Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No 1901/2006, as amended

Mebendazole

Vermox
Vermox forte

DE/W/0103/pdWS/001

Rapporteur:	Germany
Finalisation procedure (day 120):	17.12.2018

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Vermox, Vermox forte
INN (or common name) of the active substance(s):	mebendazole
MAH (s):	Janssen Research & Development U.K
Pharmaco-therapeutic group (ATC Code):	P02CA01
Pharmaceutical form(s) and strength(s):	100 mg tablets, 500 mg tablets, 20 mg/mL suspension

I. EXECUTIVE SUMMARY

Changes are proposed in sections 4.2, 4.4 and 5.2 of the SmPC and relevant sections of the PL (please refer to chapter II. and V. of this public AR).

Summary of outcome

☐ No change

☒ Change

- ☐ New study data
- ☒ New safety information: section 4.4 of the SmPC
- ☐ Paediatric information clarified
- ☐ New indication

II. RECOMMENDATION

Specific wording related to paediatric use is proposed for the following sections of the SmPC:

SmPC:

4.2 Dosage and administration

1. for countries where the oral suspension is authorised:

   Paediatric population
   TRADENAME oral suspension should be considered for patients such as young children who are unable to swallow the tablet.

   and for countries where no oral suspension is licensed:

   Paediatric population
   "Tablets may be chewed or swallowed whole. Crush the tablet before giving it to a young child. Always supervise a child while they are taking this medicine."

2. for the indication ***strongyloidiasis*** in EU countries where it is approved:

   '*Paediatric population / Children and adolescents (≥2 to 16 years)*
   Data on efficacy and safety in children and adolescents ≥2 years to 16 years are limited. Mebendazole should be used only, if there is no therapeutic alternative.'

3. for the indication ***Taeniasis***:

   '*Paediatric population / Children and adolescents (≥2 to 16 years)*
   Data on efficacy and safety in children and adolescents ≥2 years to 16 years are limited. Mebendazole should be used only, if there is no therapeutic alternative.'

4. for the indications **trichinosis** and **echinococcosis**:

   4.1 Therapeutic indications
   'Official guidelines should be taken into consideration. Official guidelines will normally include WHO and public health authorities' guidelines.'

   4.4 Special warnings and precautions for use
   As higher doses and longer treatment is recommended in patients with Trichinellosis and Echinococcosis, careful consideration should be given when treating patients with severe chronic hepatic diseases and/or bone marrow depression."

   and

   These patients should be closely monitored with hematological, liver and renal function tests. Consider discontinuing TRADENAME if clinically significant laboratory abnormalities are found. 'Official guidelines should be taken into consideration.

Children under 2 years of age:
TRADENAME has not been extensively studied in children below the age of 2 years. Currently available data are described in section 4.4, 4.8 and 5.2, but no recommendations on a posology can be made.
Because of the lack of sufficient safety data, TRADENAME should not be used in children below the age of 1 year (see section 4.4, 4.8 and 5.2).

4.4 Warnings and precautions
Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience. (see section 4.8)
TRADENAME has not been extensively studied in children below the age of 2 years. Therefore, TRADENAME should be used in children aged 1-2 years only if the potential benefit justifies the potential risk.
Because of the lack of sufficient safety data, TRADENAME should not be used in children below the age of 1 year.

5.2 Pharmacokinetic properties
'Paediatric population:
Limited data of the mebendazole concentrations in plasma are available in children and adolescents 1 to 16 years of age. These data do not indicate substantially higher systemic exposure to mebendazole in subjects 3 to 16 years of age compared to adults. In subjects 1 to <3 years of age, systemic exposure is higher than in adults due to higher mg/kg dose relative to adults."

PL:

The changes proposed for the SmPC should be included in the relevant sections of the PL.

A Type IB variation on the proposed changes to the SmPC/PL should be submitted by the MAH, within 60 days after finalisation of the procedure for medicinal products included in the worksharing, if not already included.

For medicinal products with the same active substance and pharmaceutical form, the submission of a type IB variation is requested within 90 days of publication of the public assessment report.

III. INTRODUCTION

The MAH Janssen Research & Development U.K provided a Clinical Overview which reviews clinical study-based information on mebendazole use in paediatric subjects. The Clinical Overview was provided as part of the documentation submitted to the National Competent Authority (NCA) in the context of the worksharing for paediatric studies, in accordance with Article 45 of the Regulation (EC) No. 1901/2006, as amended on medicinal products for paediatric use.

The MAH proposed the following regulatory action as described as SmPC and PL proposals above in section II.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

- An annex including SmPC wording of sections 4.1, 4.2 and 4.4 related to the paediatric use of the medicinal product, and related PL wording.

Background
Mebendazole (methyl-5-benzoylbenzidazole-2-carbamate) is a broad-spectrum anthelmintic. In therapeutic indications, mebendazole acts locally in the patient's gastrointestinal tract where it exerts its anthelmintic effect by interfering with cellular tubulin formation in the intestines of worms. Mebendazole binds specifically to tubulin and causes ultrastructural degenerative changes in the worm's intestine. As a result, the glucose uptake and the digestive functions of the worm are disrupted to such an extent that an autolytic process occurs.

Mebendazole was first approved in Belgium in March 1971. In the EU, mebendazole is approved in the following formulations and countries:

- **100 mg oral tablets**: Austria, Belgium, Cyprus, Czech Republic, Denmark, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Romania, Slovakia, Spain, Sweden, and United Kingdom.
- **20 mg/mL suspension**: Belgium, Cyprus, Denmark, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, and United Kingdom.
- **500 mg oral tablets**: Belgium, Germany, Italy, and Luxembourg.

Indications
The approved indications, which are for both adult and paediatric patients, vary across the EU countries.
According to the current CCDSs (Company Core Data Sheet) the indications are as follows for the different formulations:

Mebendazole 100 mg oral tablet and **20 mg/mL oral suspension formulations** are indicated for the treatment of single or mixed gastrointestinal infestations by

- *Enterobius vermicularis* (pinworm),
- *Trichuris trichiura* (whipworm),
- *Ascaris lumbricoides* (large roundworm),

- *Ancylostoma duodenale* (hookworm),
- *Necator americanus* (hookworm),
- *Strongyloides stercoralis* (threadworm),
- *Taenia* spp. (tapeworm).

Most of the countries approved all of the indications contained in the CCDS for the 100 mg oral tablet and 20 mg/mL oral suspension formulations (where available); however, a few countries only retained specific indications. *S. stercoralis* (threadworm) and/or *Taenia* spp. (tapeworm) are the 2 indications that some countries chose not to approve (Cyprus, Malta, UK, Iceland, Sweden, Portugal [only *Taenia* spp.] Romania and Spain).

Mebendazole 500 mg tablets are indicated for the treatment of single or mixed gastrointestinal infestations by

- *Enterobius vermicularis* (pinworm),
- *Trichuris trichiura* (whipworm),
- *Ascaris lumbricoides* (large roundworm),
- *Ancylostoma duodenale* (hookworm),
- *Necator americanus* (hookworm).

- Furthermore, in patients living in heavily endemic areas, regular treatment with mebendazole 500 mg (3 to 4 times a year) will substantially reduce the overall worm load and keep it well below the level of clinical significance.

For the 500 mg oral tablets, the approved indications in EU countries are not consistent with the indications contained in the CCDS for this formulation.
None of the helminthic indications contained in the CCDS for the 500 mg tablet formulation are approved in any of the EU countries. This is because the EU countries took a more restrictive approach towards the standard dosing regimen; the repetitive 100 mg dosing regimen was preferred to the single 500 mg dosing regimen. The 500 mg tablet was reserved only for the treatment of serious parasitic infections requiring higher dosages.
An overview of the approved indications is given in Table 1.

Table 1: Mebendazole 500 mg Tablet Therapeutic Indications in Summary of Product Characteristics Across European Union Countries

CCDS/ Country	Indications			
	Enterobius vermicularis (pinworm); *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); *Ancylostoma duodenale*, *Necator americanus* (hookworm)	Inoperable or Not Radically Operable Echinococcoses (*Echinococcus granulosus* [Hydatid Disease] or *Echinococcus multilocularis*)	Follow-up Treatment or Prophylaxis of Operated Cases of Echinococcoses/ Hydatid Disease	Trichinella Infestation (*Trichinella spiralis* Infection or Trichinosis)
CCDS	✓			
Belgium and Luxembourg		✓	✓	
Germany		✓		✓
Italy		✓	✓	

CCDS=Company Core Data Sheet.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Mebendazole 100 mg and 500 mg tablets as well as 20 mg/mL suspension were used in all of the submitted studies. One study was performed with mebendazole capsules.

Assessor's comment (Day 70):
In one controlled study (Albonico, M. et al., 1994) the formulation was not given. One controlled study was performed with mebendazole capsules (Brugmans, J. P. et al., 1971).
There are only two controlled studies which were performed with a mebendazole suspension/syrup: Cabrera et al., 1980 and study Study R 17 635/48, 1975.

Regarding the compliance of the mebendazole suspension in children, the MAH proposes to include the following recommendation in section 4.2 of the SmPC and section 3 of the PL:

> *SmPC – 4.2 Dosage and administration*
> *[Only if the oral suspension is authorized]*
> *TRADENAME oral suspension should be considered for patients such as young children who are unable to swallow the tablet.*
>
> *PL - Section 3 How to use TRADENAME*
> *[Only if the oral suspension is authorized]*
> *Consider using TRADENAME oral suspension for patients such as young children who are unable to swallow the tablet.*

The inclusion of this wording will depend on the MAH's response to question 4 (see chapter IV.3).

IV.2 Non-clinical aspects

1. Introduction

No non-clinical information was submitted.

Assessor's comment (Day 70):
*The MAH is asked to justify the lack of non-clinical information (**Question 1 of Day 70 RSI**).*

Summary of MAH's Response to Question 1 of the Day 70 RSI
Nonclinical safety studies on mebendazole were conducted in the 1970s to support the initial Food and Drug Administration (FDA) approval of VERMOX® in 1974. Juvenile animal toxicity studies were not required at the time of approval; however, a comprehensive battery of nonclinical studies was conducted in multiple species to evaluate the safety of mebendazole. These studies include single- and repeat-dose toxicity and evaluations for mutagenicity, reproductive toxicity, and carcinogenicity. More importantly, clinical experience in the last 4 decades has demonstrated the safe use of mebendazole in paediatric patients.

Conclusion:
Mebendazole was well tolerated in single-dose studies with very low oral toxicity, which may be related to the low solubility and poor bioavailability.
In repeat-dose studies up to 13 weeks in rats, findings at ≥40 mg/kg/day were related to the liver (increased liver weights with histopathology correlates and serum chemistry changes) as well as changes in the testes and spermatogenesis that was attributable to poor condition. Mortality due to enteritis was present at high dose of 160 mg/kg/day.
Results from the 13-week dog study showed hepatic effects (increased liver weights as well as some altered hematology and clinical chemistry values) at doses ≥10 mg/kg. However, following repeated-dose administration up to 24 months in dogs, there were no pathology findings that were attributable to mebendazole treatment up to 40 mg/kg/day.
No mutagenic activity was observed with mebendazole in bacterial reverse mutation tests. Mebendazole was aneugenic *in vitro* in mammalian somatic cells at a threshold concentration of 115 ng/mL. *In vivo* tests also revealed aneugenic activity but no structural chromosomal damage.
Mebendazole had no carcinogenic effects at doses as high as 40 mg/kg/day when administered daily over 2 years in carcinogenicity tests in mice and rats.
Male rat fertility was not affected with doses up to 40 mg/kg/day for 60 days. When female rats were dosed at up to 40 mg/kg/day for 14 days before gestation and during pregnancy, no significant effect upon fetuses and offspring were observed, though there was slight maternal toxicity.
In an embryo-fetal development toxicity study in mice, doses of ≥10 mg/kg/day were observed to be maternally toxic, embryotoxic (fetal resorption were 100% at 40 mg/kg) and fetal abnormalities were present.
Mebendazole was embryotoxic and teratogenic in pregnant rats at single oral doses as low as 10 mg/kg when administered on GD 7, 8, or 9.
Embryo-fetal development toxicity studies in rats treated at GD 6 to 15 revealed no adverse effects on dams or their progeny at dosages up to 5 mg/kg/day. Dosing at ≥10 mg/kg/day resulted in maternal toxicity, embryotoxicity (fetal resorptions were 100% at 40 mg/kg/day), decreased fetal weight, and increased incidence of skeletal malformations were observed.
Dosing of hamsters and rabbits did not result in embryotoxicity or teratogenicity at dosages up to 40 mg/kg/day in embryo-fetal development studies.
In a peri-and postnatal toxicity study in rats, mebendazole did not adversely affect dams or their progeny at 20 mg/kg/day. At 40 mg/kg, a reduction of the number of live pups was observed and there was no survival at weaning. No abnormalities were found.

Note by the assessor:
The individual toxicological studies are not presented in this AR.

Assessor's comment (Day 90, assessment of response to question 1):
The toxicological properties of mebendazole have been sufficiently demonstrated and were adequately implemented in the preclinical part section 5.3 of the SmPC.
Issue solved.

IV.3 Clinical aspects

1. Introduction

1.1 Pharmacodynamic (PD) Results in Paediatric Subjects

There were no PD clinical studies for mebendazole in paediatric subjects included in the 2008 line listing.

1.2 Pharmacokinetics (PK)

As stated in the current mebendazole CCDSs the following PK data are available:

Absorption
Following oral administration, <10% of the dose reaches the systemic circulation, due to incomplete absorption and to extensive pre-systemic metabolism (first-pass effect). Maximum plasma concentrations are generally seen 2 to 4 hours after administration. Dosing with a high fat meal leads to a modest increase in the bioavailability of mebendazole.

Distribution
The plasma protein binding of mebendazole is 90 to 95%. The volume of distribution is 1 to 2 L/kg, indicating that mebendazole penetrates areas outside the vascular space. This is supported by data in patients on chronic mebendazole therapy (e.g., 40 mg/kg/day for 3-21 months) that show drug levels in tissue.

Metabolism
Orally administered mebendazole is extensively metabolized primarily by the liver. Plasma concentrations of its major metabolites (amino and hydroxylated amino forms of mebendazole) are substantially higher than those of mebendazole. Impaired hepatic function, impaired metabolism, or impaired biliary elimination may lead to higher plasma levels of mebendazole.

Elimination
Mebendazole, the conjugated forms of mebendazole, and its metabolites likely undergo some degree of enterohepatic recirculation and are excreted in the urine and bile. The apparent elimination half-life after an oral dose ranges from 3 to 6 hours in most patients.

Steady-state pharmacokinetics
During chronic dosing (e.g., 40 mg/kg/day for 3-21 months), plasma concentrations of mebendazole and its major metabolites increase, resulting in approximately 3-fold higher exposure at steady-state compared to single dosing.

Assessor's comment (Day 70):
*These PK data are also included in section 5.2 of the German SmPC. Information for other SmPCs within the EU are not provided. The MAH is asked to comment (**Question 2 of Day 70 RSI**).*

No information is given on the PK data for paediatrics in the relevant section of the SmPC (please see next Day 70 comment below).

MAH's Response to Question 2 of the Day 70 RSI

In the clinical overview submitted as part of the Article 45 procedure (EDMS-ERI-130956535), the Marketing Authorization Holder (MAH) stated that PK information is given in all summaries of product characteristics (SmPCs) within the European Union (EU) in line with the Company Core Data Sheet (CCDS). The MAH reviewed all EU SmPCs, and confirms that these SmPCs are consistent with the CCDS. In a few countries there were differences in the formatting or sub-sectioning of the information, but the information presented is essentially the same.

Assessor's comment (Day 90, assessment of response to question 2):

Issue solved.

Pharmacokinetics of Mebendazole in Paediatric Subjects

One study (*Toppare MF, Gocmen A, Kiper N. Plasma level of mebendazole in children with hydatid disease. Ann Trop Paediatr. 1992; 12:441-444*) is included that reported PK data for mebendazole in paediatric subjects.

Toppare conducted a single arm, PK study of mebendazole in 24 paediatric subjects (11 girls and 13 boys) with hydatid disease. The children were aged 18 months to 16 years (mean age: 8.5 years) and were given mebendazole orally for 9 months to 2 years (mean: 11.7 months) in a dose of 50 mg/kg in 3 divided doses with fatty meals.

The plasma levels in all 24 children were measured after 2-6 months (mean: 3 months) of drug therapy. Blood samples were obtained 4 times: just before drug administration, and at 2, 4 and 6 hours after one-third of the daily drug dose (17 mg/kg) had been taken. In 10 children (mean age: 8 years), the plasma level of mebendazole was also measured immediately after the initial dose of the drug at the beginning of the therapy. The plasma concentration of mebendazole was determined by high performance liquid chromatography (HPLC) after extraction with chloroform at pH 11.

The plasma levels of mebendazole are shown in Table 2 below.

Table 2: Plasma Level of Mebendazole after the Initial Dose and During Chronic Use in Children

Time	Plasma level, ng/mL		
	Mean (SD)	Minimum	Maximum
After the initial dose (n=10)			
2 hours	14.82 (2.69)	12.0	19.0
4 hours	23.86 (6.53)	14.0	32.0
6 hours	21.52 (6.88)	14.0	32.0
During chronic therapy (n=24)			
0 hour	13.58 (3.83)	5.0	20.0
2 hours	18.83 (5.85)	8.0	28.0
4 hours	25.76 (9.81)	4.8	39.0
6 hours	23.66 (9.78)	6.0	37.8

SD=standard deviation.

The plasma level showed a peak at 4 hours after ingestion of the drug. The mean 4-hour value was 1.9 times the basal value. The difference between the initial plasma levels and levels at 4 hours was statistically significant ($p<0.05$).

Assessor's comment (Day 70):
*The MAH is asked to discuss and comment these paediatric PK data in context with PK data from adult subjects/patients. Information on paediatric PK data may be considered for inclusion in section 5.2 of the SmPC (**Question 3 of Day 70 RSI**).*

Summary of the MAH's Response to Question 3 of the Day 70 RSI

Only one study containing mebendazole PK data in children is found in the literature. Toppare et al. (1992) conducted a single-arm, PK study of mebendazole in 24 paediatric subjects (11 female and 13 male) with hydatid disease. The children were aged 18 months to 16 years (mean age: 8.5 years) and were given mebendazole orally for 9 months to 2 years (mean: 11.7 months) in a dosage of 50 mg/kg/day in 3 divided doses with fatty meals. The formulation administered to the subjects was not stated by the authors, but may have been a suspension as subjects were dosed by weight.

The plasma levels in all 24 children were measured after 2 to 6 months (mean: 3 months) of drug therapy. Blood samples were obtained at 4 time points: just before drug administration, and at 2, 4, and 6 hours after one-third of the daily drug dose (17 mg/kg) had been taken. In 10 children (mean age: 8 years), the plasma level of mebendazole was also measured immediately after the initial dose of the drug at the beginning of therapy. The publication does not include a further analysis stratified by age or age group.

The data from the article by Toppare, Witassek, and other studies conducted in adults are summarized in the following Table 3:

Table 3: Summary of Mebendazole Plasma Exposure Data in Children and Adults in Studies Reported in the Literature

Study	N	Dosage	Mean Maximal Plasma Exposure (C_{max}, ng/mL)
Children			
Toppare (1992)[84]	10 24	17 mg/kg initial dose 50 mg/kg/day, 17 mg/kg/dose	23.86±6.53 (range 14-32) ng/mL 25.76±9.81 (range 4.8-39) ng/mL
Adults			
Witassek (1981)[93]	7	29-63 mg/kg/day (mean 39 mg/kg/day) for approx. 20 months	98 ng/mL (range 53-203 ng/mL)[a]
Corti (2009)[23]	8 8	13.7 mg/kg single dose 13.7 mg/kg/day × 8 days, with ritonavir	31.0±26.0 ng/mL 11.5±6.2 ng/mL
Bekhti (1985)[9]	11 10 9	43 mg/kg/day[b] 64 mg/kg/day[b] 86 mg/kg/day[b]	49.6±22.0 ng/mL[c] 84.3±63.7 ng/mL[c] 130 ± 136 ng/mL[c]
Braithwaite (1982)[11]	5	10 mg/kg single dose	69.5±40.4 ng/mL
Tanaka (1986)[83]	8	2×100 mg tablet, single dose (approx. 3 mg/kg)	39.4±39.5 ng/mL

[a] Reported in reference as molar units: 0.33 µmol/L (range 0.18-0.69 µmol/L).
[b] Body weight of subjects not available; 70 kg used to estimate mg/kg dose.
[c] C_{max} value determined from mean plasma concentration vs time data, as reported in publication.

More recently, a clinical study was conducted by the MAH in which paediatric subjects with gastrointestinal helminth infections received a single oral 500 mg dose of mebendazole as a

new fast-disintegrating**, chewable formulation** (Study GAI3003, 2016). The PK data from blood samples were obtained over a 24-hour period post-dose from approximately 40 paediatric subjects ranging in age from 1 to 16 years.
The PK results of this study are summarized in the following table (Table 4), including analyses stratified by age group and a comparison to PK data in healthy adult subjects who received the same dose in Study GAI1002 (2014).

Table 4: Mean (SD) Mebendazole Pharmacokinetic Parameters in Paediatric Subjects and Healthy Adult Subjects

	GAI3003(Pediatric)*			GAI1002 (Adult)*	
Parameter	1 to <3 yrs	3 to <7 yrs	7 to 16 yrs	Fed	Fasted
N	22	12	10	16	16
Dose (mg/kg)	45.7	28.2	17.3	7.04	7.04
(Range)	(29.4 - 56.2)	(23.6 - 34.5)	(10.5 - 25.6)	(5.66 - 9.82)	(5.66 - 9.82)
C_{max} (ng/mL)	210 (212)	49.9 (26.8)	34.2 (13.8)	56.2 (35.8)	14.0 (9.17)
t_{max} (h)[a]	2.5	2.0	3.0	4.0	1.5
	(1.0 – 8.0)	(0.98 – 3.0)	(1.0 – 8.0)	(2.0 – 6.0)	(0.50 – 3.0)
AUC_8 (ng.h/mL)	697 (367)[b]	242 (139)[c]	182 (66.3)	ND	ND
AUC_{last} (ng.h/mL)	1,320 (844)	416 (215)	387 (190)	400 (194)[d,e]	111 (60.0)[d,e]

Abbreviations: AUC_8=area under the concentration-time curve from time zero to 8 hours; AUC_{last}=area under the concentration-time curve from time zero to infinity; C_{max}=maximum plasma concentration; ND=not determined; SD=standard deviation; t_{max}=time to reach maximum concentration.
[a] Median (Range)
[b] n=21
[c] n=9
[d] n=15
[e] AUC_{24}, for comparison to AUC_{last} in pediatric subjects; the last sample was taken approximately 24 hours postdose in the PK substudy. Thus, for this study AUC_{24}=AUC_{last}
*In pediatric subjects, parameters were determined based on concentrations in whole blood fingerstick samples; in adults, parameters were determined based on concentrations in venous plasma samples.

Maximal concentrations of mebendazole were attained 1 to 3 hours post-dose in most subjects and remained measurable at the last sampling time at 24 hours post-dose. There was a high degree of inter-subject variability in mebendazole blood concentrations. Based on C_{max} and area under the concentration-time curve (AUC) values, higher exposures were seen in the youngest age group (age 1 to 3 years) as expected from the higher mg/kg dose; in older paediatric subjects (age 3-7 years and age 7-16 years). Drug exposure was similar to that in adult subjects who received the same mg dose in another study.

Conclusion:
Overall, data on the PK of mebendazole in paediatric subjects are limited and show substantial inter-subject variability. The data suggest a similar dose-exposure relationship as in adults, although the data show greater exposure in the youngest paediatric subjects compared with adults due to a higher mg/kg dose. Importantly, the available PK data in both adult and paediatric subjects characterize the small fraction (estimated to be less than 10%) of the orally administered dose of mebendazole that reaches the systemic circulation. The majority of an orally administered dose remains in the gastrointestinal tract where it is active locally against gastrointestinal helminths.

On the basis of the above data, the MAH proposes the following general statement in Section 5.2 of the SmPC regarding the paediatric population:

"Limited drug concentration data are available in children and adolescents 1 to 16 years of age. These data do not indicate substantially higher systemic exposure to mebendazole in subjects 3 to 16 years of age compared to adults. In subjects 1 to <3 years of age, systemic exposure is higher than in adults due to higher mg/kg dose relative to adults."

Assessor's comment (Day 90, assessment of response to question 3):
The MAH's proposal is supported. Based on the PK data available for children and adults the following statement

'Paediatric population:
Limited data of the mebendazole concentrations in plasma are available in children and adolescents 1 to 16 years of age. These data do not indicate substantially higher systemic exposure to mebendazole in subjects 3 to 16 years of age compared to adults. In subjects 1 to <3 years of age, systemic exposure is higher than in adults due to higher mg/kg dose relative to adults."

should be included in section 5.2 of the SmPC.

Issue solved provided that the text will be implemented in the SmPC.

2. Clinical studies

The MAH 'Janssen Research & Development U.K 'submitted the following paediatric studies

- 42 clinical studies where clinical reports were available and /or described in literature articles or abstracts

for mebendazole, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. In addition, 1 paediatric pharmacokinetic article and 4 paediatric clinical studies were included that had not been submitted in the 2008 line listing.

2.1 Enterobiasis/ *Enterobius vermicularis* (pinworm)

Controlled Studies
Five randomized, placebo-controlled and/or active-controlled studies and 2 non-randomized, controlled studies of mebendazole in paediatric subjects with enterobiasis were presented by the MAH in tabular format (table not shown here).

Non-controlled Studies
Seven non-controlled studies of mebendazole in paediatric subjects with enterobiasis were presented by the MAH in tabular format (table not shown here).

Assessor's comment (Day 70):

ENTEROBIASIS

Controlled studies:

The age of the paediatric subjects ranged from <2 to 21 years. In some of the controlled studies which included paediatric patients below the age of 2 years, the results were not analysed according to this age group. Thus, no information on efficacy and safety is given for the age group below 2 years.
Efficacy as cure rates of mebendazole for the treatment of Enterobiasis / Enterobius vermicularis (Pinworm) was assessed after administration of different doses (range 25 – 200 mg mebendazole) as a single dose once or repeated at different intervals or a single dose for 2-3 consecutive days. Cure rates were determined at different time points according to the dosing regimen.
In general, a single dose of 100 mg mebendazole was effective 2 weeks after treatment with cure rates of about > 90%. Subjects who were positive at this time points indicated that a repeated or second dosing is mostly necessary.
As concluded by the author Sarmah, H.C., 1988, the low efficacy of 60% after administration of a single dose of 200 mg mebendazole is due the concomitant infestation by ascariasis.

No study was performed with the suspension of mebendazole.
Information regarding the kind of crushing the tablets is lacking.

<u>Non-controlled studies:</u>
There was no study conducted with children below the age of 2 years. The age range was between 2 – 25 years or not reported in one of these studies (Balagopal, R., 1974).
The administered dose was 100 mg of mebendazole as a single dose – repeated if ineffective – or a single dose of 100 mg at different time points or bid for 3 consecutive days. Cure rates ranged from 96% to 100%. One (Karnauhov, V.K. et al., 1987) out of seven studies was conducted with 20-50 mg of mebendazole once or twice at 2-week intervals in children 2 – 10 years old. Cure rate was given as 'Good response' and not further defined.
In 3 studies, the paediatric subjects suffered from mixed infections.

No study was performed with the suspension of mebendazole.
Information regarding the kind of crushing the tablets is lacking.

<u>Conclusion:</u>
As a result, the following dosage regimens were recommended in the SmPCs within the European Member States:

- *Single dose of 100 mg with repeating of the treatment at different time intervals*

or

- *Single dose of 100 mg at 3 consecutive days with repeating of the treatment at different time intervals*

*It should be pointed out that the recommended dosage regimens extend to the 100 mg tablet as well as to the 20 mg/ml suspension. However, no study was performed with the suspension of mebendazole. There are no data regarding comparable efficacy between these different formulations. The MAH is asked to comment and provide the appropriate data (**Question 4 of Day 70 RSI**).*

Furthermore, instructions for the use of the tablet in children should be given in more detail. Provided the mebendazole suspension is not approved and/or available and no comparable efficacy between the tablet and oral suspension could be demonstrated, instructions for the use of the tablet formulation in children should be given in more detail e. g. regarding the kind of crushing, solubility of the crushed tablet, amount of the recommended crushed liquid,

*compatibility with food, probable taste sequestering. An appropriate wording in the relevant sections of the informative texts will depend on the outcome of the MAH's response (**Question 5 of Day 70 RSI**).*

Summary of the MAH's Response to Question 4 of the Day 70 RSI

Mebendazole has been shown to have the essential requirements of an antihelmintic, such as low cost, excellent tolerability, wide spectrum of action, and oral administration; however, the mebendazole tablet formulation maybe difficult to swallow in some patients (e.g. young children). In this case, the use of the oral suspension formulation could be an alternative.

In literature, three clinical studies could be identified which demonstrated that treatment with the tablet formulation and the oral suspension formulation resulted in similar levels of bioavailability or efficacy.

Dawson et al (1985)

In a clinical pharmacology study that evaluated the relative bioavailability of tablet, capsule and suspension formulations of mebendazole, Dawson et al (1985) showed that, based on urinary excretion data, systemic bioavailability of mebendazole was low but similar when administered as tablet or oral suspension. The authors conducted a randomized, bioavailability study of 4 different doses of mebendazole in 13 healthy male subjects (mean age of 24 years).

de Oliveira Gomes (1974)

In an open-label study conducted in 50 children aged 3 to 10 years, de Oliveira Gomes (1974) showed that the suspension formulation of mebendazole presented similar efficacy in comparison to other studies that used the tablet formulation, as well as excellent tolerance and agreeable taste. In this study, all children were positive for *Ascaris lumbricoides*, *Enterobius vermicularis*, *Ancylostoma*, and *Trichuris trichiura*. All children received mebendazole 5 mL (100 mg) suspension twice daily, before breakfast and before dinner for 3 days.

However, no direct statistical comparisons were made between the oral suspension and tablet formulation.

Cabrera and Cruz (1980)

Cabrera and Cruz (1980) conducted a nonrandomized, dose comparison study in 269 subjects, of which 177 were children (age not specified) who were positive for *A. lumbricoides*, *T. trichiura*, or hookworm. 15 Subjects received 1 of 3 treatments: mebendazole 300 mg twice daily for 1 day (treated: n=30), 100 mg twice daily for 3 days (treated: n=19), or mebendazole 600 mg single dose (treated: n=21). In some children, the drug was given in the form of suspension (rationale not provided; 300 mg twice daily for 1 day: 19/30 (63.3%) treated; 100 mg twice daily for 3 days: 11/19 (57.9%) treated; 600 mg single dose: 12/21 (57.1%) treated).

In conclusion, among children with ascariasis both the suspension and tablet formulations were equally effective based on cure rate. In children with trichuriasis, the tablet produced a higher cure rate than the suspension formulation. In children with hookworm infestations, the suspension formulation was slightly more effective than the tablet. A possible limitation of this study was the small number of subjects for each of the treatment arms.

In addition, a search of the Company Global Safety Database was performed for all cases that met the following criteria:

- Mebendazole as suspect or suspect-interacting drugs
- Medically confirmed and not medically confirmed
- AEs coded to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 Preferred Terms (PTs) of choking or choking sensation or tracheal obstruction or upper airway obstruction or asphyxia
- All types of cases (e.g., spontaneous/clinical study/registry, etc.)
- Version of case: highest version in date range
- Cases received cumulatively through 13 September 2016; cases that were in workflow at the time of the database search were not captured as part of this search

The search retrieved a total of 1 case (reported in 2004): A 2 year-old female (20040700017), with an unknown medical history, received mebendazole 100 mg (tablets, oral) for the treatment of worms. No concomitant medications were reported. After being given a mebendazole tablet, the patient immediately began to choke. Attempts to revive the patient were unsuccessful and she died. An autopsy confirmed that the tablet became lodged in her airway.

In conclusion, the data presented above, which was identified from the literature review of clinical studies and the global safety database analysis, showed that the bioavailability and efficacy of the oral suspension is similar to the tablets.
Further, the data highlight that there is a risk of choking when using tablets in small children. Several countries included the possibility to chew or crush the tablets. Moreover, the World Health Organization (WHO) guidelines for the treatment of helminth infections state that tablets should be broken into smaller pieces, or crushed, for administration to young children, and older children should be encouraged to chew mebendazole tablets. However, the mebendazole 100 mg and 500 mg solid tablets were never studied by the Company when administered in a crushed form, therefore, the CCDSs contain a statement recommending using the oral suspension (when available) in young children.
For countries that do not have the oral suspension formulation licensed the following instruction for section 4.2 of the SmPC is proposed:

> *"Tablets may be chewed or swallowed whole. Crush the tablet before giving it to a young child. Always supervise a child while they are taking this medicine."*

Assessor's comment (Day 90, assessment of response to question 4):
Based on the presented data, it can be concluded that the bioavailability (by urinary excretion examination) and efficacy (by cure rates) of the oral suspension is similar to the tablets. Additionally, taken into consideration the recommendation of the WHO guidelines the following instructions for section 4.2 of SmPC and section 3 of the PL are proposed:

for countries where the oral suspension is authorized:

> *SmPC – 4.2 Dosage and administration*
> *Paediatric population*
> *TRADENAME oral suspension should be considered for patients such as young children who are unable to swallow the tablet.*
>
> *PL - Section 3 How to use TRADENAME*
> *Paediatric population*
> *Consider using TRADENAME oral suspension for patients such as young children who are unable to swallow the tablet.*

and for countries where no oral suspension is licensed:

SmPC – 4.2 Dosage and administration
Paediatric population
"Tablets may be chewed or swallowed whole. Crush the tablet before giving it to a young child. Always supervise a child while they are taking this medicine."

PL - Section 3 How to use TRADENAME
Paediatric population
"Tablets may be chewed or swallowed whole. Crush the tablet before giving it to a young child. Always supervise a child while they are taking this medicine."

Issue solved provided that the text will be implemented in the SmPC.

Summary of the MAH's Response to Question 5 of the Day 70 RSI
Please see response to question 4.

Assessor's comment (Day 90, assessment of response to question 5):
Please see comment to question 4.

Issue solved provided that the text will be implemented in the SmPC.

2.2 Ascariasis/*Ascaris lumbricoides* (large roundworm), Trichuriasis/*Trichuris trichiura* (whipworm), and Ancyclostomiasis/*Ancylostoma duodenale* and Necatoriasis/*Necator americanus* (hookworm)

Controlled Studies
Three randomized, placebo-controlled and/or active-controlled studies and 12 non-randomized, controlled studies of mebendazole in paediatric subjects with ascariasis, trichuriasis, or hookworm were presented by the MAH in tabular format (tables not shown here).

The summaries of the following controlled studies are presented in more detail due to different dosages and formulations with different doses:

a) One study was performed with a suspension of mebendazole:

Cabrera et al., 1980 conducted a non-randomized, dose comparison study in 269 subjects, of which 177 were children (age not specified) who were positive for *A. lumbricoides*, *T. trichiura,* or hookworm. Subjects received either mebendazole 300 mg twice daily for 1 day (n=68), mebendazole 100 mg twice daily for 3 days (n=51), or mebendazole 600 mg single dose (n=58). **In some children, the drug was given in the form of suspension**. Efficacy results are shown in Table 5.

Table 5: Results of Treatment of Soil-Transmitted Helminthiases With Mebendazole Among Children Using Different Doses, Regimen And Form Of Drug (Cabrera et al., 1980)

Drug form	300 mg bid for 1 day		100 mg bid for 3 days		600 mg (single dose)	
	Number treated	Cure rate (%)	Number treated	Cure rate (%)	Number treated	Cure rate (%)
A. lumbricoides						
Suspension	19	93.8	11	100	12	60.5
Tablet	11	88.9	8	100	9	75.0
Total	**30**	92.0	**19**	100	**21**	66.6
T. trichiura						
Suspension	15	53.8	10	50.0	12	60.0
Tablet	11	100	10	88.8	11	75.0
Total	**26**	70.0	**20**	70.6	**23**	66.6
Hookworm						
Suspension	8	71.4	7	40.0	8	71.4
Tablet	4	66.6	5	100.0	6	40.0
Total	**12**	70.0	**12**	70.0	**14**	58.3

bid=twice daily.

Among children with *A. lumbricoides*, both mebendazole suspension and tablet were equally effective. Overall, mebendazole 100 mg twice daily for 3 days had the highest cure rate (100%) followed by mebendazole 300 mg twice daily for 1 day (92%), and the lowest cure rate was seen with mebendazole 600 mg single dose (66.6%). In children with *T. trichiura*, the tablet formulation gave much higher cure rate than the suspension for all 3 regimens. In children with hookworm, the results did not follow a regular trend but the suspension was slightly favored over the tablet with the exception for the dose of 100 mg bid for 3 days.

b) Two different mebendazole formulations manufactured by Janssen and Nordia were used in the following study:

Wesche D. and Barnish G., 1994 conducted a randomized, double-blind, controlled study in 100 paediatric subjects (exact age unknown; the majority of subjects were aged 8-13 years). Stool samples were collected pretreatment and approximately 3 weeks after treatment and analyzed microscopically in a blinded setting by a quantitative dilution technique to count the eggs of intestinal helminths. The percentages of subjects positive at baseline were 85.7% for *A. lumbricoides*, 86.9% for *T. trichiura*, and 98.8% for hookworm (mostly *N. Americanus*). Subjects were randomized to receive treatment with either:

- Mebendazole (Janssen) 100 mg tablet twice daily for 3 days (n=22)
- Mebendazole (Nordia) 100 mg tablet twice daily for 3 days (n=21)
- Mebendazole (Janssen) 4 x 100 mg tablets as a single dose (n=16)
- Pyrantel pamoate 125 mg tablet (10 mg/kg) single dose (n=21)
- Control (n=20): this group initially received no treatment but, due to the high infection rate at the 3-week assessment, subjects were subsequently treated with mebendazole (Janssen) 4 x 100 mg tablets as a single dose

Efficacy results at 3 weeks after treatment are shown in Table 6.

Table 6: Cure Rates and Egg Reduction Rates (Wesche and Barnish, 1994)

	A. lumbricoides		*T. trichiura*		Hookworm	
	CR	ERR	CR	ERR	CR	ERR
MBD (Janssen) 100 mg bid for 3 days (n=22)	95%	99.9%	65%	99.1%	91%	99.9%
MBD (Nordia) 100 mg bid for 3 days (n=21)	83%	99.9%	67%	98.1%	19%	87.7%
MBD (Janssen) 400 mg (n=16)	91%	99.9%	27%	94.1%	12%	84.4%
Pyrantel pamoate (n=21)	65%	99.6%	16%	70.9%	5%	24.5%
No treatment (n=20)	12%	-	16%	-	10%	-

CR=cure rate; ERR=egg reduction rate; MBD=mebendazole.

The authors concluded that both mebendazole formulations (Janssen and Nordia) administered as 100 mg twice daily for 3 days were equally effective against *A. lumbricoides* and *T. trichiura* but that mebendazole (Janssen) 100 mg twice daily for 3 days was significantly more effective than mebendazole (Nordia) in the treatment of hookworm. The single dose of mebendazole (Janssen) was not significantly better than pyrantel pamoate in the treatment of *A. lumbricoides* and *T. trichiura*. Pyrantel pamoate was least effective of all the evaluated interventions.
The difference in efficacies of the 2 mebendazole formulations corresponded to differences in dissolution, disintegration, and particle size of the formulations.

c) Different dosage regimens were compared in the following study:

Study R 12 564/3522, 1975 (Janssen Pharmaceutica) was a non-randomized, active- and placebo-controlled study in 178 subjects aged 2 to 12 years with *A. lumbricoides* infection, and concomitant *T. trichiura* in all except 1 subject; 4 subjects were lost to follow-up and excluded from the analysis. The worm burden was estimated by the Stoll egg count technique or formol-ether technique before treatment and 1 month after the treatment. Stool examinations were conducted blind. Subjects received one of the following 8 treatments:

- Mebendazole single dose of 100 mg (n=22) or 300 mg (n=24), or 100 mg bid for 2 days (n=22)
- An active comparator: levamisole 2.5 mg/kg single dose (n=24), pyrantel pamoate 11 mg/kg single dose (n=23), thiabendazole 25 mg/kg twice daily for 2 days (n=22), or piperazine citrate 100 mg/kg/day for 2 days (n=21)
- Placebo (n=20)

Cure rates and % egg reductions are summarized by treatment in Table 7.

Table 7: Summary of Efficacy for *A. lumbricoides* and *T. trichiura* (Study R 12 564/35)

Treatment and dosage	% egg reduction		Cure rate (%)	
	A. lumbricoides	*T. trichiura*	*A. lumbricoides*	*T. trichiura*
Levamisole 2.5 mg/kg single dose (n=24)	98%	9%	67%	8%
Pyrantel pamoate 11 mg/kg single dose (n=23)	95%	11%	65%	4%
Thiabendazole 25 mg/kg bid for 2 days (n=25)	85%	16%	33%	0
Mebendazole 100 mg single dose (n=21)	98%	23%	48%	0
Mebendazole 100 mg bid for 2 days (n=21)	67%	61%	76%	67%
Mebendazole 300 mg single dose (n=24)	99%	79%	58%	33%
Piperazine 100 mg/kg once a day for 2 days (n=21)	96%	21%	43%	0
Placebo single dose (n=19)	25%	21%	16%	5%

For *A. lumbricoides*, the order of effectiveness by cure rate for single dose anthelmintics was levamisole (67%), pyrantel pamoate (65%), mebendazole 300 mg (58%), and mebendazole 100 mg (48%).
For multiple-dose anthelmintics, the highest *A. lumbricoides* cure rate was seen with mebendazole 100 mg twice daily for 2 days (76%), followed by piperazine citrate (43%), and thiabendazole (33%). These cure rates were superior to placebo. Mebendazole 100 mg twice daily for 2 days was the only effective treatment against *T. trichiura*, producing a 67% cure rate and mean egg reduction of 61%.

Non-controlled Studies
Twenty-one non-controlled studies of mebendazole in paediatric subjects with ascariasis, trichuriasis, or hookworm were presented by the MAH in tabular format but are not shown here.

Assessor's comment (Day 70):

ASCARIASIS, TRICHURIASIS, ANCYCLOSTOMIASIS, NECATORIASIS

Controlled studies:
The ages in these studies ranged from 2 - 38 years or were not reported. One study included children below the age of 2 years (N = 7/97 for the mebendazole group; Sarmah, H.C., 1988). Another study by R.P. Davison, 197, included paediatric subjects between 14 months – 10 years. None of these patient population were analysed by age group.
Thus, no particular information on efficacy and safety are available for the age group below 2 years.
Doses of 100 mg bid for 3 to 5 consecutive days for the treatment of Ascariasis, Trichuriasis, Ancyclostomiasis, and/or Necatoriasis revealed higher cure rates than higher single dose of 200 mg – 600 mg mebendazole.

One study (Cabrera et al., 1980) compared the effectiveness of a mebendazole suspension versus a tablet formulation against A. lumbricoides, T. trichiura and hookworm with different dosage regimens. Overall, mebendazole 100 mg twice daily for 3 days had the highest cure

rate (100%).

Among children with A. lumbricoides, both mebendazole suspension and tablet were equally effective. In children with T. trichiura, the tablet formulation gave much higher cure rate than the suspension for all 3 regimens. In children with hookworm, the suspension was slightly favored over the tablet with the exception for the dose of 100 mg bid for 3 days.

No further studies were available which were performed with a mebendazole suspension.

Non-controlled studies:
The overall age range was 0 – 21 years or was not reported. Paediatric subjects below the age of 2 years were included in 6 out of 21 studies. However, cure rates were not analysed by age groups. Thus, no data on efficacy and safety are available for paediatrics below the age of 2 years.

One Study R 17 635/48 was conducted to evaluate the therapeutic effectiveness and safety of ***2% mebendazole syrup*** *in various helminthiases. Subjects were treated with 2% mebendazole syrup at a dose of 100 mg twice daily for 3 days. All A. lumbricoides (n=40) and Ankylostoma sp. (n=5) infections were cured. Of 26 subjects with T. trichiura infections, 24 (92.3%) were cured. No side effects were reported.*

It should be noted, that Study R 17 635/51 was conducted ***with flubendazole (?)****. Otherwise not justified, the MAH should delete this study (****Question 6 of Day 70 RSI****).*

Conclusion:

Generally, a single high dose >100 mg of mebendazole is less effective than low dose of 100 mg bid for 3 days for the treatment of helminthiases caused by A. lumbricoides, T. trichiura, Ankylostoma sp., and N. americanus.

As a consequence, the following dosage regimens are recommended for the treatment of these helminthiases in the SmPCs across the European member states:

- *100 mg bid to tid for 3 to 4 consecutive days*

Repeating of the treatment in case of insufficient efficacy is recommended in some but not all EU countries.

Summary of the MAH's Response to Question 6 of the Day 70 RSI
Study R 17 635/51 was conducted with mebendazole; however, the wrong clinical report was previously submitted. The correct report entitled *"The effect of single dose of mebendazole on the egg reduction rates (ERR) and cure rates (CR) in patients with Ascaris-, Trichuris- and hookworm infestations"* is included as part of this response document.

Assessor's comment:
The results of the study do not affect the previous comment on day 70.
Issue solved.

2.3 *Strongyloides stercoralis* (threadworm)

Controlled Studies
Two non-randomized, controlled studies of mebendazole in paediatric subjects with *S. stercoralis* were presented by the MAH in tabular format.

Vandepitte, J., 1973 conducted a non-randomized, placebo-controlled study in a total of 281 children (age not specified) from 2 schools. The study population was divided into 4 groups as follows:

- Group 1: 100 mg mebendazole twice daily for 4 consecutive days (n=109 from School 1)
- Group 2: 100 mg mebendazole twice daily for 3 days (n=52 from School 1 whose stools contained *T. trichiura* eggs ≥10,000/g)
- Group 3: 100 mg mebendazole twice daily for 3 days (n=64 from School 2; average age and weight:: 2 months to 7 years, 18 kg)
- Group 4: placebo twice daily for 3 days (n=56 from School 2; average age and weight: 3 months to 7 years, 21 kg)

The percentages of subjects positive at baseline across the 4 treatment groups were 61.5% to 69.6% for *A. lumbricoides*, 89.0% to 100.0% for *T. trichiura*, 67.3% to 92.2% for *A. duodenale*, and 9.6% to 23.2% for *S. stercoralis*.
Fresh stool samples were directly examined to count eggs (or larvae); samples were analyzed pretreatment and at 8 days to 3 weeks after treatment. Efficacy was assessed using the percentage reduction in eggs per gram of stool.
The *S. stercoralis* cure rate and egg reduction rate were both 100% in Group 2. Cure rates were 46.2% in Group 1, 41.7% in Group 3, and 0% in the placebo group (Group 4); egg reduction rates were 76.7%, 90.9%, and an increase of 85.1%, respectively.
Safety data were not reported. The authors concluded that mebendazole efficacy was less marked with *S. stercoralis* than for the other infections.

Richard-Lenoble, D. 1985 conducted a non-randomized, dose comparison study in a total of 300 subjects, including 122 children from the Catholic mission of Donguila who were aged 6 to 13 years. Subjects were positive for *A. lumbricoides* (77.7%), *T. trichiura* (100%), *A. duodenale* (73%), and *S. stercoralis* (9.5%).
Subjects received either mebendazole 100 mg twice daily for 3 days (n=84) or mebendazole 400 mg single dose (n=38).
Cure rates for *S. stercoralis* were 100% with the 3-day regimen and 90% with the single dose.
No side effects were observed. The authors concluded that, with all parasites, the single-dose regimen led to a 10 to 15% loss of mebendazole efficacy.

Non-controlled Studies
Three non-controlled studies of mebendazole in paediatric subjects with *Strongyloides stercoralis* were presented by the MAH in tabular format but are not shown here.

Assessor's comment (Day 70):

STRONGYLOIDIASIS

Controlled studies:
There are only two studies performed with children. About 30 subjects with S. stercoralis could be identified. Age was not reported in one study. One study included an age group from 6 – 13 years.
No data are available for paediatrics below the age of 6 years.
Cure rates are ranging from 40% to 100% with mebendazole 100 mg bid for 3 to 4 days.

Non-controlled studies:
The age range in these 3 studies was 0 – 15 years. However, the age groups were further specified. Thus, no individual data for the age below 2 years are available.
In one study (Karnauhov, V.K. et al., 1978) the dosing in children between 2 -10 years was given with 20 – 50 mg mebendazole, but not further specified.
The dosage regimens of the other two studies were mebendazole 100 mg bid for 3 to 4 days with cure rates of 50% and 65%.

Conclusion:
*It should be noted that the indication **Strongyloidiasis** is not approved in all EU countries. It is approved in:*

- *Austria, Belgium and Luxembourg, Germany, Ireland, Italy, Norway, Portugal, Slovakia, Czech Republic*

and not approved in:

- *Cyprus, Malta, UK, Ireland, Sweden, Denmark, Greece, Netherlands, Portugal, Romania and Spain.*

The posology were 100 mg bid for 3 consecutive days within the appropriate EU countries with the exception of the Czech Republic who recommends a higher mebendazole dose of 200 mg twice daily in adolescents.
The submitted data on efficacy of mebendazole in terms of cure rates and posology for the treatment of strongyloidiasis paediatric patients are insufficient. The few studies do not substantiate this indication for the paediatric population. The WHO recommends albendazole or ivermectin for strongyloidiasis in children but does not recommend mebendazole due to a suboptimal effect against the infection. The MAH is asked to discuss these alternative therapies by data in comparison to mebendazole for the paediatric population. If the benefit-risk assessment of the alternative therapies will be negative, a warning may be necessary e. g.:

> *Paediatric population / Children and adolescents (≥2 to 16 years)*
> *Since clinical data on the use of mebendazole in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks (see section 4.4). Currently available data are described in section 5.2.*

or

> *Paediatric population / Children and adolescents (≥2 to 16 years)*
> *Data on efficacy and safety in children and adolescents ≥2 years to 16 years are limited. Mebendazole should be used only, if there is no therapeutic alternative. Currently*

available data are described in section 5.2.

*The wording in the relevant sections of the informative texts will depend on the outcome of the MAH's response (**Question 7 of Day 70 RSI**).*

Summary of the MAH's Response to Question 7 of the Day 70 RSI

A brief review of the advantages and disadvantages of the 3 drugs recommended by the WHO or CDC (i.e., thiabendazole, ivermectin, and albendazole) is presented below:

Thiabendazole:

Thiabendazole is still recommended by the WHO for the treatment of *S. stercoralis*. However, it is no longer the drug of choice to treat *S. stercoralis.* It reveals a high frequency of side effects (particularly in the gastrointestinal and neuropsychiatric systems).

Ivermectin:

The current drug of choice for treating *S. stercoralis* is ivermectin according to the WHO and CDC. Ivermectin was found to be more effective than other anthelmintic drugs such as albendazole, as confirmed by a Cochrane systematic review which includes 7 studies, enrolling 1,147 subjects. In studies comparing ivermectin with albendazole, parasitological cure was higher with ivermectin. There were no statistically significant differences in AEs.

In studies comparing ivermectin with thiabendazole, there was little or no difference in parasitological cure. However, AEs were less common with ivermectin.

Two clinical studies from Marti et al (1996) and Khieu et al (2013) conducted in **paediatric subjects** only present data on the efficacy of ivermectin in the treatment of *S. stercoralis* in children (*please see Table 8 of the response document*).

The 2 above-mentioned studies demonstrated the high efficacy of a single dose of ivermectin in the treatment of *S. stercoralis* in children. The efficacy and the advantage of a single dose treatment favors ivermectin as treatment of choice for uncomplicated strongyloidiasis, especially given the low frequency of mild side effects observed (Marti et al, 2013). The study from Khieu et al (2013) did not determine the efficacy of ivermectin against other soil-transmitted helminths. However, the study from Marti et al (1996) showed that ivermectin was highly efficacious against *A. lumbricoides*, showed some activity against *T. trichiura*, but failed to cure hookworm infections.

Albendazole:

Albendazole has to be administered for at least 3 consecutive days as does thiabendazole. As highlighted by Marti et al (1996), although the cure rates for albendazole were generally lower compared with thiabendazole, the rare occurrence and mild nature of its side effects offer some advantages, leading to better compliance by the patients.

Four clinical studies from Pene (1982), Gadzer and Roy (1987), Mojon (1987), and Rossignol (1993) present data on the efficacy of albendazole in the treatment of *S. stercoralis* in children (*please see Table 9 of the response document*).

In total, 21 children < 12 years with a single infestation with *S. stercoralis* received 100 mg twice daily for 3 consecutive days. The cure rate as reported by Pene (1982), Gadzer and Roy (1987), Mojon (1987), and Rossignol (1993) were 50% (1/2), 100% (n = 4), 64% (7/11) and 43% (3/7), respectively.

Mebendazole:
After this submission, 2 additional placebo-controlled studies were identified by a literature search and evaluated the efficacy of mebendazole in children with single or mixed helminths infections. Of these 2 studies, only the study from Krubwa et al (1974) evaluated the CCDS dosage (i.e., 100 mg twice daily for 3 days). The study from Musgrave used the appropriate daily dose but the duration of treatment was 1 day longer.
(*Please refer also to table 10 of the response document.*)

Musgrave et al (1979)
conducted a randomized, double-blind, placebo-controlled study to evaluate the efficacy of mebendazole in the treatment and control of enteric helminths in 122 children (age range, **3-14 years**) from a community near the Gulf of Carpentaria and from a community in Cape York Peninsula in northern Queensland. Subjects with 1 or more intestinal helminths were divided into 2 equal groups to receive either mebendazole 100 mg twice daily for 4 days (except for children weighing less than 20 kg who received 50 mg twice daily for 4 days) or placebo. *S. stercoralis* infestations were cured in 14 of 21 affected subjects (67%) in the mebendazole group and in 1 of 16 affected subjects (6%) in the placebo group ($p<0.001$).

Krubwa et al (1974)
conducted a placebo-controlled study to evaluate the efficacy of periodic administration of mebendazole in treating children with mixed worm infections who were living in permanently infected surroundings and permanently exposed to reinfection. A total of 120 children attending a primary school at Livulu, Zaire were selected for this study based on coprologic examinations (age range, **6-9 years** [mean 7.3 years]; 50 boys, 70 girls). Sixty-four subjects received mebendazole 100 mg twice daily for 3 consecutive days and this treatment was to be repeated every 3 months for 4 treatment courses. The other group of 56 subjects received placebo on the same schedule.

Assessor's comment (Day 90, assessment of response to question 7):
In total, 125 children (n = 61, age 3 – 14 years and n = 64, age 6 – 9 years) could be identified for the treatment of *S. stercoralis* (single or mixed worm infections) with mebendazole in the additional two submitted placebo-controlled studies.
Cure rates (%) for *S. stercoralis*: were: 67% (Musgrawe et al. 1979) and 41.7% after the first treatment and 95.8% with 99.7% reduction in larvae after fourth treatment course (Krubwa et al, 1974).
Although mebendazole is not among the drugs recommended by the WHO and CDC for the treatment of *S. stercoralis* in children, there is sufficient information available to support keeping this indication in the CCDS for mebendazole.
Based on this conclusion the following information should be given in section 4.2 of the SmPC for the indication ***strongyloidiasis*** in EU countries where it is approved:

> '*Paediatric population / Children and adolescents (≥2 to 16 years)*
> *Data on efficacy and safety in children and adolescents ≥2 years to 16 years are limited. Mebendazole should be used only, if there is no therapeutic alternative.'*

Issue solved provided that the text will be implemented in the SmPC.

2.4 *Taenia species* (tapeworm)

None of the 42 studies identified for the Clinical Overview by the MAH provided data for mebendazole in the treatment of *Taenia species* (tapeworm) in children.

Assessor's comment (Day 70):

TAENIASIS

The indication Taeniasis has been approved for the species T. saginata and T. solium in Austria, Belgium and Luxembourg, Germany, Ireland, Italy, Norway, Portugal, Slovakia, and Czech Republic with the dosage regimen of 100 mg mebendazole bid for 3 consecutive days and additional in Czech Republic with 200 mg bid for 3 days for adolescents.

However, no data on efficacy and safety of mebendazole for the treatment of these Taenia species are available for the paediatric population.
*As there are alternative therapies for this indication with Praziquantel for children >2 years and Niclosamid for children <2 years and older, mebendazole should not be used for the treatment of Taenia species. Otherwise not justified, the MAH is asked to delete this indication (**Question 8 of Day 70 RSI**).*

Summary of the MAH's Response to Question 8 of the Day 70 RSI
Despite the absence of clinical studies conducted only in children infected with *Taenia* spp., some data are available that demonstrated the efficacy and safety of mebendazole in the treatment of *Taenia* spp. infections in adults and children. The clinical trial program was reviewed to identify studies that evaluated the treatment of *Taenia* spp. using the 100 mg regimen recommended in the CCDS for mebendazole. Three clinical studies including adults and children (Marchand, Swartzwelder, Chin-Thack) were identified that evaluated the treatment of *Taenia* spp. using the mebendazole 100 mg tablet (Table 8).

Table 8: Pivotal Clinical Studies – Efficacy of Mebendazole Against *Taenia spp.* (Tapeworm)

First Author (Year)	Study Design	Population Including Subjects With *Taenia Spp.* Single Infection	Mebendazole Dose	Comparator	Efficacy Results With Mebendazole
Marchand (R 17635/19) (1973)[61]	Open-label	52 male and female subjects with *Taenia* spp. Infection treated (including adults and children, age not reported)	100 mg twice daily for 3 days	None	Cure rate: 88%
Swartzwelder (1973)[81]	Multiple dose (for this infection)	132 subjects treated in total including 17 subjects with *Taenia;* demographics provided did not include subjects with *Taenia*, but other subjects in study were aged 2 to 24 years and ~60% were male	100 mg or 200 mg twice daily for 4 days	None	Cure rate: 9/17 cured; 5/17 probably cured (negative for 2-3 months after treatment); 3/17 not cured initially (100 mg bid for 4 days); all 3 were retreated with 200 mg bid for 4 days; 2 cured by retreatment and 1 was reported as under observation
Chin-Thack (1974)[19]	Open-label	76 subjects (age and gender not reported) with single *Taenia* spp. infection	100 mg twice daily for 3 days	None	Cure rate: 78.9%

The 3 clinical studies presented above evaluated the effectiveness of the mebendazole 100 mg tablet for the treatment of *Taenia* spp.; however, none assessed efficacy in only paediatric subjects. Two of the studies (Marchand, Swartzwelder) assessed efficacy in both adult and paediatric subjects and in the third (Chin-Thack) the subjects' ages were not reported. None of the studies employed the regimen for adults recommended in the mebendazole CCDS, which is **two 100 mg tablets twice daily for 3 days**.

In addition, a clinical expert statement written by Snoeckx in 2003 reviewed the literature available at that time regarding the clinical efficacy of mebendazole in taeniasis (either *T. saginata* or *T. solium*). The literature search was conducted on 04 August 2003 for all clinical data on the use of mebendazole in taeniasis and cysticercosis using the Company Literature Management Database. Studies with fewer than 5 evaluable subjects treated with mebendazole for taeniasis were not included due to their limited added value. Studies that pooled treatment results across various helminthic infections without specific details for taeniasis were also excluded. Most of the studies that were included in this review were uncontrolled or case series, did not distinguish between *T. saginata* and *T. solium* infections, or provided only pooled results across the 2 *Taenia* spp. No clinical data on the use of mebendazole in cysticercosis were identified.

Results for *T. solium* infections were reported in 3 studies only. Treatment with mebendazole

- 100 mg twice daily for 3 consecutive days
  resulted in a cure rate of 53% (8 of 15 subjects) in the study by Hegde and 83% (15 of 18 subjects) in the study by Marchand.

In the third study, 64% (7 of 11 subjects) were cured after treatment with mebendazole

- 100 to 200 mg twice daily for 2 to 4 days;
  all 5 subjects treated with the highest dose of mebendazole
- 200 mg twice daily for 4 days were cured.

In the studies evaluating mebendazole treatment for *T. saginata* infections, cure rates were as follows:

- 100 mg twice daily for 3 days: 64% and 90% in 149 and 30 subjects, respectively
- 200 mg twice daily for 4 days: 80% in 10 subjects
- 300 mg twice daily for 3 days: 95% and 100% in 41 and 6 subjects, respectively

Eleven studies reported treatment results with mebendazole for intestinal infections with unspecified *Taenia* spp with different doses regimens. A single mebendazole treatment regimen, either 100 or 200 mg twice daily for 3 days, was evaluated in 9 studies and cure rates ranged from 37.5% to 90%. One of these studies (Carvalho et al, 1973) was conducted solely in children younger than 15 years of age and the cure rate with 100 mg twice daily for 3 days was 89% (8 of 9 children).
The author concluded that the available data suggest efficacy of mebendazole in taeniasis. Acceptable cure rates were achieved with a dose of 100 mg twice daily for 3 days, and higher doses seemed to result in a somewhat higher cure rate. The author therefore concluded that the recommended dose in the CCDS, 200 mg twice daily for 3 days, is appropriate.

Assessor's comment (Day 90, assessment of response to question 8):
Children treated for *Taenia* spp. are rather limited. The studies available included an age range from 2 – 76 years and were not analysed by age groups.
Although mebendazole is not among the drugs recommended by the WHO and CDC for the treatment of *Taenia* spp. in children, there is sufficient information available to support keeping this indication in the CCDS for mebendazole. Mebendazole could be considered as an appropriate alternative treatment in children showing resistance to praziquantel or niclosamide.
Based on these data the following information for the indication ***Taeniasis*** is proposed for section 4.2 of the SmPC:

'*Paediatric population / Children and adolescents (≥2 to 16 years)*
Data on efficacy and safety in children and adolescents ≥2 years to 16 years are limited. Mebendazole should be used only, if there is no therapeutic alternative.'

Issue solved provided that the text will be implemented in the SmPC.

2.5 Echinococcosis or Trichinosis

Four clinical studies completed by 26 January 2007 provide data for mebendazole in the treatment of echinococcosis and trichinosis in paediatric subjects; these studies were not included in the 2008 line listing.

Summaries of these controlled and non-controlled studies are presented below.

Summary of the controlled study:

Göçmen, A. et al., 1993 analyzed the general characteristics of 56 childhood cases of cystic hydatid disease (age 5 to 15 years) to compare the results of mebendazole therapy versus surgery. Pulmonary radiograms and ultrasonography were used in the diagnosis. The cysts were localized primarily to the lungs.
Twenty-seven subjects were surgically-treated, with 8 having recurrence after a mean period of 3.6 years. Thirty subjects received regular mebendazole treatment, in a dose of 50 mg/kg with a mean duration of treatment of 11.7 months. Twenty-one subjects were cured and discontinued the therapy; 9 subjects were still using the drug, of whom 7 had experienced dramatic

improvement; and the remaining 2 subjects had minimal radiographic changes but subjective improvement in general condition. The lung cysts vanished leaving minimal scars, while the liver cysts turned into inactive forms.
The recurrence rate of drug-treated children (1 out of 20) was lower than that of the surgically treated children (8 out of 27); however, this was not statistically significant. The authors concluded that mebendazole is the drug of choice for treatment in children, due to its lack of side effects, the low risk of recurrence, and the fact that all of the subjects benefited from the therapy, with the majority eventually obtaining a cure.

Summaries of the non-controlled studies:

Al-Bassam, A., et al., 1999 conducted a non-controlled study in 21 subjects aged 3-12 years infected with *E. granulosus*. All subjects were treated pre-operatively with mebendazole 50 mg/kg/day for 1 to 8 weeks (average 2 weeks). In 16 subjects, mebendazole was continued postoperatively for 1 to 6 months. All subjects underwent surgical treatment.
Mebendazole was administered to prevent recurrence in the case of accidental spillage of cyst contents. There were no cases of extrahepatic intra-abdominal cyst formation secondary to intraoperative spillage.

Messaritakis, I., 1991 conducted a non-controlled study in which 39 subjects aged 2-14 years (mean age 7.5 years) infected with *E. granulosus* received mebendazole orally for 12 weeks (100-200 mg/kg/day with a maximum daily dose of 6 g) in divided doses with meals. Nine subjects who failed to respond received a second course of treatment after an interval of 3 to 6 months. Subjects were followed up for a mean duration of 63 months.
The successfully treated lung cysts and hepatic cysts were smaller than those which persisted ($p<0.05$). Of the 39 subjects, 20 subjects were cured (3 of them after a second course) and 2 subjects with multiple cysts avoided at least one operation. Nine of the 20 cured subjects had multiple cysts in one or more organs. No serious side effects of mebendazole were observed.
The authors concluded that high doses of mebendazole can be used as an effective alternative treatment against *E. granulosus* in children, especially in cysts of medium and small size.

Ozdemir, D. et al., 2005 evaluated all children up to 17 years of age and their adult households exposed to the consumption of infected meat during an outbreak in Turkey of trichinellosis caused by *Trichinella britovi*. In 47 (62%) of 76 children with suspected trichinellosis, the diagnosis was serologically confirmed. Mean age of confirmed cases was 12.8 years (range 2 to 17 years). The incubation period was similar in children and adults, but myalgia, facial and/or eyelid edema, eosinophilia, and increased serum creatine kinase were significantly less common in children than in adults. Mebendazole 25 mg/kg/day, divided into 3 doses, was administered for 14 days to all children. Severely symptomatic children were also treated with 20 mg/day prednisolone for 7 days.
The average time to symptom resolution was 7.9 days (range 3 to 42 days) after the beginning of mebendazole treatment. Myalgia persisted for the longest with a mean duration of 14.2 days, but 1 child had myalgia and muscular weakness up to 42 days post infection. Serum muscle enzyme and eosinophil count dropped to normal levels by 5 weeks after beginning treatment. No children had an increase in serum electrolytes or hypoalbuminemia. No cardiac or neurologic complications were observed. No child reported adverse effects attributable to mebendazole. Increased liver enzyme values were detected in a 14-year-old child 10 days after the beginning of mebendazole therapy without any signs of liver failure; blood count and liver functions returned to normal 7 days after stopping the mebendazole therapy.
All children completely recovered within 2 months after the outbreak.

Assessor's comment (Day 70):

ECHINOCOCCOSIS

Controlled study:
It should be pointed out that there is only one controlled study (mebendazole versus surgery) for the treatment of cystic echinococcosis (caused by Echinococcus granulosus) in paediatric patients.
The included age group was >5 up to 15 years. Patients was given mebendazole 50 mg/kg BW in 3 divided doses with a mean duration of treatment of 11.7 months. However, information on the mebendazole formulation and kind of preparation are missing. The MAH is asked to comment.
There was no statistically significant recurrence rate between both treatment groups.

No controlled study is available on alveolar echinococcosis caused by Echinococcus multilocularis.

Non-controlled studies:
There are only 2 studies performed in children aged 2 – 14 years. The dosage regimens are different and amounted to be 50 mg/kg/day for 1 to 8 weeks (Al-Bassam, A., et al., 1999) and 100-200 mg/kg/day for 12 weeks (Messaritakis, I., 1991).
Based on these data, a conclusion on an appropriate dosage regimen cannot be done, as basic conditions and study design are comparable.

No non-controlled study is available on alveolar echinococcosis caused by Echinococcus multilocularis.

TRICHINOSIS

There is only one prospective, non-controlled study including children aged 2 to 17 years. Mebendazole was administered at the dose of 25 mg/kg/day divided into 3 daily doses for 14 days.

Conclusion:
Data on the efficacy (and consequently safety) regarding the treatment of cystic Echinococcosis caused by Echinococcus granulosus in paediatrics are poor.
No data are provided for the treatment of alveolar Echinococcosis caused by Echinococcus multilocularis.
Furthermore, the efficacy regarding the treatment of Trichinosis in paediatrics is not supported by sufficient data.
None of the studies regarding the indications cystic and alveolar echinococcosis, trichinosis were performed in children below the age of 2 years.

The current dosage regimens are within the recommendation by the WHO, but supporting data are lacking.

With the exception of Norway, these indications are approved for the 500 mg tablet formulation and only in few European countries such as Belgium, Luxembourg, Germany and Italy for echinococcosis and for trichinosis only in Germany (see Table 1).

The 500 mg tablet was reserved only for the treatment of serious parasitic infections requiring higher dosages. The MAH is asked to provide data on alternative treatment of these serious parasitic infections and discuss them as well.
In addition, as stated, the MAH is currently assessing the more recent data available from the literature for adults and children with echinococcosis and trichinosis. The MAH is asked to provide these data for justification of these indications.
*Furthermore, instructions for the use of the tablet in children should be given in more detail. Provided the mebendazole suspension is not approved and/or available and no comparable efficacy between the tablet and oral suspension could be demonstrated, instructions for the use of the tablet formulation in children should be given in more detail e. g. regarding the kind of crushing, solubility of the crushed tablet, amount of the recommended crushed liquid, compatibility with food, probable taste sequestering. An appropriate wording in the relevant sections of the informative texts will depend on the outcome of the MAH's response (**Question 9 of Day 70 RSI**).*

Summary of the MAH's Response to Question 9 of the Day 70 RSI
Treatment Recommendations for Cystic and Alveolar Echinococcosis

Cystic echinococcosis
Currently, surgery is still considered to be the treatment of choice as it has the potential to remove *Echinococcosis granulosus* cysts and lead to a complete cure. It can be performed successfully in up to 90% of subjects (in case of cyst that does not have a risky localization or if the disease is not too advanced). However, surgery may be impractical in subjects with multiple cysts localized in several organs and if surgical facilities are inadequate. In these situations, chemotherapy and PAIR (puncture – aspiration – injection– reaspiration) technique offer alternative treatment options, especially in inoperable subjects and in subjects with a high surgical risk.
Over 2,000 well documented cases of cystic echinococcus have been treated by chemotherapy with benzimidazoles. An evaluation of subjects during a 12-month follow-up period after chemotherapy revealed that 10% to 30% of subjects were cured, 50% to 70% of subjects were improved (as shown by degeneration of cysts and/or significant size reductions), and 20% to 30% of subjects were failures (as demonstrated by no morphological changes in cysts characteristics). Chemotherapy appears to be more effective in young subjects than older subjects.
Albendazole and mebendazole have been extensively evaluated using animal models and used on over 2,000 patients. These 2 drugs show definite efficacy against echinococcus, the following oral dosages are recommended:

- for mebendazole: 40 to 50 mg/kg/day in 3 divided doses for at least 3 to 6 months
- for albendazole: 10 to 15 mg/kg/day in 2 divided doses. Cyclic treatment with intervals of 14 days was originally recommended by the manufacturer, and 3- to more than 6-monthly courses have been regarded as necessary for treating patients with single or multiple cysts. However, recent data have shown equal or improved efficacy of continuous treatment for 3 to 6 months or longer without an increase of adverse effects. In a recent comparative study, this type of treatment was more effective than chemotherapy with mebendazole. Therefore, cyclical albendazole treatment seems to be no longer advisable.
- The use of praziquantel, a heterocyclic pyrazinoisoquinoline derivative, has been proposed at a dose of 40 mg/kg once a week concomitantly with benzimidazoles. According to the manufacturer, the plasma levels of albendazole metabolites

(sulphoxide) are increased 4.5 times if praziquantel is given simultaneously, and this may increase the rate of side effects.

There are hints from several studies that postoperative treatment of patients can reduce the rate of recurrences. Based on these hints, it is recommended for cases in which spillage of protoscoleces may have occurred during surgery to initiate postoperative chemotherapy with albendazole or mebendazole immediately after operation for at least 1 month (albendazole) or 3 months (mebendazole).

Alveolar echinococcosis

According to the WHO/OIE Manual on Echinococcosis in humans and animals, treatment of alveolar echinococcus involves a variety of options, including surgery and chemotherapy. Albendazole and mebendazole are the 2 drugs of choice for chemotherapy of alveolar echinococcus.

- The recommended dosage of mebendazole is 500 mg tablets in daily doses of 40 to 50 mg/kg administered in 3 divided doses after meals.
  Following continuous administration of mebendazole for 4 weeks, it is advised to adjust the dose so that it resulted in plasma levels of >250 nmol/L (74 ng/mL). In certain circumstances the dose may be adjusted to a level higher than the recommended amount – but, it should not exceed 6 g/day in adult subjects. The duration of treatment is at least 2 years after radical surgery or continuously for many years in inoperable patients, as well as after incomplete resection or liver transplantation. Continuous administration of mebendazole for more than 17 years has been documented in some patients.
- Albendazole is given as 400 mg tablet or as a 4% suspension at daily doses of 10 mg/kg to 15 mg/kg (in 2 divided doses).
  According to the original recommendation of the manufacturer, repeated cycles of 28 days of treatment should be followed by a wash-out phase without chemotherapy of 14 days. However, recent data indicated that a continuous albendazole treatment of alveolar echinococcosis is at least equally or more effective and well tolerated. Sporadically albendazole was given in higher doses of 20 mg/kg/day for up to 4.5 years. The duration of necessary chemotherapy has not yet been determined but might well be life-long for most of the patients without complete resection of the alveolar echinococcosis lesions.

A brief review of efficacy data from clinical studies using albendazole as chemotherapy treatment for cystic echinococcosis in children is presented in Table 14 (please see response document). No clinical studies were identified that described the use of albendazole as chemotherapy treatment for alveolar echinococcosis (only few case reports were identified and are not presented here).

Review of Literature Data for the Use of Mebendazole for the Treatment of Trichinosis and Echinococcosis

Following the review of literature data, the MAH determined that there was sufficient data to support the use of mebendazole for the treatment of trichinosis and echinococcus in adult and paediatric populations. Therefore, the MAH updated the CCDSs for mebendazole (100 mg and 500 mg tablets) to add the treatment of trichinosis and echinococcus (caused by *Echinococcus granulossum* and *Echinococcus multilocularis*) as new indications. The scientific rationale and detailed documentation that support these changes to the CCDSs are presented in a separate clinical overview submitted as part of the response document (EDMS-ERI-137474977).

Instructions for the Use of Mebendazole Tablets in Children

See MAH's response to question 4 and 5.

Assessor's comment (Day 90, assessment of response to question 9):
Based on the available data the use of mebendazole for the treatment of trichinosis and echinococcosis in children ≥2 years of age can be supported. As the chemotherapy with mebendazole is associated with further treatment options in these severe diseases, it is proposed to add the following note (in general also for adults) in section 4.2 of the SmPC and section 3 of the PL:

> *'Official guidelines should be taken into consideration. Official guidelines will normally include WHO and public health authorities' guidelines.'*

However, a final decision cannot be done at present, **as the separate clinical overview submitted as part of the response document (EDMS-ERI-137474977) is missing. The MAH is asked to provide this document (Question 1 of the draft final AR, Day 90).**

Issue not solved.

Summary of the MAH's Response to Question 1 of the draft final AR (Day 90)

EFFICACY

Trichinosis
Several articles reported data from studies using mebendazole for the treatment of trichinosis in populations with age ranges including children (Kusolsuk et al, 2010; Akkoc et al, 2009; Turk et al, 2006; Blondheim et al, 1984; Vujošević et al, 1979; Neghinaet al, 2011; Schellenberg et al, 2003; Sonnet and Thienpont, 1977). However, no specific analyzes were performed based on age group in most of these studies.
Three studies were identified that provided data specifically on children.

Echinococcosis
Several articles reported data from studies using mebendazole for the treatment of *E. granulossum* infections in populations with age ranges including children (Vutova et al, 2012; Franchi et al, 1999; Teggi et al, 1993; Davis et al, 1989; Davis et al, 1986; Vutova et al, 1999; Erdincler et al,1997; Bartolini et al, 1992; Teggi et al, 1989; Kammerrer et al, 1984; Gil-Grande et al, 1983; Benazzou et al, 2010). However, no specific analyzes were performed based on age group in these studies.
Three studies were identified that provided data specifically on children.

None of the studies reviewed in Section 4.3.2.2 of the Clinical Overview reported data regarding the use of mebendazole for the treatment of *E. multilocularis* infections in children. It has to be noted that the uncontrolled, case review study from Wilson et al (1980) included subjects whose age at diagnosis of the disease ranged from 12 to 82 years (age range at time of treatment not specified) and the open-label study from Reuter et al (2000) included subjects whose age at the time of analysis ranged from 13 to 80 years. However, no specific analyzes by age group were conducted.

SAFETY

For *Trichinella* and *Echinococcosis*, higher and longer therapy of mebendazole is recommended.

These 2 indications are being added to the CCDS. As impaired hepatic function, impaired metabolism, or impaired biliary elimination may lead to higher plasma levels of mebendazole and higher doses and longer therapy is needed for these 2 indications, the CCDS will be updated to add a warning and precaution for these indications, stating:

> *"As higher doses and longer treatment is recommended in patients with Trichinellosis and Echinococcosis, careful consideration should be given when treating patients with severe chronic hepatic diseases and/or bone marrow depression."*

Based on the review of postmarketing data regarding neutropenia, abnormal liver function tests, and hepatitis as well as WHO guidelines, the Company proposed to monitor hematologic and liver function tests while patients are treated with high doses of mebendazole. In addition, based on the review of postmarketing cases of glomerulonephritis seen with higher doses of mebendazole, the Company recommends the monitoring of renal function while patients are being treated with high doses of mebendazole. Based on postmarketing data, the Company recommends that in patients with *Trichinella* or *Echinococcus* consideration be given to discontinuation of mebendazole if significant laboratory abnormalities are found. Therefore, the following will be stated in the CCDS:

> *"These patients should be closely monitored with hematological, liver and renal function tests. Consider discontinuing TRADENAME if clinically significant laboratory abnormalities are found."*

Assessor's comment (Day 120, assessment of the MAH's response to CHMP members' comments to the draft final AR [Day 90]):
The MAH has submitted the requested clinical overview via E-mail on 15 November 2018 EDMS-ERI-137474977, dated 17 May 1917, which is mainly focussed on the indications Trichinosis and Echinococcosis. Although these indications are widely assessed, no particularly new data on the efficacy were reported. The conclusion as already stated (please see comment to question 9) will still remain. However, based on the submitted safety data, the wording (applicable to adults and paediatrics) proposed by the applicant should be considered in section 4.4 of the SmPC such as:

> *"As higher doses and longer treatment is recommended in patients with Trichinellosis and Echinococcosis, careful consideration should be given when treating patients with severe chronic hepatic diseases and/or bone marrow depression."*

and

> *"These patients should be closely monitored with hematological, liver and renal function tests. Consider discontinuing TRADENAME if clinically significant laboratory abnormalities are found."*

Issue solved.

1. Safety aspects referring to warnings and precautions

In general, the adverse events reported in the studies were mild with gastrointestinal symptoms including diarrhea, vomiting, and abdominal pain. One specific adverse events of interest are convulsions in children including in infants below 1 year of age, have been reported very rarely during post-marketing experience.

Among the 2008 line listing studies, none reported convulsion as an adverse reaction.
A search of the Company Global Safety Database was performed. A total of 16 cases were received, as shown in Table 9.

Table 9: Characteristics for Cases Involving Use of Mebendazole; Mebendazole/Quinfamide Reporting HLGT Seizures in ≤18-Year-Old Subjects (n=16)

Characteristic		Number of Cases
Patient Sex	Male	11
	Female	5
Patient Age (Years)	<1 year	3
	1-12	11
	12-18	2
Indication	Nematodiasis	1
	Enterobiasis	9
	Infection prophylaxis	1
	Helminthic infection	2
	Unknown indication	3

HLGT=High Level Group Term.

Of the 16 cases, 13 cases were children >1 year old.
(*Note: The individual cases were described in more detail in the MAH's Clinical overview.)*

Variations in the recommended lower age limit for paediatric subjects across EU countries were summarized by the MAH in tabular format for each formulation (table not shown here). The MAH proposes to harmonize the warning with regards to convulsions as follows:

SmPC – 4.4 Warnings and precautions

Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience. (see section 4.8)

TRADENAME has not been extensively studied in children below the age of 2 years. Therefore, TRADENAME should be used in children aged 1-2 years only if the potential benefit justifies the potential risk.
Because of the risk of convulsions, TRADENAME should not be used in children below the age of 1 year.

PL – Section 2 Warnings and precautions

Convulsions (seizures) have been reported, including in infants. TRADENAME should only be given to children under 2 year of age if your doctor has specifically prescribed it.

Assessor's comment (Day 70):
The proposal for the wording in the SmPC and PL is considered to be acceptable, also taken into consideration the few studies on efficacy on children below the age of 2 years.

*Six out of the reported 16 cases of seizures were children with history of seizures and/or epilepsy. The MAH is asked to discuss this issue for inclusion of an appropriate warning (**Question 10 of Day 70 RSI**).*

Summary of the MAH's Response to Question 10 of the Day 70 RSI
The search of the GMS global safety database retrieved 17 cases (1 additional case was received after the initial Article 45 analysis) reporting seizures in patients who received mebendazole.
The distribution of the PTs (PT= Preferred Term) of interest is presented in Table 10 below for the 17 cases retrieved.

Table 10: Frequency of MedDRA PTs of Interest in Mebendazole Cases Reporting Seizures (n=17)

MedDRA PTs	Number of Events[a]
Seizure	11
Generalised tonic-clonic seizure	3
Benign rolandic epilepsy	1
Epilepsy	1
Petit mal epilepsy	1
Seizure cluster	1

Key: MedDRA= Medical Dictionary for Regulatory Activities; n= Number; PT= Preferred Term.
a: A single case may report more than 1 MedDRA PT of interest.

The demographics and case characteristics for the cases are presented in Table 16 (*please see response document*). The mean age is 5.23 years, the median age is 5 years, and the age range is 0.08 years to 14 years.

Of these 17 cases, 1 case (20041004022) involving a 2-year-old male was confounded by concomitant administration of the measles, mumps, and rubella vaccine. Additionally, 1 case (20160712886) involving a 14-year-old male was confounded due to his significant medical history of a diffuse intrinsic pontine glioma. The remaining 15 cases were stratified as follows:

- Cases in patients <1 year of age (n=3)
- Cases in patients ≥1 and <3 years of age (n=3)
- Cases in patients ≥3 and <11 years of age (n=8)
- Cases in patients ≥11 and <18 years of age (n=1)

Cases in Patients <1 Year of Age
Three cases (HOAFF6774, JANOR39486, JAUSA3240) reported seizures in patients <1 year of age. These 3 cases are briefly described below (*please see response document*).
Of the cases summarized above, all 3 reported a plausible temporal relationship between exposure to the drug and the AE.

Cases in Patients ≥1 and <3 Years of Age
Three cases (20061201356, 20101207504, JAGER26706) reported seizures in patients ≥1 and <3 years of age. These 3 cases are briefly described below (*please see response document*).
Of the cases summarized above, all 3 reported a plausible temporal relationship between exposure to the drug and the AE.

Cases in Patients ≥3 and <11 Years of Age
A total of 8 cases reported seizures in patients ≥3 and <11 years of age. These cases are reviewed in Table 17 (*please see response document*). Of these 8 cases, all 8 reported a plausible temporal relationship between exposure to the drug exposure and the AE.

Cases in Patients ≥11 and <18 Years of Age
One case (20041202496) reported seizures in patients ≥11 and <18 years of age and is described briefly below (*please see response document*). This case reported a plausible temporal relationship between exposure to the drug and the AE.

Pre-existing history risk:
Six of the 17 cases involved patients who either had a known history/diagnosis of epilepsy/seizures prior to mebendazole treatment (*for more detailed information of the cases, please see response document*).
Seizure thresholds can be affected with illness, stress, or low blood sugar, among other factors. In addition, seizures are known to occur with mebendazole. There is insufficient evidence to suggest that a pre-existing history of seizure/epilepsy increases the risk of developing seizures on mebendazole based on the low number of cases reporting a history of controlled seizures prior to mebendazole treatment and possible other causes for a decreased seizure threshold, such as illness and possible poor diet (especially when experiencing a helminthic infection).

Assessor's comment (Day 90, assessment of response to question 10):
The conclusion of the MAH, that there is insufficient evidence to suggest that a pre-existing history of seizure/epilepsy increases the risk of developing seizures with mebendazole, is supported. Thus, there is no need to include a warning related to the use of mebendazole in children with history of seizure or epilepsy.
Issue solved.

MAH'S RESPONSE TO CHMP MEMBERS' COMMENTS TO THE PPdAR (Day 70)

Comments were received from two member states (MSs) by Day 85.

One MS (MS 1) had the following comment:

Question 1 of MS 1:

SmPC/PL
[MS] agrees with the Rapporteur´s conclusions but has one comment with regards the proposed harmonization of text in section 4.4:

> ***SmPC - 4.4 Warnings and precautions***
> *Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience. (see section 4.8)*
>
> *TRADENAME has not been extensively studied in children below the age of 2 years. Therefore, TRADENAME should be used in children aged 1-2 years only if the potential benefit justifies the potential risk.*
> *Because of the risk of convulsions, TRADENAME should not be used in children below the age of 1 year.*

The last sentence implies somehow that there is a specific risk for convulsions in children at the lowest age. According [to table 9] there have in total been 16 cases of convulsions reported for the whole paediatric population of which only three cases have been reported in children <1 year. Although the exposure most likely has been much higher in the age cohort 1-12 years for

which the majority of cases of convulsions have been reported, the low number of reports in children <1 year doesn´t seem to support the proposed wording without further justification. At present it seems more appropriate that any cautionary statement of use of mebendazole in children <1 year should be based on the lack of safety data in this subgroup rather than based on the risk for convulsions unless the proposed wording is further justified. Moreover, in addition to a justification the narratives of the three cases of convulsions in children <1 year should be provided.

Summary of the MAH's Response to Question 1 of MS 1

A total of 51 citations were retrieved from the literature search, which were reviewed for evidence suggestive of an association of seizure with the use of mebendazole in children ≤18 years. Of these, 3 were deemed relevant to the research question, and are presented below.

El Kalla S. and Menon NS. Mebendazole poisoning in infancy. Ann Trop Paediatr (1990) 10(3): 313-314.

Accidental mebendazole poisoning in an 8-week-old infant and respiratory arrest with tachyarrhythmia associated with continuous seizures is reported. Exchange transfusion was undertaken as a life saving measure. Mebendazole, like piperazine citrate, has considerable neurotoxicity, especially in infancy, and we propose the use of exchange transfusion as a mean of mebendazole elimination in infants.

Montresor A, Awasthi S, and Crompton DWT. Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis. Acta Trop. (2002) 86(2-3): 223-232.

Considerable experience and limited quantitative evidence indicate that infections with the soil-transmitted helminths *A. lumbricoides* and *T. trichiura* usually start to become established in children aged 12 months and older. Since children living in countries where the infections are endemic are at risk of morbidity, even those as young as 12 months may need to be considered for inclusion in public health programmes designed to reduce morbidity by means of regular anthelminthic chemotherapy. This situation raises the question as to whether such young children should be given anthelminthic drugs. Systems for the absorption, distribution, metabolism and elimination of drugs do not fully develop until children are in their second year of life. Current knowledge, however reveals that the incidence of side effects linked to benzimid-azole drugs in young children is likely to be the same as in older children. Accordingly, we conclude that albendazole and mebendazole may be used to treat children as young as 12 months if local circumstances show that relief from ascariasis and trichuriasis is justified.

MAH Comment:

This article reviewed the use of benzimidazoles in children younger than 24 months of age. It stated that systems for the absorption, distribution, metabolism and elimination of drugs do not fully develop until children are in their second year of life. While the article stresses the benefit versus risk in patients 12 to 24 months it does not support treating patients below the age of 1 year. Because of the possible differences in absorption, distribution, metabolism and elimination in children less than 1 year of age, convulsions could be more of a risk in this age group.

Crabbe R, Amery WK. Mebendazole and seizures in children. Janssen Research Foundation. Pharmacovilance Report. February 1991.

Two cases of generalized seizures in infants were reported during mebendazole treatment. A clear causal relationship with mebendazole could not be established.

However, due to the seriousness of the events, precautionary measures are proposed for this age group.

MAH Comment:

The article hypothesizes that mebendazole, when taken orally, undergoes a high "first pass" effect in the liver, resulting in very low plasma levels and very low bioavailability. However, in children under the age of 1 year, metabolic maturation of the liver may be incomplete and a higher dose of mebendazole may reach the systemic circulation. If the drug is able to cross the blood-brain barrier in such infants, these higher plasma concentrations could lead to a higher penetration into the central nervous system with secondary neurotoxicity.

Assessor's comment (Day 90, assessment of response to question 1 of MS 1):
As required by [MS 1] the 3 narratives have been submitted.
The resulting conclusion by the MAH regarding the warning against treating infants less than 1 year of age due to the risk of convulsion are supported. Based on the specific pharmaco-kinetics in children less than 1 year of age, the warning as proposed is slightly modified, based on the comments received by SE and UK (see below).

SmPC - 4.4 Warnings and precautions
Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience. (see section 4.8)
TRADENAME has not been extensively studied in children below the age of 2 years. Therefore, TRADENAME should be used in children aged 1-2 years only if the potential benefit justifies the potential risk.
Because of the lack of sufficient safety data, TRADENAME should not be used in children below the age of 1 year.

Issue solved provided that the text will be implemented in the SmPC.

A second MS (MS 2) had the following comments:

Question 1 of MS 2 – Clinical data

We note that of the 16 cases of seizures associated with mebendazole use, 13 cases occurred in children over 1 year old. No further details are given. To help clarify the risk of seizures associated with mebendazole use in the paediatric age group, the MAH should provide the case narratives for all children less than 18 years of age with reported seizures with focus on those occurring in children younger than the age of two years.

Summary of the MAH's Response to Question 1 of MS 2
Please see response to question 10.

Assessor's comment (Day 90, assessment of response to question 1 of MS 2):
The case narratives stratified by age groups have been provided. Please refer to response to question 10.
Issue solved.

Question 2 of MS 2 – Pharmaceutical data

PK data are available for children aged 18 months to 16 years, however no further analyses stratified by age group have been performed. The MAH is requested to discuss and comment on these paediatric PK data with reference to PK data from adult subjects, as these data should be considered for inclusion in section 5.2 of the SmPC.

Summary of the MAH's Response to Question 2 of MS 2
Please see response to question 3.

Assessor's comment (Day 90, assessment of response to question 2 of MS 2):
Please see response and comment to question 3.
Issue solved.

Question 3 of MS 2 – SmPC/PL

We note the Rapporteur's discussion: "*In particular, there are nearly no data which support the currently approved indications in children below the age of 2 years. As no new data will be available, this age group should be excluded, especially the age group below 1 year. Paediatric patients between 1 – 2 years of age may be treated by a justified benefit-risk assessment*."

In Section 4.2 of the SmPC [of this MS], Mebendazole (100 mg tablets and 100 mg/5ml syrup formulations) is licensed for children over the age of 2 years. Section 4.4 states that it is not recommended for use in children under the age of 2 years. Although parasitic infestations discussed as part of this Article 45 procedure are not common in [this MS], mebendazole is used as first line in the treatment for those indications approved in the SmPC. Alternatives for treatment exist but they are often used off label. Given that the efficacy and safety of mebendazole in children younger than the age of 2 years cannot be determined from the assessed studies, the proposed SmPC revisions represent a significant change which is not supported by the available data. Thus, [this MS] considers that mebendazole should not be used in children below the age of 2 years as the benefit: risk profile has not currently been established. Taking into account the rapporteur's proposal that there might be scope for use in the 1 to 2 years age group, the MAH is requested to discuss the totality of the data in children aged 1 year to 2 years to further clarify the benefit: risk of mebendazole in this age group. Based on this assessment, the MAH and rapporteur should determine whether changes to sections 4.2 and/or 4.4 would be needed in line with the SmPC guidelines. Finally considering the lack of robust data for the mebendazole suspension in the assessed studies, the rapporteur is asked to clarify if the proposed changes will also affect the SmPC for the mebendazole suspension, taking into account that this product is likely to be used in very young children.

Summary of the MAH's Response to Question 3 of MS 2
This search of the GMS global safety database retrieved 419 cases reporting AEs occurring in patients ≤2 years of age (or classified as neonate, infant or child) who received mebendazole. Eighty-eight cases concerned patients exposed to mebendazole during pregnancy or breast feeding and were excluded from further review. The remaining cases were divided into those where the patient was taking dosage/formulations listed in the 100 mg CCDS (305 cases) and

those taking dosage/formulations listed in the 500 mg CCDS (26 cases). Where the dosage was unknown the cases were included under the 100 mg review.

Case review – 100 mg Dosage/Formulations

The demographics and case characteristics for the cases are presented in Table 18 (*please see response document*).

The 100 mg CCDS cases were then divided into those that occurred to patients ≤1 year of age (or designated as infant) (47 cases), and those that occurred to patients between 1 and 2 years of age and designated as infant or child (176 cases). Any cases that did not fit into these criteria were excluded from review (82 cases).

Cases in Patients ≤1 Year of Age

The 47 cases were divided into nonserious and serious cases and the events were subdivided into those listed in the CCDS and those unlisted in the CCDS. Table 11 list the serious PTs experienced by these patients.

Table 11: Serious PTs Occurring Using Formulations Included in the 100 mg CCDS to Patients Under 1 Year of Age (n=5)

Listed	No of PTs [a]	Unlisted	No of PTs [a]
Generalised tonic-clonic seizure	1	Pyrexia	2
Urticaria	1	Anxiety	1
Seizure	1	Respiratory disorder	1
		Breath sounds	1
		Otitis media	1
		Drug dependence	1
		Tonsillitis	1
		Hallucination	1
		Mouth injury	1

Key: AE=adverse event; CCDS= Company Core Data Sheet; n=total number of cases; No=number of; PT= Preferred Term.
a: A single case may report more than 1 AE.

The nonserious PTs for patients ≤1 year of age are not presented here.

Cases in Patients >1 and ≤2 Years of Age

The 176 cases concerning patients >1 and ≤2 years of age were divided into serious and non-serious cases. Table 12 shows the serious PTs that these patients experienced.

Table 12: Serious PTs Occurring Using Formulations Included in the 100 mg CCDS in Patients between the Age of 1-2 Years Old (n=14)

Listed	No of PTs[a]	Unlisted	No of PTs[a]
Diarrhoea	3	Asphyxia	1
Vomiting	3	Conjunctivitis	1
Generalised tonic-clonic seizure	1	Fall	
Anaphylactic reaction	1	Haematuria	1
Abdominal pain upper	1	Haemolysis	1
Angioedema	1	Melaena	1
Epilepsy	1	Oral mucosal eruption	1
Seizure	1	Pneumonia	1
		Pruritus	1
		Pyrexia	1
		Rash papular	1
		Syncope	1
		Weight decreased	1

Key: AE=adverse event; CCDS= Company Core Data Sheet; n=total number of cases; No=number of; PT= Preferred Term.
a: A single case may report more than 1 AE.

Note:
The nonserious cases summarized by the MAH in tabular format are not presented here.

Of the 14 serious cases that occurred in patients between >1 and ≤2 years old, 8 cases did not report enough information for detailed medical assessment. Three cases involved infants who experienced convulsions and these cases are discussed in the seizure section. Two cases concerned reactions to mebendazole:

- Case (20120205405), concerned a 2-year-old male patient treated with mebendazole 100 mg tablet for threadworm, who experienced an anaphylactic reaction after taking his second dose of mebendazole. He was not given any more mebendazole and recovered. However, no further details are available for this case, precluding meaningful medical assessment.
- Case (JAGER41814), concerned a 1.25-year-old female patient who was treated with mebendazole 100 mg tablet for enterobiasis who experienced a generalized papular rash and Quinke's edema 4 days after 3 days of mebendazole therapy. However, no further details are available for this case, precluding meaningful medical assessment.

One serious case (20040700017) was fatal; a 2-year-old girl choked on a 100 mg mebendazole tablet which then became stuck in her airway causing her death from asphyxiation.

Case review – 500 mg Dosage/Formulations

The demographics and case characteristics for the cases were presented in tabular format (table not shown here).

The 500 mg CCDS cases were then divided into those containing events that occurred to patients ≤1 year of age (or designated as infant) (2 cases), and those that occurred to patients between 1 and 2 years of age and designated as infant or child (5 cases). Any cases that did not fit these criteria were excluded from review (18 cases).

Cases in Patients ≤1 Year of Age

Only serious cases were received for patients ≤1 year of age. The events of those cases were divided into those listed in the CCDS and those unlisted in the CCDS. Table 24 (*please see response document*).

Of the 2 serious cases, 1 concerns case HOAFF6774 which is discussed in the seizure section. The remaining case 20160725809 concerns a 1-year-old female patient who was treated with 10 mL single dose mebendazole suspension for the treatment of intestinal worms and developed diarrhea and fever which continued for 72 hours. The infant had been in good health before receiving mebendazole. She was treated with oxymetazoline, lactobacillus, zinc, paracetamol and amoxicillin and recovered.

Cases in Patients >1 and ≤2 Years of Age

The cases were divided into serious and nonserious cases and the events were subdivided into those listed in the CCDS and those unlisted in the CCDS. The 1 serious case (JASWE11381), reported the listed event of urticaria, which occurred 1 day after a 24 month old female patient received treatment with mebendazole for intestinal parasites. The patient was admitted to hospital and recovered.

Review of Literature – Use of Mebendazole in Children ≤2 Years of Age

Joseph SA, Montresor A, Casapia M, Pezo L, Gyorkos TW.
Adverse Events from a Randomized, Multi-Arm, Placebo-Controlled Trial of Mebendazole in Children 12-24 Months of Age. *Am J Trop Med Hyg (2016)* 95(1): 83-87.

A randomized multi-arm, placebo-controlled trial of mebendazole, administered at different times and frequencies, was conducted in children 12 months of age living in Iquitos, Peru. Children were followed up to 24 months of age. The association between mebendazole administration and the occurrence of a serious or minor AE was determined using logistic regression. There were a total of 1,686 administrations of mebendazole and 1,676 administrations of placebo to 1,760 children. Eighteen serious AEs (ie, 11 deaths and 7 hospitalizations) and 31 minor AEs were reported. There was no association between mebendazole and the occurrence of a serious AE (odds ratio [OR] =1.21; 95% confidence interval [CI]=0.47, 3.09) or a minor AE (OR=0.84; 95% CI=0.41, 1.72).

Montresor A, Awasthi S. and Crompton DWT.
Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis. *Acta Trop*. (2002) 86(2-3): 223-32.

Considerable experience and limited quantitative evidence indicate that infections with the soil-transmitted helminths *A. lumbricoides* and *T. trichiura* usually start to become established in children aged 12 months and older 65. Since children living in countries where the infections are endemic are at risk of morbidity, even those as young as 12 months may need to be considered for inclusion in public health programmes designed to reduce morbidity by means of regular anthelminthic chemotherapy. This situation raises the question as to whether such young children should be given anthelminthic drugs. Systems for the absorption, distribution, metabolism and elimination of drugs do not fully develop until children are in their second year of life. Current knowledge, however, reveals that the incidence of side effects linked to benzimidazole drugs in young children is likely to be the same as in older children. Accordingly, we conclude that albendazole and mebendazole may be used to treat children as young as 12 months if local circumstances show that relief from ascariasis and trichuriasis is justified.

Clinical Study Report MEBENDAZOLGAI3003.
A Double-Blind, Randomized, Multi-Center, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Dose of a 500-mg Chewable Tablet of Mebendazole in the Treatment of Soil-Transmitted Helminth Infections (*Ascaris lumbricoides* and *Trichuris trichiura*) in Paediatric Subjects. Janssen Research & Development (06 April 2016).

278 (94.2%) out of 295 subjects completed the double-blind treatment phase and entered the open-label follow-up phase. All subjects were black with a mean age of 7.8 years. The actual age range of the subjects enrolled was 1 to 15 years, inclusive. The distribution of subjects across sexes was similar in both the treatment groups with 51.5% female and 48.5% male children. Of the 295 subjects randomized in the study, 167 subjects were infected with *A. lumbricoides* and 243 subjects were infected with *T. trichiura*. Among them, 115 subjects were infected with both worms. Thirteen subjects also had hookworm infestation. The majority of the study population was made up of subjects with light or moderate infestation soil-transmitted helminth infestation. Only a small percentage of subjects had severe *A. lumbricoides* infestation (4.4%).

During the double-blind phase, the total incidence of treatment-emergent adverse events (TEAEs) was low and comparable between the 2 treatment groups; 9/144 (6.3%) subjects in mebendazole group and 8/140 (5.7%) subjects in the placebo group. None of the individual TEAEs (by preferred term) were reported in more than 2 subjects in either of the treatment groups. No TEAEs were reported in the 24 subjects aged <3 years (12 subjects received placebo and 12 subjects received mebendazole). The most commonly occurring (2 subjects from either of the treatment groups) TEAEs during the double-blind phase included nasopharyngitis, cough, and abdominal distension. All TEAEs were mild to moderate in severity and none were severe.

Conclusion

Safety Profile for Children between the Ages of 1 and 2

Based on the totality of data, there are no new safety related risks for children 1 to 2 years of age. The reported AEs, both serious and nonserious were either labeled, not reported in high numbers, lacked important information to make a meaningful assessment, were unrelated to drug, were manageable events, or could be mitigated by utilizing a different formulation of mebendazole. In addition, recent publications and 1 recently completed paediatric clinical study also concluded that mebendazole is generally safe in children from 12 to 24 months of age with the benefits outweighing the risks.

In conclusion, as initially mentioned in the clinical overview submitted as part of the Article 45 procedure, the MAH proposes to harmonize the warning with regards to convulsions as follows:

> *"Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience. (see Adverse reactions)*
> *TRADENAME has not been extensively studied in children below the age of 2 years. Therefore, TRADENAME should be used in children aged 1-2 years only if the potential benefit justifies the potential risk.*
> *Because of the risk of convulsions, TRADENAME should not be used in children below the age of 1 year."*

Assessor's comment (Day 90, assessment of response to question 3 of MS 2):
Due to the special pharmacokinetics in children less than 1 year of age the warning proposed by the MAH for SmPC section 4.4 is supported with a slight change of the wording (underlined) regarding this age group:

"Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience. (see Adverse reactions)
TRADENAME has not been extensively studied in children below the age of 2 years. Therefore, TRADENAME should be used in children aged 1-2 years only if the potential benefit justifies the potential risk.
Because of the lack of sufficient safety data, TRADENAME should not be used in children below the age of 1 year."

Please refer also to response and comment of the question from Sweden.

Issue solved provided that the text will be implemented in the SmPC.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Mebendazole is licensed for paediatric use in the treatment of single or mixed gastrointestinal infestations by *Enterobius vermicularis* (pinworm), *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (large roundworm), *Ancylostoma duodenale, Necator americanus* (hookworm), *Strongyloides stercoralis* (threadworm), and *Taenia* spp. (tapeworm) as well the larval stages of *Echinococcus granulosus* and *E. multilocularis*. Not all indications and formulations (100 mg, 500 mg tablet, and oral suspension) are approved in all of the European Member States. There are some limited clinical data in the paediatric population regarding particular indications. However, based on the review of the presented paediatric data, the rapporteur concludes from the submitted studies that there are no significant new data regarding the efficacy and safety of mebendazole used for the indications as approved in children.
However, there are recommendations for additions to the informative texts as listed below.

- **Recommendation**

Specific wording related to paediatric use is proposed for the following sections of the SmPC:

SmPC:

4.2 Dosage and administration

1. for countries where the oral suspension is authorised:

   Paediatric population
   TRADENAME oral suspension should be considered for patients such as young children who are unable to swallow the tablet.

   and for countries where no oral suspension is licensed:

   Paediatric population
   "Tablets may be chewed or swallowed whole. Crush the tablet before giving it to a young child. Always supervise a child while they are taking this medicine."

2. for the indication ***strongyloidiasis*** in EU countries where it is approved:

   '*Paediatric population / Children and adolescents (≥2 to 16 years)*
   Data on efficacy and safety in children and adolescents ≥2 years to 16 years are limited. Mebendazole should be used only, if there is no therapeutic alternative.'

3. for the indication ***Taeniasis***:

   '*Paediatric population / Children and adolescents (≥2 to 16 years)*
   Data on efficacy and safety in children and adolescents ≥2 years to 16 years are limited. Mebendazole should be used only, if there is no therapeutic alternative.'

4. for the indications **trichinosis** and **echinococcosis**:

4.1 Therapeutic indications
'Official guidelines should be taken into consideration. Official guidelines will normally include WHO and public health authorities' guidelines.'

4.4 Special warnings and precautions for use
As higher doses and longer treatment is recommended in patients with Trichinellosis and Echinococcosis, careful consideration should be given when treating patients with severe chronic hepatic diseases and/or bone marrow depression."

and

These patients should be closely monitored with hematological, liver and renal function tests. Consider discontinuing TRADENAME if clinically significant laboratory abnormalities are found. 'Official guidelines should be taken into consideration.

Children under 2 years of age:
TRADENAME has not been extensively studied in children below the age of 2 years. Currently available data are described in section 4.4, 4.8 and 5.2, but no recommendations on a posology can be made.
Because of the lack of sufficient safety data, TRADENAME should not be used in children below the age of 1 year (see section 4.4, 4.8 and 5.2).

4.4 Warnings and precautions
Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience. (see section 4.8)
TRADENAME has not been extensively studied in children below the age of 2 years. Therefore, TRADENAME should be used in children aged 1-2 years only if the potential benefit justifies the potential risk.
Because of the lack of sufficient safety data, TRADENAME should not be used in children below the age of 1 year.

5.2 Pharmacokinetic properties
'Paediatric population:
Limited data of the mebendazole concentrations in plasma are available in children and adolescents 1 to 16 years of age. These data do not indicate substantially higher systemic exposure to mebendazole in subjects 3 to 16 years of age compared to adults. In subjects 1 to <3 years of age, systemic exposure is higher than in adults due to higher mg/kg dose relative to adults."

PL:

The changes proposed for the SmPC should be included in the relevant sections of the PL.

A Type IB variation on the proposed changes to the SmPC/PL should be submitted by the MAH, within 60 days after finalisation of the procedure for medicinal products included in the worksharing, if not already included.

For medicinal products with the same active substance and pharmaceutical form, the submission of a type IB variation is requested within 90 days of publication of the public assessment report.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

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