related ADRs in children is not found. However, a general conclusion may not be adequate due to the low number of cases overall. It has also to be considered that MTC is contraindicated in Germany under the age of 2.

Doses:

Only in about half of the cases in children (17 of 37) the dosage used is also reported. Frequently, doses are described inappropriately (e.g. regarding single or daily doses). This especially applies to rectal forms (6 cases). All reports in the oral dosage forms comply with the treatment recommendations

Pharmaceutical form:

Of the 37 cases reported, 24 concerned oral formulations (usually oral solution), 9 rectal formulations, and only 1 i.v. dosage forms. 3 cases were unknown.

The number of reports for the intravenous form appears to be significantly lower than for the other forms.

Cases of death:

There is one report of a 9-year old child reported as „sudden death“. However, the dose is unknown, and it is only known that this was due to oral administration. All other information was too insufficient to draw any causality conclusions.

Conclusion:

It is concluded that due to the low number of reports, only restricted conclusions appear to be possible. The drawing up of a general safety profile of MTC is not considered to be possible on these data.

When considering the limitations of the database, it appears that there is no significant difference in the safety profile for children and adolescents.

The low number of reported cases in children below the age of 12 years in comparison to adults may also be due to an overall lower exposure. However, not exposure data according to age are available, and therefore, this remains unclear. The low number of reports in children under 2 years may be due to the restrictions of use in children in Germany, which may prevent reporting of events when used off-label.

Overall Discussion of Safety:

The overall evaluation of safety showed that there is a considerable burden of adverse reactions attributed to CNS related effects of MTC, especially to the occurrence of extrapyramidal reactions.

Contrary to what is stated by the company, this risk appears not only to be related to overdosing and poisoning, but, to a considerable part, also occurs when the currently recommended dosing instructions (maximum single dose of 0.15 mg/kg, maximum daily dose of 0.5 mg/kg, additional doses after 6 hours at the earliest) are adhered to.

There is no clear indication whether there is a differential risk in the different age groups, as the MAH has only insufficiently evaluated their safety database. A literature review and the poor methodology in most pharmacoepidemiologic studies were not able to differentiate properly between age groups. However, the overall safety documentation shows a tendency for safety problems occurring in longer-term administration and in the young age group. However a clear distinction according to age groups or duration of exposure cannot be made from the data provided.

As has been shown in the pharmacokinetic section, the use of MTC in the very young age group should not be recommended, as obviously elimination is slowed. Some of the data provided do indicate a considerable occurrence of extrapyramidal reactions in the very young. Therefore, from the assessor's view, it is concluded that – due to immaturity of drug metabolism and blood-brain barrier in very young children, MTC should not be used in children below the age of 1 year. This corresponds well to the proven efficacy in the setting of PONV, the only indication for which acceptable proof of efficacy has been presented, and in which acceptable results were achieved for children beyond the 1 year age cut-off only.

In the efficacy section, from the presented studies, it could be seen that for the short-term administration, safety, especially extrapyramidal symptoms appear not be a relevant problem. This may be related to the postoperative setting where all patients are still under considerable sedation, which may prevent the occurrence of extrapyramidal reactions.

V. FORMER RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION (DAY 89)

➤ Overall conclusion

Based on the material provided by the MAH, currently, no clear recommendation regarding the information relating to children to be included in the SPC/PIL for metoclopramide containing products can be made. This is based on the following facts:

- The MAH has not made a proposal for the information to be included
- The licensing status regarding contraindications and proposed age range is too divergent within Europe to reach a conclusion within the scope of an article 45 procedure. In order to harmonise the paediatric information with full scope, an overall safety evaluation of the compound could be regarded to be necessary.

Before a final conclusion can be reached, the MAH is requested provide satisfactory answers to the Request for Supplementary Information.

Based on the review of efficacy and safety of the compound metoclopramide, the rapporteur considers that, from a scientific point of view, the only pharmaceutical form to be used for the compound in children should be the i.v. form.

Member States with divergent licensing status (regarding proposed age range and possible contraindications for paediatric use) are especially requested to comment on the acceptability of the proposal, including possible legal implications.

For the i.v. form, the following wording should be included in the SPC/PIL

4.1. Therapeutic indication:

Paediatric population:

Metoclopramide is indicated for the treatment of postoperative nausea and vomiting for children from 1 year of age.

4.2. Posology:

Paediatric population:

For the treatment of postoperative nausea and vomiting, metoclopramide should be administered after the termination of the surgical procedure.

The recommended dose is 0.15 mg/kg b.w. given as a slow injection (at least 3 minutes).

The maximum dose in 24 hours is 0.5 mg/kg b.w. If additional doses are needed, these should be separated by at least 6 hours.

Metoclopramide should not be used in children younger than 1 year as there are insufficient data regarding efficacy and safety of the product in this patient population.

The following warnings/safety information related to the use in the paediatric population should be included in the SPC:

Section 4.4.: Warnings/Precautions:

Extrapyramidal disorders may occur, particularly in children and young adults and/or when high doses are used (see undesirable effects). These adverse reactions usually resolve completely after treatment discontinuation. A symptomatic treatment may be necessary.

Section 4.8 undesirable effects:

Nervous system and psychiatric disorders:

Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even following administration of a single dose of the drug, particularly in children and young adults (see Section 4.4.).

Drowsiness, decreased level of consciousness, confusion, hallucination.

The occurrence of these reactions is dose dependant.

...(proposed text for methaemoglobinaemia “particularly in neonates” should be deleted because of restricted age range proposed).

For all rectal and oral forms, the following is recommended to be included in the SPC:

Section 4.2.

Paediatric population:

Use in the paediatric population is not recommended.

➤ **Recommendation**

Based on the data submitted, the MAH should provide a response to the request for supplementary information as described in chapter VI as part of this worksharing procedure. (see section IV “Request for supplementary information”)

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

List of questions:

Question 1:

It appears that the divergent licensing status of the compound within Europe, has prevented the MAH from presenting a clear and outspoken proposal for harmonisation of the paediatric information to be contained in the SPC as regards the indications and dosage. From a regulatory point of view, it appears at the moment uncertain whether any compromise could at all be regarded to be feasible, considering the divergent opinions of the MSs in the past, ranging from a multitude of indications without age restriction to a general contraindication for the paediatric population (up to the age of 16).

The MAH should provide the following:

- a) Provide a full overview on the licensing status for children across Europe
- b) Make a clear statement whether a harmonisation of indications and posology is indeed not intended with this article 45 procedure.
- c) Declare whether the proposals made in the core safety document should be a proposal for harmonisation of paediatric information across Europe. If this is the case, the company should check whether all items are indeed suitable for such an article 45 procedure (=whether the information contained does indeed refer to specific paediatric needs only).

Question 2:

The evaluation of the documentation on efficacy has revealed that for most of the indications, the presented studies do not show a clear treatment effect that is superior to placebo. Therefore, in the indications:

- Chemotherapy and radiotherapy induced nausea and vomiting
- Other situations with nausea and vomiting
- Gastrointestinal motility disorders (including GERD and other motility disorders)
- Digestive tract explorations

further material should be presented by the applicant in order to show efficacy.

If a second-line indication is aimed at, the MAH should present any available material in support of second line and/or combined treatment.

Question 3:

- a) The pharmacokinetic data presented are rather scarce and it is at the moment unclear whether PK information regarding children should at all be included in a harmonised manner into the SPC/PIL. The MAH should make a proposal.
- b) The PK studies presented do show prolonged clearance in premature infants and newborns. From a pure PK point of view, a safe dosing for this patient population, and for the whole patient population younger than 1 year of age may not be possible. The MAH should comment. Newer results of studies on the PK and metabolism of the compound and the known facts on the development of metabolic capacities in newborns should be taken into account.

Question 4:

In the evaluation of their own safety database, the MAH has stated that almost all “extrapyramidal events” have been seen in patients treated with doses higher than the ones recommended (up to 0.5 mg/kg daily). However, this is not supported by the literature data, which document occurrence of these effects in lower doses also. Therefore, a re-evaluation of the safety database should be performed, in order to identify the following:

- a) Present the numbers of patients with extrapyramidal events according to doses and/or dose groups and for duration of treatment
- b) With regard to the differential licensing status according to age in Europe, please evaluate also the number of such events according to age. To this end, not only pure number of reported events should be provided, but also an estimation of prescription data according to age, if available in order to be able to estimate and compare the rate of extrapyramidal events in all age groups.
- c) Evaluate the numbers of death and reasons for death and relatedness to MTC in comparison to adults, in order to exclude a differential risk in children.

Question 5 (pre-clinical):

The position of the Applicant, that the submitted studies and the retrieved published papers do not provide any relevant information for the paediatric assessment in the context of this EU work-sharing procedure is endorsed. Nevertheless, the Applicant is asked to comment, whether the impairment of sexual behaviour seen after administration of metoclopramide to the perinatal rats might be relevant for consideration of therapeutic use of metoclopramide in pregnant women, and whether the current recommendations for use during pregnancy and lactation might need modifications.

VII. CHMP MEMBER STATES COMMENTS

FR

We globally support the rapporteur's assessment report that it is not yet possible to propose a harmonised SPC for metoclopramide, whatever the formulation is considered, before subsequent data become available for an in-depth assessment across all European member states.

As requested by the RMS, we add some information on the current licensing status in France of the in children approved drugs containing metoclopramide.

In France, the IV formulation is only indicated in children weighing more than 20 kg for the prevention and treatment of chemotherapy induced nausea and vomiting.

Recently two separate oral solutions (2,6 mg/ml) were granted in children and indicated in the treatment of nausea and vomiting not induced by chemotherapy. One of these formulations is intended to be used in children weighing between 1 or 15 kg, i.e. from birth to nearly 4 years of age, whose dose is administered by an adapted syringue to this age range. The other oral formulation is intended to be used in children weighing between 15 or 50kg, i.e. from nearly 4 years of age to 18 years of age, whose dose is administered by an adapted syringue to this age range as well.

The breakable 10 mg suppositories is approved to be administered in children weighing more than 20 kg in the treatment of delayed nausea and vomiting induced by chemotherapy.

The last available formulation that may be administered to children is the breakable 10 mg tablet which is approved in children weighing more than 20 kg in the treatment of delayed nausea and vomiting induced by chemotherapy.

Of note, the corresponding contra-indication regarding the age or weight limit of children for each formulation is consistent with the targeted paediatric population as mentioned in the indications and posology sections of the SPC.

Assessor's comment

The comment from France was the only comment received for this procedure. However, although clearly welcomed, this was not really the most helpful and needed comment, as the situation in France was taken as the basis for the submission of the MAH anyway. The missing of comments from MSs such as NL and IT, where there obviously exists a grossly divergent situation, or from MSs where other MAHs are considered to be the "originator" is therefore considered quite a drawback for the full evaluation of the procedure.

The RMS has therefore taken the decision to evaluate the data submitted on a scientific basis only, disregarding the complicated situation of divergent regulatory status of the compound. MSs may/should therefore choose to fully consider their national situation in the implementation of the recommendations.

VIII. REPONSES OF THE APPLICANT:

Question 1:

It appears that the divergent licensing status of the compound within Europe, has prevented the MAH from presenting a clear and outspoken proposal for harmonisation of the paediatric information to be contained in the SPC as regards the indications and dosage. From a regulatory point of view, it appears at the moment uncertain whether any compromise could at all be regarded to be feasible, considering the divergent opinions of the MSs in the past, ranging from a multitude of indications without age restriction to a general contraindication for the paediatric population (up to the age of 16).

The MAH should provide the following:

- a) Provide a full overview on the licensing status for children across Europe
- b) Make a clear statement whether a harmonisation of indications and posology is indeed not intended with this article 45 procedure.
- c) Declare whether the proposals made in the core safety document should be a proposal for harmonisation of paediatric information across Europe. If this is the case, the company should check whether all items are indeed suitable for such an article 45 procedure (=whether the information contained does indeed refer to specific paediatric needs only).

Summary of the MAH's response:

a) Licensing status for children across Europe:

The MAH gives an overview on the status in Europe for the 13 MSs in which the MAH has licenses for the product. A short overview is included in the response document, and a full display of the status is included as appendix 1.

In most of the countries, the situation grossly resembles the situation described for France, where a multitude of pharmaceutical forms and indications are licensed (see Chapter III).

Grossly deviating situations apply for NL and IT, which are briefly described:

In NL, as also reported before, the indication is restricted to severe nausea and vomiting with known cause, where the treatment with other medication has proven to be insufficient or impossible. Pharmaceutical forms are solution for injection, suppositories with 10 and 20 mg, tablet, and oral solution of 100 mg/100 ml. The oral formulations are furthermore restricted to nausea and vomiting not caused by operation or chemotherapy. The dosage is restricted to 0.5 mg/kg per day. Warnings are included similar to the ones proposed by the applicant in their CCSI.

In IT, section 4.2. of the SPC includes the general remark that the substance is not suitable for use in children under 16 years of age. There are therefore no restrictions for adolescents between 16-17 years.

It is furthermore of note that the indication "postoperative nausea and vomiting" is only licensed in Italy and Portugal, but not in the other countries. However, in most other countries, a non-specified "nausea and vomiting" indication is licensed.

b) Statement regarding the intention to harmonise the paediatric information throughout Europe:

The MAH clearly states that a harmonisation of the product information is not intended with this procedure. However, the company suggests that in the paediatric population the posology should be restricted to a dose of 0.5 mg/kg/day, except for the CINV and RINV indications, and that a clear recommendation for the use of the 2.6 mg/ml oral solution should be made.

c) The company presents a proposal for a harmonized safety information to be included into the SPC of all licensed products

The company furthermore suggests that in consideration of the divergent licensing status across Europe regarding pharmaceutical forms approved for use in paediatric population and in order to avoid inconsistencies within the national SPCs in the same country, that specific recommendations for use in terms of approved patients populations, and pharmaceutical forms are added nationally in appropriate sections of the European SPCs. The following proposal for a harmonised safety information is made:

Section 4.4 Special Warnings and Precautions for use

Extrapyramidal disorders may occur, particularly in children and young adults and/or when high doses are used (see 4.8 Undesirable effects). These adverse reactions resolve completely after treatment discontinuation. A symptomatic treatment may be necessary (benzodiazepines in children).

Respect the time interval (of at least 6 hours in children less than 15 years) specified in the dosage section between each metoclopramide administration, even in case of vomiting and rejection of the dose, in order to avoid overdose

Section 4.8 Undesirable effects

Nervous system and psychiatric disorders

Extrapyramidal symptoms: acute dystonia and dyskinesia, parkinsonian syndrome, akathisia, even following administration of a single dose of the drug, particularly in children and young adults (see 4.4 Special Warnings and Precautions for use)

Blood and Lymphatic system disorders

Methaemoglobinaemia which could be related to NADH cytochrome b5 reductase deficiency, particularly in neonates (see 4.4 Special Warnings and Precautions for use).

Section 4.9 Overdose

Treatment for extrapyramidal disorders is only symptomatic (benzodiazepines in children).

Assessment of the MAH's response:

- a) A final overview on 13 MSs has been gained by the material provided by the applicant. However, there is still a majority of countries for which no information is available. This is of course an unwanted situation.
- b) The intention of the MAH is noted.
- c) The proposal for the harmonised safety information is noted. It is considered that the proposal has to be considered mostly adequate, and the safety information should be included as modified and given in section I of this Assessment Report. The proposal includes only the sentences where the treatment of children is mentioned. All other parts of are not relevant for the article 45 procedure and can therefore be modified and assessed outside the scope of this procedure. The age cut-off proposed for adequate dosing (15 years) has not been substantiated by data. Therefore, it has been deleted in the proposal.

Overall Conclusion: Issues resolved.

Question 2:

The evaluation of the documentation on efficacy has revealed that for most of the indications, the presented studies do not show a clear treatment effect that is superior to placebo. Therefore, in the indications:

- Chemotherapy and radiotherapy induced nausea and vomiting
- Other situations with nausea and vomiting

- Gastrointestinal motility disorders (including GERD and other motility disorders)
- Digestive tract explorations

further material should be presented by the applicant in order to show efficacy.

If a second-line indication is aimed at, the MAH should present any available material in support of second line and/or combined treatment.

Summary of the MAH's response:

The MAH states that a further search in databases until June 2010 did not find new clinical studies with metoclopramide in children. The MAH refers to the updated version of the Cochrane review for antiemetics, in which metoclopramide is mentioned as a comparator, or reference.

Regarding this reference, the company further states that only few studies with small numbers of patients were included. The MAH mentions one study (Cubeddu 1997) cited by the Cochrane 2009 review, which reported reduction of gastroenteritis vomiting with 58% for ondansetron, 33% for metoclopramide, and 17% for placebo..

The MAH further mentions that MTC is listed on the WHO Model List of Essential Medicines for Children, neonates excluded, as follows and without anymore details for the three formulations: injectable 5 mg/2 mg, oral liquid 5 mg/5 ml, tablets 10 mg but not in neonates.

Assessment of the MAH's response:

The applicant has obviously undertaken an appropriate effort to produce new evidence for safety and efficacy. However, apart from the Cochrane review, nothing could be retrieved. However, the Cochrane review did not include any new data regarding metoclopramide. The study cited by the applicant (Cubeddu 1997) has been included in the Assessment at Day 89 already.

The mentioning of the WHO List of Essential Medicines does not really help in the evaluation of safety and efficacy in the paediatric population, as long as the data or conclusions underlying the List cannot be presented.

Overall Conclusion:

Issue formally resolved.

However, the concerns regarding proof of efficacy of MTC in children fully remain. The conclusions drawn in the Day 89 AR are therefore considered still valid. The efficacy of MTC in the a.m. indications has only insufficiently been proven. A considerable risk of adverse events has been shown with the use of MTC in children (see above in the Day 89 AR, and in the following questions). Therefore, the overall risk-benefit ratio in the indications mentioned above is considered to be negative.

The availability of more reliable (more efficacious) medication (Serotonin-antagonists) contributes to this overall conclusion.

Question 3:

- a) The pharmacokinetic data presented are rather scarce and it is at the moment unclear whether PK information regarding children should at all be included in a harmonised manner into the SPC/PIL. The MAH should make a proposal.
- b) The PK studies presented do show prolonged clearance in premature infants and newborns. From a pure PK point of view, a safe dosing for this patient population, and for the whole patient population younger than 1 year of age may not be possible. The MAH should comment. Newer results of studies on the PK and metabolism of the compound and the known facts on the development of metabolic capacities in newborns should be taken into account.

Summary of the MAH's response:

a) The MAH was unable to retrieve any additional study or data on the PK or metabolism of MTC in the paediatric population.

The MAH furthermore states that the data obtained in those studies with oral or IV administration in children from 1 month to 14 years of age were quite consistent with an elimination half-life in the range of 4-5 hours, distribution volume in the range of 3 to 5 l/kg, and plasma clearance in the range of 0.56 to 0.66 l/h/kg.

The company, however, expresses the wish to refrain from including any PK information regarding children into the SPC.

b) The MAH refers back to the data provided by the two studies of Kearns (Kearns 1 1988 and Kearns 2 1988) which had been included in the initial submission already. The observed lower clearance with prolonged half life in the youngest infant in one study, and in 30% of the participants in the other study, might indeed be due to the compromised metabolic capacity for phase II enzymes in preterm or mature newborns. In adults an N-4 sulfate conjugate has been reported to account for 32% of an oral dose, however, no such data are available in children. The MAH concludes that indeed a 0.15 mg/kg dose every 6 hours might lead to excessive plasma concentrations of the parent drug in newborns with a terminal half life that exceeds 10 hours. The MAH therefore concludes that in the absence of PK data for this age group, no dose recommendation can be given for preterm or full term neonates.

Assessment of the MAH's response:

a and b):

The answer of the applicant is formally accepted, as there is obviously no additional data available. Therefore, the assessment of the Day 89 AR is still valid, that *administration of MTC in premature infants and infants younger than 1 month of age cannot be recommended from a PK point of view.*

When considering the overall consequences of no dosing recommendation being available, and the usual paediatric doses resulting in possible or likely overdoses in this population, with the resulting increased risk of CNS adverse effects, it is concluded that – for all formulations – section 4.3. of the SPC should include a clear contraindication for this age group.

The MSs should consider that this is a minimal requirement to be included in the SPC and may be adapted to the previously established regulations for the use of MTC in children. However, the introduction of a contraindication (where a clear risk of inadequate dosing and subsequent risk of adverse effects has been identified) is clearly different from a non-indication or a non-recommendation that has previously been included for different age groups in the different MSs.

Overall Conclusion:

Issue resolved with amendment of the paediatric information to be included in the SPC (contraindication for neonates).

Question 4:

In the evaluation of the safety data, the MAH has stated that almost all “extrapyramidal events” have been seen in patients treated with doses higher than the ones recommended (up to 0.5 mg/kg daily). However, this is not supported by the literature data, which document occurrence of these effects in lower doses also. Therefore, a re-evaluation of the safety database should be performed, in order to identify the following:

- a) Present the numbers of patients with extrapyramidal events according to doses and/or dose groups and for duration of treatment
- b) With regard to the differential licensing status according to age in Europe, please evaluate also the number of such events according to age. To this end, not only pure number of reported events should be provided, but also an estimation of prescription data according to age, if available in order to be able to estimate and compare the rate of extrapyramidal events in all age groups.
- c) Evaluate the numbers of death and reasons for death and relatedness to MTC in comparison to adults, in order to exclude a differential risk in children.

Summary of the MAH's response:

The company now submits a safety review for metoclopramide and extrapyramidal disorders (EPD) in children covering the period from 01 November 2002 to 31 July 2005. The company apologizes for not having submitted this document earlier

a) The MAH tries to clarify that the assumption of the question, that there was a statement claiming that almost all EPDs were occurring in patients treated with high doses or overdose is not correct. They linked this high number to the inquiries performed by the French Regulatory Authorities focusing on EPDs in children.

The conclusions from this inquiry, however, were that there was a “predominance” of cases in which the recommended daily dose, the dose per intake and the interval of administration were not respected, as well as the recommended formulation per age.

In the following, the company refers to the previously submitted two safety reports (“Extrapyramidal syndromes and serious neurological adverse reactions observed with metoclopramide in children” from the Regional Pharmacovigilance Centre of Strasbourg of 2004, and “Risk Benefit Assessment for Children”, a report provided by Sanofi-Avantis to the French Regulatory Authority of October 2005).

In these reports, the daily dose was higher than the recommended dose (=higher than 0.5 mg/kg/day) in 78% and 74% of the cases in France in the two reports, and in 67% of the cases outside of France in the report by the MAH.

The MAH admits that this high frequency might be linked to a more important reporting of cases of overdose compared to cases at recommended doses. Therefore, the MAH refers to two epidemiological studies that were referenced in the previous expert overview (Studies: Manniti-Ippolito 2004, and Lifshitz 2002; see page 42 of this report) and which are regarded to report the percentage of EPD cases with overdose more accurately.

The evaluation of these two studies with 9 cases in the Ippolito study and 52 cases in the Lifshitz study results in a percentage of 19% of the children that were dose with a higher daily dose than 0.5 mg/kg, or a single dose higher than 0.25 mg/kg.

The company concludes that the frequency of overdose in cases of EPD from spontaneous reporting is high (about 70-80%), however, it is much lower in cases for epidemiological studies, and that it is difficult to estimate which frequency is the most accurate, as the spontaneous reports might be biased unbalanced reporting, and the number of cases in the epidemiological studies is rather low.

The company, however, presents the requested information regarding the duration of treatment. The evaluation revealed a total number of 608 cases of EPDs in patients younger than 18 years. The included preferred terms are listed.

From the 608 cases the time of onset of the events was as follows:

- 214 reports with a treatment duration less than 24 hours (of which 24 were with less than 1 hour)
- 279 reports with a treatment duration of 1-2 days
- 75 reports with a treatment duration of 3-7 days
- 1 report with a treatment duration of “a few days” not otherwise specified
- 7 reports with a treatment duration of more than 7 days
- 2 cases with a treatment duration of less than 1 month (not otherwise specified)
- 52 cases of unknown duration.

The MAH concludes that in most cases EPD onset was within 2 days after treatment start.

b) For the evaluation of the EPD cases per age,
For the evaluation of the EPD cases per age, the a.m. 608 cases were again used.

Two cases could not be included in the evaluation, as no age was specified.

The company first presents an evaluation of the total number of cases according to age differentiated by the country of origin of the report (France or other), which shows that the number of cases is very high in the youngest age group (157 cases out of 606). However, the percentage of cases for this age group from the total number of cases is quite different between France (31%) and the other countries (14%).

The following table shows the case distribution of the youngest age group:

Table 3 - Cases distribution of EPD by age in the group [0-1 year[

Age group	France	Other countries	Total
[0 - 6 months [73	17	90
[6 - 9 months [54	6	60
[9 - 12 months [5	2	7
Total	132	25	157

The interpretation of the company is, that EPDs are reported almost exclusively in infants less than 9 months in France, and in other countries in infants less than 6 months.

According to the MAH, sales data according to age groups are only available for France (years 1997-2005 have been evaluated). Therefore only the French data are evaluated. The following has been found out:

- There are very few sales for children in the 0-9 months age group for formulations other than the 2.6 mg/ml drops.
- The sales for the youngest age group (0-9 months) is twice or more than twice lower than for the age groups (9-29 months, and 2.5-7 years). When the different weight of the children is taken into account, the estimated number of treatment days in the age group 0-9 months is lower than in the age group 9-29 months, and similar to the one for the 2.5-7 years age group. The company interprets this estimation as an indicator that the high number of cases in France in the youngest age group is not related to a higher exposure but to a higher number of reported cases of EPD.

In the following the total number of EPD cases in children according to age is presented. An overview is given in the following table:

Table 4 - Cases distribution by age of cases of EPD, total cases of adverse reactions and percentage of cases of EPD

Age group (year)	Total cases EPD in children	Total cases of adverse reactions in children	Percentage of cases of EPD
[0 - 1 [157	238	66
[1 - 2 [17	42	40
[2 - 3 [16	42	38
[3 - 4 [12	28	43
[4 - 5 [28	41	68
[5 - 6 [18	23	78
[6 - 7 [30	40	75
[7 - 8 [26	35	74
[8 - 9 [21	26	80
[9 - 10 [27	34	79
[10 - 11 [30	36	83
[11 - 12 [42	47	89
[12 - 13 [35	41	85
[13 - 14 [35	38	92
[14 - 15 [51	62	82
[15 - 16 [39	48	81
[17 - 18 [22	32	69
Total	606	853	71

The following interpretation is given by the MAH:

- The frequency of EPD (percentage of total adverse reactions) is high in all age groups, however, the frequency is very high in those younger than 1 year, and in all age groups older than 4 years (between 66% to 92%). Between 1 and 4 years, the proportion is lower, around 40%.

The conclusion of the MAH is that, from the analysis of the case distribution by age and country, that the reporting frequency of cases in France in the age group 0-9 months is higher than that in other age groups and other countries. The same trend was noticed in the previous reports of the MAH submitted to the AFSSAPS in 2005. EPDs are the most frequent reported adverse reactions in children.

c) The MAH presents a summary narrative of all 16 medically confirmed cases of the total of 17 cases of fatal outcome in children (1 reported by a consumer).

The following is displayed by the MAH:

- In 5 cases, death occurred quickly after i.v. or i.m. injection of MTC and was assessed to be possibly related to cardiac arrest, which is listed in the CCSI (listed adverse reaction)
In two of these 5 cases (a 12 month old boy and a 3 year old girl, MTC seemed to be the most suspect cause of death.

The remaining three cases also had other possible reasons for the sudden death observed (1 case of concomitant medication (10 year old girl), 1 case of dehydration (31-month old boy), and 1 case of pneumonia (3 month old boy).

- In 6 cases, the route of administration was oral (n=5) or unknown (n=1). In all these cases have possible underlying other causes of death which were the following:
 - 1 case (5 year old boy) with previous episodes of pallor, being vaccinated in close relationship to death, and taking ibuprofen additionally. This boy received oral drops for four days before the event.
 - 1 case of a 5 month infant treated with antibiotics and dextrometorphan found dead at sleep with toxic levels of both dextrometorphan and MTC found in the blood.
 - 1 case of a 3 year old boy with fever, convulsions, and respiratory failure (diagnosed as possible meningitis. He was treated for 1 day.
 - further 3 cases with the underlying disease being a possible additional reason for death:
 - A 6 month old boy with gastroenteritis, otitis, and fever.
 - A 22 month old girl with dehydration and severe metabolic disorder (the reporter stated exclusion of causal role of MTC)
 - A 1 month old girl with poor weight increase, cough after milk intake and thus “undiagnosed underlying disease”.
- In 6 further cases, the death was considered to be secondary to other adverse reactions:
 - 1 case of Reye syndrome in an 11-year old girl which was treated for 3 days with lysine acetylsalicylate, paracetamol, and amoxicillin.
 - 2 cases of anaphylactic shock or angioedema with a 17 year old girl having been treated with sulphuride i.m., MTC and hyoscine butylbromide experiencing anaphylactic shock 5 minutes later, and with a 16 year old boy having been administered lysine acetylsalicylate 500 mg and MTC by i.v. route who was found dead half an hour later.
 - 1 case of neuroleptic malignant syndrome (NMS) in a 17 year old boy hospitalized for right intraparenchymatous temporoparietal haemorrhage secondary to vascular malformation. He was treated with MTC i.v. and experienced fever at 42 °C, muscle rigidity, shivers and CPK increase diagnosed as NMS and died 24 hours later.
 - Two further cases of shock, one in a 4-month old girl receiving an i.v. infusion of MTC and developing decrease of consciousness, restlessness, decreased blood pressure, convulsions and respiratory arrest, and one in a 14 year old girl experiencing fatal shock with insufficient further information.

For the 16 medically confirmed cases of death, the MAH concludes the following:

- In 4 cases MTC was seen as the most suspect cause.
- In 11 cases an alternative explanation was identified or could be suggested.
- In 1 case insufficient information was provided to enable a judgement on causality

In the following, the MAH has provided a table of all cases with fatal outcome displaying the cause of death and comparing the cases in children with those in adults. This table is not reproduced in the AR, but the results are summarized only:

A total of 86 cases were included in this analysis, of which (as displayed above) 16 were cases occurring in children. 4 cases were unclassified, as the age of the patient was unknown.

With regard to the type of adverse reactions leading to death it is concluded that:

- In 34 cases of the 66 adult cases a cause of death different from the ones observed in children was reported.
- In 48 cases (34 in adults and 14 in children) the adverse reaction was of the same type between adults and children.

The following table shows the distribution of the cases with the same type of adverse reaction leading to death:

Table 6 - Distribution of cases of the same type of adverse reactions between adults and children leading to death

First main reaction	Adults	Children
Cardiac arrest / cardiorespiratory arrest / death / sudden death / sudden infant death syndrome /	13	5
Respiratory arrest / respiratory depression / respiratory disorder / respiratory distress / respiratory failure	4	2
Anaphylactic reaction / anaphylactic shock / anaphylactoid shock / angioedema	3	3
Convulsion	1	1
Neuroleptic malignant syndrome	5	1
Shock / circulatory collapse / hypotension	8	2
Total	34	14

The MAH summarises that the number of cases of the same type of adverse reactions between adults and children with fatal outcome was higher in adults compare to children for cardiorespiratory arrest, neuroleptic malignant syndrome, and shock.

The cases originated from France in 38% of the cases, from Japan in 28%, and from other countries in 33%. As sales data are allegedly only available to the MAH in France, no further comparisons on relative reporting frequency were made. The MAH concludes that therefore, the data cannot be properly evaluated.

Assessment of the MAH's response:

The newly submitted safety analysis is not reproduced here, as the evaluations presented in the previous submission, and the analysis presented in the answer to the request for supplementary information appear to be more comprehensive, as regards the included time interval and numbers. Therefore, in the following, only the responses to the questions are analysed.

a) The presentation of the company makes clear that the high frequency of overdose cases in the spontaneous reports might be biased by differential reporting, and that there is some indication for a smaller frequency when looking at epidemiological studies. However, the company has not fulfilled the request to present their cases (numbers) according to dose and dosing frequency of treatment.

The evaluation of the treatment duration revealed that in cases with EPD treatment duration is usually short, with most cases having been treated for less than 2 days until onset of the adverse event.

The omission of the presentation of the numbers as per dose and dosing frequency as requested can be considered acceptable, as it has become clear that EPDs occur possibly at a relatively high frequency in children that are not overdosed.

It can furthermore be concluded that EPDs usually occur at an early time-point of treatment.

b) The intention of the question was to possibly gain insight into the frequency of EPD events in the different age groups. The mere number of events (with the highest numbers in the infant group) suggests that the risk may be much higher in the younger age group, which would – as the events are considered relatively serious events as such – against the benefit of treatment of those young children.

However, the evaluations performed did not really allow a clear conclusion. At first it seems that reporting frequency in France is much higher than in all other European countries involved (however, the MAH did not state how many). Furthermore, sales data that could be put in relation to the reporting frequency are only available for France. This makes any meaningful comparisons useless. Formally, the request for further information has been fulfilled. However, it remains somehow unsatisfactory, as it is hard to believe that the company would not be able to gain insight into prescription data from other countries where it acts on behalf of the national MA holders.

Nevertheless it can be concluded that EPDs are high in numbers and are most frequently reported in the infant age group.

The reporting frequency therefore supports a strong association of this relatively severe and serious adverse reaction to age, and can be regarded to contribute to a negative benefit risk ratio in this population.

c) The evaluation of deaths has been done as requested. It can be seen that there is a considerable burden of reported deaths in the paediatric age group. The evaluation and display of cases, and the conclusions on relatedness, however, cannot be followed in all cases. This is due to the relatively short presentations, however, it is also due to the fact that in a couple of cases (the 11 cases with alternative explanations) a different conclusion could also be possible. The comparison with the numbers of deaths reported in adults concludes that the numbers are clearly lower, however, this is considered inappropriate as long as prescription data are not available in differential manner. Contrary to the conclusions of the company, one could also state that the burden of fatal events is relatively high with the medication, and that this would contribute negatively to the overall risk-benefit evaluation.

Overall Conclusion:

Issues resolved.

Conclusion: MTC is burdened with a high frequency of reporting of EPD adverse events and a considerable number of MTC related deaths in the pediatric age group which contributes negatively to the overall risk benefit ratio, considering the relatively benign conditions to be treated, and the alternative medications available.

The even higher number of EPD events in the infant population contributes to the overall recommendation not to use the substance in children younger than 1 year.

Question 5 (pre-clinical):

The position of the Applicant, that the submitted studies and the retrieved published papers do not provide any relevant information for the paediatric assessment in the context of this EU work-sharing procedure is endorsed. Nevertheless, the Applicant is asked to comment, whether the impairment of sexual behaviour seen after administration of metoclopramide to the perinatal rats might be relevant for consideration of therapeutic use of metoclopramide in pregnant women, and whether the current recommendations for use during pregnancy and lactation might need modifications.

Applicant's Response:

The conclusions made in the published article (Gonzales 2000 [6]) cited in the critical expert overview for metoclopramide paediatric assessment dated November 2009 on the impairment of sexual behavior in male rats following a neonatal administration of metoclopramide should be viewed with a certain amount of caution. Some critical information or examinations are missing from this publication which would have enabled the authors to conclude to a possible drug-effect.

The following are of particular note:

- There is only one treated group; therefore a possible dose-effect could not be established.
- The administered dose is 100 µg: the dose is not expressed as mg/kg with respect to the bodyweight of the animals as the weight of neonate rats is not given.
- There is no information on the rationale for the choice of the dose administered; in addition no exposure information is given to enable any relevant extrapolation to man
- There is no information on the 10 neonate rats/group treated from PND3 to PND6: from how many litters? Are they from culled litters?
- There is no information on any clinical examination performed for the period PND6 to PND90 for the control and treated animals (clinical signs, body weight change, postweaning landmarks e.g. cleavage of the balanopreputial gland of males...)
- On day 90, the examinations are limited to latency and frequency of mounts, intromission and ejaculation; there are no histological examinations of reproductive organs and in addition no biochemical/hormonal examinations.

Furthermore, it should be noted that as mentioned in the ICH S5A guideline, the rat as a species is well-recognized with regards to its disadvantages as to the sensitivity to sexual hormones and to dopamine agents in particular.

This is illustrated in a review article [Ben-Jonathan N, Lapensee CR and Lapensee EW. What can we learn from rodents about prolactin in humans? *Endocrine reviews*. 2008;29:1-41]. It is mentioned that *“The regulation of pituitary prolactin production/release is more complex and centralized in rodents than in humans. .../...Although the inhibitory action of dopamine is undisputed, many of the prolactin secretagogues, which are so prevalent in rodents, are less critical in humans.”* The author conclusion on overall regulation of prolactin was: *“rodents cannot serve as an appropriate model.”*

With regard to impairments of sexual behaviours in human, a causal relationship with the intake of metoclopramide during lactation or pregnancy has not been until now suspected in individual cases as impairments of sexual behaviours occur several years after the intake of metoclopramide and the physicians are not aware of such adverse reactions with metoclopramide. No cases were recorded in the

data of the MAH with metoclopramide and no cases were identified in the literature (from 1950 in Medline, 1974 in Embase and 1983 in Derwent Drug File). A causal relationship could be assessed only based on epidemiological studies on this topic, however no such epidemiological studies were identified in the literature which involved metoclopramide or D₂ antidopaminergic drugs.

In a recent study [Matok I, Gorodisher R, Koren G, Sheiner E, Wiznitzer A and Levy A. The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med. 2009;360:2528-35], Matok investigated the safety of metoclopramide use in the first trimester of pregnancy. In this large cohort of 3458 pregnant women the study concluded that exposure to metoclopramide in the first trimester of pregnancy is not associated with significantly increased risks of congenital malformations, low birth weight, or perinatal death. By using definitions of major and minor congenital malformations that were developed by the Metropolitan Atlanta Congenital Defects Program of the Centers for Disease Control and Prevention (CDC) no specific genital anomalies were reported. These data provide reassurance about the safety of metoclopramide for nausea and vomiting associated with pregnancy according to the authors.

A search on labeling (section pregnancy, non clinical safety data) from other dopamine antagonists such as risperidone, droperidol, domperidone, amoxapine, clozapin and olanzapine did not show specific concern about abnormal sexual behavior, nor fertility except for amoxapine (organ hyperfunction, slight decrease in the number of fertile matings) (see US PI in Applicant's Appendix 4, which states in the section on Impairment of Fertility: "*Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.*").

Based on information and data above the company position is that current recommendations for use during pregnancy and lactation can remain unchanged. They are globally in line with the CHMP guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005 dated 24 July 2008).

Assessment of the MAH's Response:

The Applicant states that the search on labeling (section pregnancy, non clinical safety data) from other dopamine antagonists did not show specific concern about abnormal sexual behavior, nor fertility except for amoxapine. The Assessor wants to comment, that, *whereas the material presented by the MAH includes the wording: "These data do not indicate the need for any further precautions for use than those already described above."* Section 5.3 Preclinical safety data of metoclopramide-containing medicinal products authorized nationally for the German market state in the paragraph of reproduction toxicity that "*Dosages, which induced an increase in prolactin levels, caused reversible impairment of spermatogenesis in rats.*"

Nevertheless, the Applicant conclusively demonstrates that the experimental findings by Gonzales et al. [Effects of neonatal administration of an antidopaminergic drug (metoclopramide) on sexual behaviour of male rats, Archives of Andrology 45 (2000) 137-142], based on which the concern was originally raised, to which the Applicant has responded in the document under assessment, are apparently not sound enough to trigger the requirement of a new safety assessment of metoclopramide regarding reproductive toxicity or fertility.

Therefore, the Applicant's position is agreed to.

Conclusion:

Issue resolved

Note:

The Assessor would like to point out that taking into account the labelling of the German originator product, the following wording is recommended for the section on use during lactation:

Metoclopramide is excreted in breast milk. As adverse effects of metoclopramide on the central nervous system of the breast-fed infant cannot be ruled out, nursing mothers should not use metoclopramide. If treatment with metoclopramide is clearly necessary, a decision should be made whether to discontinue breast-feeding or to abstain from metoclopramide treatment.

IX. OVERALL CONCLUSION

MTC has been used and is proposed to be used by the MAH in the following indications for the use in the paediatric population:

- Nausea and vomiting:
 - o Chemotherapy and radiotherapy-induced nausea and vomiting
 - o Postoperative nausea and vomiting
- Gastrointestinal Motility disorders:
 - o Gastroesophageal reflux disease
 - o Other gastrointestinal motility disorders
- Digestive Tract Explorations

The proposed dose range in the paediatric population was, regardless of the indication and mode of administration 0.1 mg/kg/day up to 0.5 mg/kg/day.

The evaluation of available data regarding the use of the compound in children, however, sheds considerable doubt on the clinical usefulness and proof of efficacy of the compound in this patient population. There is especially no clear evidence for efficacy in all gastrointestinal motility disorders, and there is no clear evidence for efficacy in chemotherapy- and radiotherapy induced nausea and vomiting. In these indications, sufficient and possibly safer medication are available for children (Serotonin antagonists and dexamethasone for CINV, H2-blockers and PPIs (at least ranitidine and omeprazole) for gastroesophageal reflux disease.

The evidence in the indication “digestive tract explorations” is restricted to one trial only with 18 patients and a firm conclusion cannot be drawn from this study.

There is sufficient evidence for efficacy of MTC in the treatment of PONV. However, this proof of efficacy is restricted to the treatment with i.v. administration only, and when given after the termination of surgery. All oral preparations should therefore not include a recommendation for the treatment of children. As regards the recommended dose, doses from 0.15 mg/kg b.w. are recommended, to be repeated if needed, up to a daily dose of 0.5 mg/kg b.w. in 24 hours.

A restricted indication, only recommending the treatment with MTC in case of failure of other therapies cannot be recommended as MTC has been shown to provide no additional benefit if administered with a 5-HT antagonist.

As regards the documented age range for efficacy in children, the four studies with documented efficacy in the PONV indication included children from the age of 1 up to 14 years only. Therefore, the treatment of infants less than 1 year of age with proven efficacy is not documented and can therefore also not be recommended. Additional concerns regarding the lowest age group of infants are derived from the safety analysis (see below).

Furthermore, the evaluation of PK data has shown that, overall, very few data on PK are available and would not make it appropriate to be included in the SPC of MTC containing products. Furthermore, there is clear indication that in pre-term and term neonates, clearance of the drug is diminished and half-life and plasma concentrations increased.

Due to the high burden of adverse reactions regarding CNS in the infant age group anyway, and the unpredictable plasma concentrations in newborns resulting in probable overdoses, a contraindication for neonates should be included in the SPC for this age group.

The overall evaluation of safety showed that there is a considerable burden of adverse reactions attributed to CNS related effects of MTC, especially to the occurrence of extrapyramidal reactions.

This risk is not only related to overdosing and poisoning, but, to a considerable part, also occurs when the currently recommended dosing instructions (maximum single dose of 0.15 mg/kg, maximum daily dose of 0.5 mg/kg, additional doses after 6 hours at the earliest) are adhered to.

There is no clear indication whether there is a differential risk in the different age groups, however, the number of reported events (especially for CNS related events) is clearly highest in the youngest age group. A literature review and the poor methodology in most pharmacoepidemiologic studies were also not able to differentiate properly between age groups.

As has been shown in the pharmacokinetic section, the use of MTC in the very young age group should not be recommended, as obviously elimination is slowed. Some of the data provided do indicate a considerable occurrence of extrapyramidal reactions in the very young. Therefore, it is concluded that – due to immaturity of drug metabolism and blood-brain barrier in very young children, MTC should not be used in children below the age of 1 year and contraindicated for neonates.

Adequate warnings and adverse events sections regarding the occurrence of these adverse reactions in children have been proposed by the applicant and should therefore be included in the SPC.

From the presented studies, it could be concluded that for the short-term administration, safety, especially extrapyramidal symptoms in the setting of the treatment of postoperative nausea and vomiting appear not be a relevant problem. This may be related to the postoperative setting where all patients are still under considerable sedation, which may prevent the occurrence of extrapyramidal reactions.

For this indication, therefore, a positive risk-benefit ratio can be concluded.

For all other indications and dosage forms, where the proof of efficacy has to be regarded to be insufficient, and either better (=more efficacious) or safer treatment alternatives are available, the burden of adverse reactions makes the overall benefit-risk ratio negative.

X. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMA.