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

Amitriptyline

Tryptizol

UK/W/054/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	24 March 2015

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Amitriptyline
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	Tricyclic Antidepressants ATC code: N06AA09
Pharmaceutical form(s) and strength(s):	10mg, 25mg and 50mg film-coated tablets

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1 EXECUTIVE SUMMARY

Amitriptyline is a tricyclic antidepressant (TCA). It is licensed in children for nocturnal enuresis and in adults for depression. It is available as a 10mg, 25mg and 50mg film-coated tablets.

In accordance with Article 45 of the Regulation (EC) No 1901/2006 as amended, the MAH submitted 13 studies for the nocturnal enuresis, 2 for depression and 2 for 'emotionally ill/disturbed children'. The studies predate current clinical guidelines for enuresis and current diagnostic classifications for psychiatric disorders. They also predate the introduction of Good Clinical Practice (GCP) Guidelines. The efficacy data provided by these studies do not merit reflection in the product information.

Five review articles on the management of nocturnal enuresis were also submitted. These highlight the risks of death with overdose, relapse after withdrawal, tolerance, note that long QT syndrome must be excluded prior to initiation of therapy and recommend that TCAs be used only as second or third line enuresis therapy.

The cumulative safety review confirmed the known safety concerns for amitriptyline.

Toxicity in overdose, potentially resulting in death, is a class effect of tricyclic antidepressants. The review of class effects however is not within the remit of an Article 45 procedure, nor is the deletion of an indication.

Therefore, for the products already containing the paediatric nocturnal enuresis indication, it was decided to recommend restriction to third line therapy and a strengthening of the warnings as outlined in section 2 below. Amitriptyline products that are not licensed for use in paediatric enuresis should remain unchanged.

Summary of outcome

☐ No change

☒ Change

☐ New study data:

☐ New safety information:

☒ Paediatric information clarified: sections 4.1, 4.2, 4.3, 4.4 and 4.5.

☐ New indication: Paediatric indication restricted.

2 RECOMMENDATION

The product information shall be updated to implement the following restrictions. **The proposed SmPC changes are only applicable to products that are already licensed for the paediatric indication of nocturnal enuresis:**

Section 4.1: The indication shall be restricted as follows:

Amitriptyline is indicated for the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology has been excluded and no response has been achieved to all other non-drug and drug treatments (use only as third line therapy). Amitriptyline should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis

Section 4.2: The following text should be added to the posology section:

Enuresis: An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome. The dose should be increased gradually. The initial treatment course is for 3 month. If repeated courses of amitriptyline are needed, a medical review should be conducted every 3 months. When stopping treatment, amitriptyline should be withdrawn gradually.

Section 4.3:

A contraindication for use in children < 6 years should be added.

Section 4.4.

The following warning statements should be added:

Enuresis:

- An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.
- Amitriptyline for enuresis should not be combined with an anticholinergic drug.
- Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis.

Section 4.5.:

The following statement should be added: Amitriptyline for enuresis should not be combined with an anticholinergic drug.

The PL should be updated in line with the SmPC and should include a prominent warning statement that the drug should be kept securely locked and out of reach of smaller siblings because overdose may be fatal.

3 INTRODUCTION

Merck & Co submitted information on 17 completed paediatric studies for amitriptyline, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use : 13 for the indication nocturnal enuresis, two for the indication depression and two for the indication 'emotionally ill/disturbed children'.

In addition, the MAH provided five review articles on the management of nocturnal enuresis,three Periodic Safety Update Reports covering the period from June 2002 to January 2012, and a cumulative safety review..

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for amitriptyline and that there is no consequential regulatory action.

4 SCIENTIFIC DISCUSSION

4.1 Submitted documentation

The MAH submitted 13 reports for the indication nocturnal enuresis, 2 reports for the indication depression and 2 reports for the indication 'emotionally ill/disturbed children'. The majority of the studies submitted by the applicant were conducted in the 1960's and have neither a study title nor a study number. In some instances, only a statistical evaluation has been provided. It is therefore not possible to provide a list of study numbers and titles.

The MAH also provided 5 review articles on the management of nocturnal enuresis, 3 Periodic Safety Update Reports covering the period from June 2002 to January 2012, a bridging report of three paragraphs' length, and at request a cumulative safety review.

4.2 Current clinical guidelines for the treatment of enuresis

Recent treatment recommendations for nocturnal enuresis have been published by NICE, the European Society for Paediatric Urology and the International Children's Continence Society. A Cochrane review is also available. Relevant sections of the guidelines and the Cochrane review are as follows.

1. NICE clinical guideline 111 Nocturnal enuresis - The management of bedwetting in children and young people

Do not use tricyclics as the first-line treatment for bedwetting in children and young people.

If offering a tricyclic, imipramine should be used for the treatment of bedwetting in children and young people.

Consider imipramine for children and young people with bedwetting who:

• have not responded to all other treatments and

• have been assessed by a healthcare professional with expertise in the management of bedwetting that has not responded to an alarm and/or desmopressin.

If offering imipramine for bedwetting, inform the child or young person and their parents or carers:

• that many children and young people, but not all, will experience a reduction in wetness

• how imipramine works

• that it should be taken at bedtime

• that the dose should be increased gradually

• about relapse rates (for example, more than two out of three children and young people will relapse after a 3-month course of imipramine)

• that the initial treatment course is for 3 months and further courses may be considered

• about the particular dangers of imipramine overdose, and the importance of taking only the prescribed amount and storing it safely.

Perform a medical review every 3 months in children and young people who are using repeated courses of imipramine for the management of bedwetting.

Withdraw imipramine gradually when stopping treatment for bedwetting in children and young people.

Do not offer an anticholinergic combined with imipramine for the treatment of bedwetting in children and young people.

2. European Society for Paediatric Urology: Guidelines on Paediatric Urology, 2012:

Medication: In the case of high night-time diuresis, success rates of 70% can be obtained with desmopressin (DDAVP), either as tablets, 200-400 µg, or as sublingual desmopressin oral lyophilisate, 120-240 µg. A nasal spray is no longer recommended due to an increased risk of overdose (6,7) (LE: 1; GR: A). However, relapse rates are high after desmopressin discontinuation. In the case of small bladder capacity, treatment with antispasmodics or anticholinergics is possible. However, when these medications are necessary, the condition is no longer considered to be monosymptomatic. Imipramine, which has been popular for treatment of enuresis, achieves only a moderate response rate of 50% and has a high relapse rate. Furthermore, cardiotoxicity and death with overdose are described. Its use should therefore be discouraged.

3. Evaluation of and Treatment for Monosymptomatic Enuresis: A Standardization Document From the International Children's Continence Society

Neveus T et al 2010. THE JOURNAL OF UROLOGY, Vol. 183, 441-447.

Tricyclic Antidepressants: The tricyclic antidepressant imipramine was previously frequently used for enuresis and many randomized studies show that it is better than placebo (grade Ia evidence). Approximately 50% of unselected children with enuresis respond to the drug and the response rate seems to be the same in children with therapy resistant enuresis. Due to safety concerns and side effects imipramine is only relevant as third line therapy at tertiary care facilities. Another situation in which imipramine may be used is in children in whom the alarm has failed and whose families cannot afford desmopressin. The anti-enuretic dose is 25 to 50 mg at bedtime with the larger dose given to children older than 9 years. The effect is evaluated after 1 month. When there is a partial response desmopressin at the standard dose may be added, provided that the fluid intake of the child is restricted during the evening and night.37 If treatment is successful, the family should taper to the lowest effective dose and ensure that regular drug holidays of at least 2 weeks are interspersed every third month or so to decrease the risk of tolerance, which otherwise is quite high.37 The purpose of drug holidays for imipramine is different than that for desmopressin. The central problem with imipramine is that it is potentially cardiotoxic and an overdose may prove fatal.38 The drug should be kept securely locked and out of reach of smaller siblings. If there is any history of palpitations or syncope in the child, or any sudden cardiac death or unstable arrhythmia in the family, long QT syndrome must be excluded by prolonged electrocardiogram recording before imipramine treatment is considered. Although other side effects are not dangerous, they are also problematic, including mood changes, nausea or insomnia. These problems often appear earlier than the beneficial effects. Moderate side effects often gradually disappear even if treatment is continued.

4. Cochrane Database Syst Rev. 2003;(3):CD002117. Tricyclic and related drugs for nocturnal enuresis in children. Glazener CM, Evans JH, Peto RE.

The authors of the Cochrane reviewed 58 randomised trials, with many of poor quality. There was not enough information to assess the relative performance of one tricyclic against another except that imipramine was better than mianserin. They conclude that treatment with tricyclic or related drugs (imipramine, amitriptyline, viloxazine, clomipramine and desipramine but notmianserin) was associated with a reduction of about one wet night per week while on treatment. Although about a fifth of the children became dry while on treatment, most of them relapsed after treatment stopped. Long term effects are still uncertain. The limited evidence suggested that desmopressin and tricyclics might be equally effective while on treatment, but that these effects are not sustained after treatment stopped. In contrast, about half the children treated with an alarm are likely to remain dry after treatment stops but families need to provide extra support during treatment with alarms. Desmopressin is more expensive than tricyclics, but tricyclics have considerably more minor side-effects and a higher risk of overdose causing fatality. Children and their families need to be warned of the potentially lethal adverse effects of these drugs in overdose and advised on how to avoid this.

4.3 Clinical studies nocturnal enuresis

Crossover studies

These studies were performed between 1963 and 1971 in children with longstanding idiopathic or psychogenic enuresis, with a minimum of 1-3 wet nights per week at the time of the study and not taking other medications for enuresis during the study. They were randomized, double-blind, placebo-controlled and included 2 treatment periods of 4 to 6 weeks. The key endpoint was reduction in the number of wet nights per week. Some trials also evaluated the physician's appraisal of the effectiveness of treatment.

1) Poussiant performed a 2-part study in 59 patients age 5-15 with high frequency enuresis [Ref. 5.4: 50]. Part one included a 2-period (4 weeks) crossover design (n=32) and Part 2 utilized an 8-week, placebo-controlled parallel group design (n=18). Amitriptyline dose-adjusted based on age as follows: age 5-11, 25 mg and age 12-15, 50 mg. Study medication was administered nightly ~30 minutes before bedtime. In the crossover portion of the study, amitriptyline was associated with a greater reduction in the frequency of nocturnal enuresis compared to placebo ($p<0.0005$). Amitriptyline was superior to placebo in 60% of patients, with improvements ranging from $\leq$ 20% up to 99%. In the non-crossover portion, the sample size was considerably smaller (n=9 per treatment group), with greater variability in patient age and dose, and no differences were observed between the treatment groups. At least 1 side effect was reported in 46% of patients, with the irritability being most commonly reported (amitriptyline, n=7 vs. placebo, n=5).

Rapporteur's comment

Poussaint AF. Study of amitriptyline in enuresis, 1964. Both the study report and the publication of the study results have been submitted. It is not clear if this study was randomised nor is there any information with regard to blinding. Children who 'did not take their medication properly', who did not keep appointments and who had intercurrent bladder infection were excluded from analysis. 11 of 59 children were thus excluded from analysis. Reported adverse events were hearing loss, irritability, morning drowsiness, headache, decreased appetite, fatigue, stomach ache, scleral injection.

The half-life of amitriptyline is 16 ± 6 hours. The trial did not include a washout period.

These data cannot be regarded robust and do not merit reflection in the product information.

2) Hagelsteen performed a study in 12 enuretic patients 6-10 years of age [Ref. 5.4: 60]. Patients received amitriptyline (administered as a single 10 mg dose ~30 minutes before bedtime) or placebo for 4 weeks in each treatment period. Note that 4 patients were over 10 years of age and these data were excluded from the analyses. In the remaining 8 patients, no differences were observed between the treat groups with respect to the frequency of enuresis or physician appraisal of effectiveness. No side effects were reported.

Rapporteur's comment

Hagelsteen H. Drug: amitriptyline (TRYPTANOL/TRYPTIZOL), 1968

This is a clinical study report dated 1968 and encompassing three pages in its entirety. It is difficult to find the total number of children treated. Six children violated the inclusion criteria and were excluded from analysis. The investigator concludes that the total number of patients in both groups is not sufficient. No adverse reactions were reported.

These data do not merit reflection in the product information.

3) Galarza performed a study 32 enuretic patients 8-15 years of age [Ref. 5.4: 59]. Study medication was administered nightly for 6 weeks in each treatment period. Amitriptyline 25 mg was administered as a single dose ~ 30 minutes prior to bedtime. In the pooled analysis of data from both periods 1 and 2, no differences were observed between the treatment groups with respect to number of wet nights/week (AMI 3.1 vs PBB 3.2). However, analysis of data by period showed significant reduction in the number of wet nights/week in period 1 with amitriptyline (AMI 2.3 vs PBO 4.1, $p < 0.05$) and in period 2 with placebo (PBO 2.4 vs. AMI 4.1, $P < 0.001$). The investigator speculated that there was an error in medication packaging and that the treatments were not crossed over. The treatments were generally well tolerated.

Rapporteur's comment

Sondervorst M. Clinical trial of amitriptyline in the treatment of enuresis in children, 1969.

This is a statistical evaluation dated 1969, no study report as such has been submitted. Again, a child with missing data was simply excluded from analysis. No details are provided as to randomisation, blinding, adverse events, etc. The report notes that there tended to be more wet nights on amitriptyline than on placebo.

These data do not merit reflection in the product information.

4) Lambrechts conducted a study in 16 5-15 year old patients with enuresis [Ref. 5.4: 53]. Study medication was administered nightly for 4 weeks in each treatment period. Amitriptyline was dose-adjusted based on patient age as follows: age 5-10, 10 mg and age 11-15, 25 mg. Note that due to lack of efficacy in the first 10 patients treated, amitriptyline was increased to 20 mg and 50 mg in the younger and older patients, respectively. Treatment was generally well tolerated, with no side effects reported with amitriptyline. The investigator terminated the study due to slow enrollment and to dissatisfaction with the results and concluded that the limited data on 10 patients was insufficient to draw valid conclusions.

Rapporteur's comment

Lambrechts A. Summary of clinical study: drug: amitriptyline tablets, 1967

This study (report date 1967) was terminated early. These data do not merit reflection in the product information.

5) Thomson conducted a study in 35 children with enuresis [Ref. 5.4: 54]. The median age was ~8, though an age range was not provided; children under 3 years of age were excluded. Amitriptyline was initiated at 25 mg ~30 minutes before bedtime nightly in children under 12 and increased to a maximum of 75 mg according to age or failure to respond. Each treatment period lasted 6 weeks. Fewer wet nights per week were observed with amitriptyline than with placebo. This difference was noted at week 4 (AMI 2.9 vs PBO 4.2, $p < 0.001$) and continued through week 6 (AMI 3.0 vs. PBO 4.0, $p < 0.001$) and was consistent with the physician's assessment of improvement. Note that the report is incomplete and no mention is made of tolerability.

Rapporteur's comment

Heery PJ, Thomson BC. Clinical trial of amitriptyline in the treatment of enuresis in children, 1969.

This is a statistical evaluation encompassing three pages and dated 4/15/69. No study report has been submitted. There is no information on study design, inclusion/exclusion criteria, randomisation, blinding, adverse events, etc. These data do not merit reflection in the product information.

6) Bakker et al conducted a study in 61 children age 6 to 18 years with enuresis [Ref. 5.4: 55]. Patients received amitriptyline (age 6-10: 20 mg; age ≥ 11: 50 mg) or placebo nightly ~30 minutes before bedtime, each for 4 weeks. Among children age 6-10 (N=41), the mean age was 7.6 years and the gender ratio was 18/13 for males/females. For patients age 11 or older, the mean ager was 12.7 years with a gender ratio of 14/3 for males/females. Data for 41 patients was included in the analyses. A statistically significant reduction in the number of wet nights was observed with in both age groups, with a mean difference of 1-2 fewer wet nights per week with amitriptyline compared to placebo. In addition, amitriptyline was superior to placebo based on the physician's appraisal of effectiveness. Amitriptyline was generally well tolerated, with side effects reported by 4 patients; no patients discontinued due to side effects.

Rapporteur's comment

Bakker WCM, van Dam GBP. Summary of clinical study: Drug: amitriptyline (TRYPTIZO) tablets, 1969

Data from ten children aged 6 – 10 years and from three children aged 11 - 18 years were excluded from analysis for various reasons. On the other hand data from five children aged 11 - 18 years were included in the analysis despite their not meeting the inclusion criterion of at least 3 wet nights per week.

These data do not merit reflection in the product information.

7) Ingvar Ek conducted a study in 48 6-15 year old patients with enuresis [Ref. 5.4: 62, 63]. Patients were treated with amitriptyline (age 6-10: 10 mg; age 6-15: 25 mg) or placebo ~30 minutes before bedtime, receiving each treatment for 4 weeks. Among children age 6-10 assigned to low dose amitriptyline (n=22), the mean age was 7.2 years and the gender ratio was 15/7 for males/females. For patients assigned to high dose amitriptyline (n=26), mean age was 9.2 years, with a gender ratio of 13/8 for males/females. Both doses of amitriptyline were superior to placebo in treating nocturnal enuresis, based on the mean reduction in wet nights per week (~1 night/week for amitriptyline) and on the physician's appraisal of effectiveness. Treatment was generally well tolerated, with mild to moderate side effects noted in 3 high dose amitriptyline patients.

Rapporteur's comment

Ingvar Ek J. Amitriptyline tryptanol/triptizol in enuresis nocturna, 1967

This report contains the 'Summary of a clinical study' for two trials, neither of which have a title.

'Schedule I':

This was a double-blind randomised cross-over trial amitriptyline 10mg in 25 children aged 6-10 years. The duration of each cross-over period was 4 weeks. No wash-out period is mentioned between the two treatment periods. Results of 3 children were not analysed as one patient interrupted treatment, one never started treatment, and in the third the 'allocated medication was never used by the investigator'. There was no statistically significant difference in mean number of nights that the child wet the bed across all 4 weeks between amitrityline and placebo, but the difference in mean number of nights that the child wet the bed during the 4th week was statistically significant.

No side effects related to the medication were reported (the report makes no mention of adverse events).

'Schedule II':

This was a double-blind randomised cross-over trial of 4 weeks amitriptyline 25mg in 26 children aged 6-15 years. 21/26 patients completing the study were included in the evaluation. Results of 5 children were not analysed as one patient interrupted treatment, four never started treatment, and in another two the 'allocated

medication was never used by the investigator'. There was no statistically significant difference in mean number of nights that the child wet the bed during the 4th week between amitrityline and placebo, but the difference in mean number of nights that the child wet the bed across all 4 weeks was statistically significant.

Westerstahl N, Gaudino M, Ingvar Ek J. Amitriptyline tablets in enuresis nocturna, 1970.

This is a statistical evaluation of 'Schedule I'. It confirms the findings mentioned above (amitriptyline significantly better only for 4th week data but not for the mean of 4 weeks). The author concludes that the difference in mean dry nights per week (amitriptyline 2.3 versus placebo 1.5) is hardly of any practical clinical value.

These reports do not add any information that requires reflection in the product information.

8) Krasovsky Zozula et al. performed a study in 39 children age 5 to 17 years with enuresis [Ref. 5.4: 72]. The mean age of patients was 9.4 years and the gender ratio was 29/10 for males/females. Amitriptyline 25 mg or placebo was administered as a single dose ~30 minutes before bedtime. Treatment periods were 6 weeks in duration. Note that the method of allocation to a given treatment was not reported. In the 30 patients who completed the trial, treatment with amitriptyline was associated with a statistically significant lower mean number of wet nights compared to placebo. This difference was observed as early as week 4 (AMI 2.3 vs PBO 3.1, $p < 0.05$) and continued through week 6 (AMI 2.5 vs PBO 3.5, $p < 0.01$). No difference was observed with respect to physician appraisal of effectiveness. Treatment was generally well tolerated, with 2 side effects reported (sleepiness and hyperactivity).

Rapporteur's comment

Krasovsky J. Amitriptyline in the treatment of enuresis, 1970.

The protocol is hardly in line with today's standards of clinical care or Good Clinical Practice. For example, conversations with the patient were avoided as much as possible in order for no aspects of psychotherapeutic type to influence the results. Family members were not provided with any 'additional information' nor were they informed on possible side effects which might appear.

9/39 patients were excluded from analysis because they did not complete treatment.

This report does not add any information that merits reflection in the product information.

9) Garcia I performed a study in 48 children with enuresis [Ref. 5.4: 58]. Patient ranged from 3-16 years of age, with a median age of 7.5 years. Amitriptyline was administered as a single 25 mg dose ~ 30 minutes before bedtime; note that the dose could be increased in older children at the investigator's discretion. Of 48 patients randomized, 17 failed to return for follow-up. By week 3, fewer wet nights per week were reported with amitriptyline than with placebo (AMI 3.0 vs PBO 4.3, $p < 0.01$) and this difference was sustained through week 6 (AMI 3.4 vs PBO 4.6, $p < 0.05$). Treatment was generally well tolerated, with one side effect of drowsiness reported with amitriptyline.

Rapporteur's comment

Garcia F. Amitriptyline in enuresis, 1970.

The document submitted is a statistical evaluation of yet another study without study number.

There is no information on randomization, actual doses used or prespecified primary endpoint. Data from 17/48 patients were not analyzed because the patients did not return to follow-up – but it is not clear whether there were any on-treatment data for these patients or not.

This report does not add any information that merits reflection in the product information.

Other trials

10) Abruzzi conducted an active- and placebo-controlled, parallel group trial of amitriptyline, methscopolamine, and placebo in 90 children (3 to 9years of age) with nocturnal enuresis [Ref. 5.4: 78] At baseline, patients reported enuresis on 90% of nights or more. Patients were treated with amitriptyline (age 3-5: 10mg; age 5-9: 25mg), methscopalamine (age 3-5: 1.25mg; age 5-8: 2.5mg), or placebo ~30 minutes before bedtime for 30 days. Parents completed a daily recording of wettings. During the last 15 days of treatment, fewer wettings were reported in patients age 5-9 treated with the high dose amitriptyline than with placebo ($p < 0.01$), with a similar trend observed in patients age 3-5 years treated with low dose AMI ($p < 0.07$), while no difference was noted between methscopolamine and placebo. No side effects were reported.

Rapporteur's comment

Dr.Abruzzi Study. Second study on Elavil in Enuresis, 1963.

The submitted document is an internal memorandum concerning the statistical evaluation of a study that is neither specified by study title nor study number. The presented information is too sparse as to permit any conclusions on either efficacy or safety.

11) Mises conducted a 4-week open-label study of amitriptyline in 47 children age 6-18 years with primary or secondary enuresis [Ref. 5.4: 74]. Patients served as their own control in 2 week observational periods pre- and post- treatment with amitriptyline. Amitriptyline syrup (10 mg/5 ml) was administered ~30 minutes before bedtime as follows: age 6-10, 1 teaspoon (tsp) and age 11-18, 2 tsp. The dose could be increased up to 4 tsp based on patient response and tolerability. Seven patients had positive results (i.e., considerable reduction in 3 or more wet nights), while 11 patients had partial improvement; however no changes was observed in the majority of case (n=29). Treatment was generally well tolerated. Three patients experienced "mental excitation with instability" and insomnia.

Rapporteur's comment

Mises R. Amitriptyline in enuresis - Dr. Mises, 1969

This was an open-label trial conducted mostly in paediatric psychiatry inpatients. The results of this open-label trial do not merit inclusion in the product information.

12) Porot and Girad conducted a 3-month open-label study of amitriptyline in 45 children 3-16 years of age with enuresis [Ref. 5.4: 75, 76]. Patients served as their own control in 1 month observational periods pre- and post-treatment with amitriptyline. Amitriptyline syrup (10 mg/5ml) was administered based on age and in divided doses daily as follows: age 3-6, 10 mg and after 7-16, 20-50 mg. 29/45 (64%) of patients had improvement or cure of enuresis with amitriptyline. Improvement was also noted in other domains including school work, sleep, and temper. Treatment was generally well tolerated. Side effects reported included excitement (n=4), drowsiness (n=3), insomnia, (n=1) and lack of interest (n=1).

Rapporteur's comment

Porot M, Girard J. Amitriptyline in enuresis - Pr. Porot/Dr. Girard, 1969.

In this trial, the amitriptyline was administered in the morning and evening. The results of this open-label trial are for an unlicensed syrup formulation. They do not provide robust evidence of efficacy or safety and therefore do not merit inclusion in the product information.

Porot M. Expert clinical report for the purpose of obtaining a visa -- Porot, 1968.

The report contains narrative descriptions of individual patients treated with amitriptyline syrup.

The descriptions are rather shocking to read. For example, a child is described as having 'marked negroid features characterised by physique, by being very deficient in school, by enuresis'. The patient was (intentionally) treated without consent as he was 'accustomed to taking drugs …and…not interested in the results we could attain with this new therapy'.

This information does not merit inclusion in the product information.

13) Kraft conducted an open label study of amitriptyline in 38 children (primarily age 8-10 years) with nocturnal enuresis 2-3 times per week [Ref. 5.4: 61]. Patients received placebo for 1 week (n=23) or amitriptyline 20-80mg for one week (n=38); note that of these 17 patients received placebo followed by amitriptyline. Of patients treated with amitriptyline, 26/38(68%) had all dry nights or more dry than wet nights, while 2/38 (5%) were unchanged, compared to 19.23 (82%) of placebo-treated patient who reported no change or worsening. Treatment was generally well-tolerated.

Rapporteur's comment

Kraft IA, Juanita MD, Hart JTMWP, Pearce PR. Results of amitriptyline used with enuretic children (undated)

The results of this open-label trial do not provide robust evidence of efficacy or safety and therefore do not merit inclusion in the product information.

4.4 Clinical studies depression and 'emotionally ill/disturbed children'

1) LeVann conducted a randomized, double-blind, active- and placebo-controlled trial in 50 children and adolescents with reactive or hyperkinetic depression [Ref. 5.4: 73]. Children age 8-15 were treated for 6 weeks with amitriptyline 10 mg three times a day (n=17), phenobarbitone 15 mg (n=16), or placebo (n=17). Patients received 1 pill three times a day for one week, followed by 2 pills three times daily thereafter. The median patient age ranged from 13-15 years. No important statistically significant differences were observed between the treatment groups based on changes in target symptoms and little improvement was observed based on physician assessment. Treatment was generally well tolerated.

Rapporteur's comment

LeVann LJ. Use of amitriptyline in childhood depressions, 1971

The submitted document is a statistical evaluation of a study titled 'Use of amitriptyline in childhood depressions', protocol number 178.

Subjects included in the trial were diagnosed 'schizophrenic personality or behaviours, hyperkinetic/hyperactive, autistic, hyperkinetic and autistic, adjustment reaction and other'. Side effects were not to be elicited. 10 target symptoms were rated on a 0-4 scale with 0 being no symptoms and 4 being incapacitating symptoms:

anxiety/worry, tensions, irritability, insomnia, moodiness, weepiness, fits of temper, aggressiveness, antisocial conduct, abdominal pain.

The study population does not represent what is considered to be depression as per DSM-IV or ICD-10 criteria. No primary endpoint is identified, and amongst the multiple comparisons of symptom scores, amitriptyline was statistically significantly better than either placebo or phenobarbitone only for 'tensions' at weeks 4 and 5 (without adjustment for multiplicity).

The results of this trial do not merit reflection in the product information.

2)Roy performed a randomized, double-blind, active- and placebo-controlled study 51 children and adolescents with reactive or hyperkinetic depression [Ref. 5.4: 56, 57]. Patients age 5-16 were treated with amitriptyline 10 mg, phenobarbitone 15 mg, or placebo for 6 weeks. Patients received one pill three times a day, up to a maximum of 6 pills per day. While improvement some target symptoms was noted with active treatment compared to placebo at various time points, these differences were not sustained over time. In addition, no differences were observed based on physician's overall impression of effectiveness or in side effects.

Rapporteur's comment

Roy C. Use of amitriptyline in childhood behavioral disorders, 1973.

This report refers to International Study #178 – this would appear to be the same protocol as above. The report states that 'The method for appraisal turned out to be a crude one.' and 'With so many treatment comparisons made, these pretreatment differences might easily be expected to have arisen by chance.' The investigator recommends 'more rigid criteria for patient selection' in the study report.

The study population does not represent what is considered to be depression as per DSM-IV or ICD-10 criteria.

The results of this trial do not provide evidence of efficacy of amitriptyline.

Dr.Roy's Study. Table XII: Mean placebo scores, 1971.

This document does not add any relevant information that might merit reflection in the product information.

3) Krakowski conducted a double-blind, placebo-controlled study to evaluate the effect of amitriptyline in emotionally disturbed children with primarily hyperkinetic type symptoms and behavioral problems [Ref. 5.4: 51, 52]. Fifty children age 3-18 with the following diagnoses were included: adjustment reaction of childhood and adolescence, including neurotic traits, conduct disorder, or habit disorder (AMI, n=18 vs PBO, n=21); neurosis, depressive reaction (1 each for AMI and PBO); psychophysiologic disorder, gastrointestinal and respiratory reactions (AMI, n=5 vs PBO, n=3); mental deficiency, with behavior and/or habit disorder (1 each for AMI and PBO); and schizophrenia (1 each for AMI and PBO). Amitriptyline was administered at a starting dose of 10 mg two or three times a day, up to a maximum dose of 12 tablets/day. Treatment duration ranged from 1-2 months and up to 9 months; mean treatment duration was 4-12 weeks at a dose of 30 mg. Amitriptyline was effective, with 21/24 (87.5%) of patients experiencing good (marked alleviation of symptoms) to excellent (complete disappearance of symptoms) compared to 2/26 (7.7%) of patients treated with placebo. Patients who failed to respond to placebo then received amitriptyline, with an overall response rate of 34/47 (72%). Onset of effect was generally within the first 4 weeks of treatment. One patient treated with amitriptyline was discontinued due to drowsiness, otherwise treatment was generally well tolerated.

Rapporteur's comment

Psychosomatics: Table VII comparison of effects of opipramol and amitriptyline, 1995.

This is the copy of one page from a publication in Psychosomatics. As it is taken out of context it cannot be assessed.

Krakowski AJ. Amitriptyline in treatment of hyperkinetic children a double-blind study.

The submitted document is a 'rough draft of the paper with 6 tables' dated 15 May 1965. The patient population included in the trial is heterogenous and does not conform with current diagnostic categories. The report states that the parents were not informed about the nature of the inert placebo used in the study.

4) Krakowski also conducted an open-label trial of amitriptyline in 112 emotionally ill children [Ref. 5.4: 77]. Patients were age 2-18 years, with a variety of diagnoses, primarily behavior disorders, neurosis, and psychophysiologic disorders, ranging from 1 month to 8 years in duration. Amitriptyline was administered based on aged and weight, beginning at 10-40 mg/day and increasing to a maximum dose of 125 mg/day. Patients were treated for 3 months to over 9 months, with a maintenance dose of 40-75 mg/day for most patients. The majority of patients experienced an overall satisfactory response (68%), most with onset within the first 4 weeks of treatment, with responses of 57-76% in the key target behavioral symptoms. Treatment was generally well tolerated, with one patients discontinuing due to drowsiness.

Rapporteur's comment

Krakowski AJ. Outpatient treatment of the emotionally III child: A comparison of two psychotropic agents, 1965.

The study population does not represent what is considered to be depression as per DSM-IV or ICD-10 criteria. It is an open-label study and does not add any relevant information that might merit reflection in the product information.

4.5 Published clinical studies of amitriptyline in children with nocturnal enuresis

Tricyclic antidepressants (TCAs), particularly imipramine, have been suggested as worthwhile treatments for nocturnal enuresis in children since the early 1960's. The specific mechanism of action of TCAs in treating nocturnal enuresis is unclear, but is thought to be related to reduced detrussor activity, increased bladder capacity due to anticholinergic and muscle relaxant effects, and sympathomimetic or central noradrenergic effects.

The majority of controlled trials of TCAs for nocturnal enuresis were conducted prior to 1975, with relatively small samples (only 8 trials included over 100 subjects), and inclusion of few children less than 6 years of age [Ref. 5.4: 65, 66, 67, 68, 70].

Rapporteur's comment

The company quotes the below publications. The current SmPC does not include the reported adverse effects such as behaviour disturbances, mood changes, anxiety.

Ferrara P, Gatto A, Vitelli O, Romano V, Del Bufalo F, Romaniello L, et al. Nocturnal enuresis in children: a review of the literature. Curr Ped Rev 2008;4:120-31

The authors state that pharmacologic therapy is usually reserved for use in children older than 7 years. With respect to tricyclics, the authors state the following: Tricyclic antidepressants such as imipramine and, less often, amitriptyline and nortriptyline are also used but behaviour disturbances may occur and relapse is common after withdrawal. Treatment should not normally be given for more than 3 months without assessing the child for adverse effects. The most common side effects are slight nausea, sweating or palpitations, but some children may also experience mood changes or anxiety, effects that often lead to discontinuation of the treatment. All side effects can safely be expected to disappear after discontinuation of the drug. ….there are definite risks of severe cardiac side effects, including death, if the drug is overdosed. It is also dangerous to give imipramine to any child with long QT syndrome, but it is very unlikely that this arrhythmia is missed if a proper case history is taken and ECG is performed on wide indications [47]. Therefore imipramine should only be considered when all relevant first- and second-line therapies (the alarm, desmopressin and anticholinergics) have been unsuccessfully tested or not tolerated. When there is no reason to suspect cardiac arrhythmias, i.e. the child has no history of syncope or sudden palpitations and there are no cases of sudden cardiac death or unstable arrhythmias in the family. If there is any doubt regarding this, an ECG should be performed to exclude long QT syndrome. When the family is compliant, well informed and knows that the pills should be kept securely locked.

The assessor notes that a recent pharmacovigilance study using health records from 38,397 patients treated with antidepressants identified statistically significant evidence of modest QT prolongation for amitriptyline (Castro VM et al, QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ. 2013; 346: f288. Published online 2013 January 29. doi: 10.1136/bmj.f288.)

Glazener CMA, Evans JHC, Peto RE. Tricyclic and related drugs for nocturnal enuresis in children (review), 2009

This is a Cochrane Review. The authors of reviewed 58 randomised trials, with many of poor quality. There was not enough information to assess the relative performance of one tricyclic against another except that imipramine was better than mianserin. They conclude that treatment with tricyclic or related drugs (imipramine, amitriptyline, viloxazine, clomipramine and desipramine but notmianserin) was associated with a reduction of about one wet night per week while on treatment. Although about a fifth of the children became dry while on treatment, most of them relapsed after treatment stopped. Long term effects are still uncertain. The limited evidence suggested that desmopressin and tricyclics might be equally effective while on treatment, but that these effects are not sustained after treatment stopped. In contrast, about half the children treated with an alarm are likely to remain dry after treatment stops but families need to provide extra support during treatment with alarms. Desmopressin is more expensive than tricyclics, but tricyclics have considerably more minor side-effects and a higher risk of overdose causing fatality. Children and their families need to be warned of the potentially lethal adverse effects of these drugs in overdose and advised on how to avoid this.

Hjalmas K, Arnold T, Bower W, Caione P, Chiozza LM, von Gontard A, et al. Nocturnal enuresis: an international evidence based management strategy. J Urol 2004;171:2545-61.

The authors state: When nocturnal enuresis is a significant problem for the child and the child is older than 6 years, treatment for enuresis should be offered. Initial treatment will usually be the enuresis alarm or desmopressin. As regards tricyclics, the authors specifically refer to imipramine and state that together with its lower efficacy compared with desmopressin, make imipramine very much a second-choice medication, to be used when alarm and/or desmopressin therapy has failed, or in combination with desmopressin in children who are particularly difficult to treat. Medication with imipramine should be supervised by paediatric psychiatrists who have clinical experience with this dangerous drug. In paediatric psychiatry, prior to prescription of imipramine, a two-minute ECG registration is commonly performed in order to identify a possibly abnormal Q-T interval (Level of evidence for imipramine treatment: 1) (Grade of recommendation: C [cardiotoxicity]).

Neveus T, et al. Evaluation of and treatment for monosynoptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol 2010;183:441-7.

The authors state that while general advice should be given to all bed wetting children, active treatment should usually not be started before age 6 years. As regards tricyclics, the authors specifically refer to imipramine and state that due to safety concerns and side effects imipramine is only relevant as third line therapy at tertiary care facilities. The effect is evaluated after 1 month. When there is a partial response desmopressin at the standard dose may be added, provided that the fluid intake of the child is restricted during the evening and night. If treatment is successful, the family should taper to the lowest effective dose and ensure that regular drug holidays of at least 2 weeks are interspersed every third month or so to decrease the risk of tolerance, which otherwise is quite high. The drug should be kept securely locked and out of reach of smaller siblings. If there is any history of palpitations or syncope in the child, or any sudden cardiac death or unstable arrhythmia in the family, long QT syndrome must be excluded by prolonged electrocardiogram recording before imipramine treatment is considered. Although other side effects are not dangerous, they are also problematic, including mood changes, nausea or insomnia.

Robson WLM. Evaluation and management of enuresis. N Engl J Med 2009;360(14):1429-36.

The authors summarise the evidence from the Cochrance review mentioned above and conclude with respect to tricyclics owing to the unfavorable adverse event profile (which includes association with mood changes and sleep disturbances) and the risk of death with an overdose, the International Children's Continence Society recommends that imipramine be used only when all other therapies have failed. (Note: the recommendations of the International Children's Continence Society are summarised in the assessor's comment section 2.5.1 above).

In a critical review of data from a large number of predominantly older, controlled trials (n=58) including a total of 3,721 patients, when compared to placebo, treatment with tricyclics was associated with fewer wet nights and a larger proportion of patients becoming dry during treatment (achievement of 14 dry nights on treatment) [Ref. 5.4: 66].

However, many patients relapsed when treatment was discontinued. Imipramine is the most widely studied TCA for nocturnal enuresis, with only a few controlled trials assessing other TCAs, including amitriptyline (9 trials), nortriptyline (3 trials), viloxazine (2 trials), desipramine (1 trial), and clomipramine (1 trial).

Rapporteur's comment

The reference publication is the Cochrane Review mentioned above.

Major drawbacks to TCA treatment are their cardiotoxicity and possible death with overdose. With these considerations, along with lower efficacy compared to desmopressin and alarm treatment, the International Children's Continence Society recommends TCAs a second-choice medication, following failure of alarm and/or desmopressin treatment or for use in combination with desmopressin in treatment-resistant children.

4.5.1 Overview of Safety

Postmarketing adverse experiences reported to the Company were captured in the New Worldwide Adverse Experience System (NWAES) database prior to 09Jul2012, and was used for previous submissions and PSURs, including the most recent PSUR covering the past 10 years: 22-JUN02002 to 21-JUN-2007, 11-JAN-2006 to 10-JAN-2009, and 11Jan2009 to 10Jan2012 for events involving patients <18 years of age who were exposed to or treated with amitriptyline.

PSUR period 22-JUN-2002 to 21-JUN-2007

There were 62 reports received from a healthcare provider (HCP) involving patients younger than 18 years on therapy with amitriptyline hydrochloride tablet, MSD. The most commonly reported ADRs were overdose 12 (19.4%), grand mal convulsion 9 (14.5%), convulsion 7 (11.3%), accidental exposure 7 (11.3%), accidental overdose 7 (11.3%), and completed suicide 5 (8.1%). Convulsions and grand mal convulsions occurred in the context of overdose and/or accidental exposure.

There were 18 serious reports in patients aged 5 years and younger. Most reports described accidental exposures and/or overdoses with associated labeled AEs such as seizures, and coma.

At the time of that PSUR, the CCDS stated that amitripyline is not recommended for the treatment of depression in persons below the age of 18 years. Any such use should be carefully monitored by a physician, and consideration by given to drug withdrawal/cessation if symptoms suggestive of suicidality and/or lack of therapeutic efficacy are observed. Also, the overdose section of the CCDS adequately addressed pediatric management in overdose cases. [Ref. 5.3.6: 81]

Rapporteur's comment
There is a lack of adequate detail in this report as it specifies only 'most frequently reported' events and does not give adequate information on serious adverse event reports. According to Annex 13 of the report, amongst other ADRs there were 4 cases of coma (outcome not stated), 9 cases of grand mal convulsion + 7 cases of convulsion, 1 case of myoclonic epilepsy, 2 cases of status epilepticus, 5 completed suicides, 4 suicide attempts, etc.

PSUR period 11-JAN-2006 to 10-JAN-2009

NOTE: because of the overlap with the previous PSURs, reports between 11-JAN-2006 and 21-JUN-2007 were included in the summary, above. Reports after 21-JUN-2007 are included in this summary.
There were 82 reports containing 209 events involving use of amitriptyline hydrochloride in patients less than 18 years of age. Among the total reports, 69 (84%) were serious and contained 179 events. Of the 209 events, the 5 most frequently reported events were overdose 43 (53%), therapeutic agent toxicity 21 (26%), convulsion 11 (13%), coma 10 (12%) and grand mal convulsion 10 (12%). Convulsions, coma, and grand mal convulsions generally occurred in the context of overdose and/or accidental exposure. Of the 179 serious events, overdose 43 (53%) and therapeutic agent toxicity 21 (26%) were reported most frequently.

There were 28 serious reports in patients ≤5 years. These reports generally described overdose and accidental exposure with expected associated labeled AEs, such as convulsion, and coma.

At the time of that PSUR, overdose, convulsion and coma were listed in the CCDS for amitriptyline hydrochloride. [Ref. 5.3.6: 80]

Rapporteur's comment
There is a lack of adequate detail in this report as it specifies only 'most frequently reported' events and does not give individual information on serious adverse event reports.

PSUR period 11-JAN-2009 to 10-JAN-2012

There were 31 HCP-confirmed reports (29 spontaneous, 2 study cases) of use in pediatric patients. The 29 spontaneous cases contained 70 ADRs involving use of amitriptyline hydrochloride. Among the total cases, 15 (51.7%) were serious and contained 38 ADRs. Of the 70 ADRs, the most frequently reported ADRs were

overdose 6 (8.6%), off label use 4 (5.7%), coma 3 (4.3%), somnolence 3 (4.3%), toxicity to various agents 3 (4.3%), and dry mouth 3 (4.3%). Of the 38 serious ADRs, the most frequently reported ADRs were overdose 6 (15.8%), coma 3 (7.9%), and toxicity to various agents 3 (7.9%). Coma occurred in the context of overdose.

There were 3 serious reports in patients ≤ 5 y ears of age. Two reports did not report clinical AEs. One reported overdose with associated seizure and other expected AEs.

At the time of that PSUR, the CCDS of amitriptyline hydrochloride, either clearly described these ADRs specifically (i.e., overdose, coma) or describes generally synonymous ADR, as in the case of somnolence. [Ref. 5.3.6: 44]

Rapporteur's comment
There is a lack of adequate detail in this report as it specifies only 'most frequently reported' events and does not give adequate information on serious adverse event reports.

Bridging period 11-JAN02012 to 03-OCT-2012

As of 09-JUL-2012, the Company consolidated legacy databases into the Merck Adverse Reporting and Review System (MARRS), which was used to identify reports subsequent to the last PSUR period through the date of the current request (11-JAN-2012 to 03-OCT-2012). It is notable that, unlike NWAES, which differentiated between primary and suspect therapy, MARRS does not distinguish between primary and secondary suspect therapy. During this current request period the Company has received 1 report [Ref. 5.4: 45] of an adverse experience in patients under the age of 18. This case described a 6-year-old girl who experienced a grand mal seizure after an overdose due to pharmacy error. Review of this report did not show any particular pattern of adverse events overall or within a specific age group.

All published clinical literature about amitriptyline in the context of the approved pediatric indication of enuresis for the current request period (11Jan2012 to 03Oct2012) was reviewed for consistency with the safety findings reported in this request. The Company did not identify any published articles that described new or potentially important safety information on amitriptyline use in children with enuresis.

Overall, for the 10-year period covered by the 3 most recent PSURs, plus the period between the last PSUR and the current request period, the data do not raise any new safety concerns for the pediatric population. Generally, the more serious ADRs such as coma and convulsions occurred in the context of overdose or accidental exposure. There do not appear to be meaningful differences between pediatric patients ≤5 years of age and >6 years of age.

Rapporteur's comment
The company's search of published literature regarding safety in children is limited to a 10 month period. As the drug has been on the market for decennia, the restriction of the literature search to such a limited period of time is not considered justified.
The company states that there 'do not appear to be' meaningful differences between pediatric patients ≤5 years of age and >6 years of age. No data have been presented that would confirm or refute any differences in nature, frequency or severity of ADRs across different age groups. The company should provide relevant data.
The statement that 'generally' the more serious ADRs occurred in the context of overdose or accidental exposure is not reassuring.
The company should provide a cumulative safety review across all paediatric age groups. This review should include safety data from clinical trials, spontaneous reporting and published literature. Special attention should

be given to ADRs from the SOCs nervous system disorders, psychiatric disorders, injury/poisoning, cardiac disorders and to suicidality-related ADRs. Line listings should also be provided.

4.6 Review of postmarketing safety database

At request the MAH performed a cumulative review of the Merck Adverse Reporting and Review System (MARRS), the company's postmarketing safety database, for all serious and nonserious healthcare provider (HCP)-confirmed AEs reported from product approval 11-JAN-1961 through 1-MAY-2013 in the paediatric population. In addition to individual postmarketing HCP-reported cases, reports could also originate from company-sponsored studies and postmarketing literature, such as case reports/series Hum Exp Toxicol. 2006 Mar;25(3):107-10-sponsored studies. The results are presented in the table below.

Response Table 1: Cumulative Reports of All Serious and Nonserious AEs Through 1-MAY-2013

(Percentages Represent the Proportion of Total Events for A Given Age Stratum)

SOC	Neonate 0-28 days N 30 Events	Infant 28 days-1 year N 57 Events	Child > 1 year-< 12 years N 374 Events	Adolescent 12 years-< 18 years N 312 Events
Blood and lymphatic system disorders				
Antiphosopholipid syndrome	0	0	0	1 (0.32%)
Aplastic anaemia	0	0	0	2 (0.64%)
Bone marrow failure	0	0	0	1 (0.32%)
Pancytopenia	0	0	0	2 (0.64%)
Hypopcomplementaemia	0	0	1 (0.26%)	0
Lymphocytic infiltration	0	0	1 (0.26%)	0
Sub Total	**0**	**0**	**2 (0.53%)**	**6 (1.92%)**
Cardiac disorders				
Arrhythmia	0	0	6 (1.60%)	1 (0.32%)
Atrioventricular block			1 (0.26%)	1 (0.32%)
Bradycardia	0	0	1 (0.26%)	1 (0.32%)
Cardiac arrest	0	1 (1.75%)	4 (1.06%)	5 (1.60%)
Cardiac disorder	0	0	1 (0.26%)	0
Cardio-respiratory arrest	0	0	2 (0.53%)	1 (0.32%)
Cardiomegaly	0	0	1 (0.26%)	0
Conduction disorder	0	0	0	1 (0.32%)
Congestive cardiomyopathy	0	0	1 (0.26%)	0
Cyanosis	1 (3.3%)	0	3 (0.80%)	0
Myocarditis	0	0	1(0.26%)	0
Nodal rhythm	0	0	1 (0.26%)	0
Palpitations	0	0	1 (0.26%)	0
Sinus tachycardia	0	1 (1.75%)	0	0
Supraventricular tachycardia	0	0	1 (0.26%)	1(0.32%)
Tachycardia	0	3 (5.26%)	8 (2.13%)	3 (0.96%)
Torsades de pointes	0	0	0	1 (0.32%)
Ventricular extrasystoles	0	0	1 (0.26%)	0
Ventricular fibrillation	0	0	3 (0.80%)	0
Ventricular tachycardia	0	0	4 (1.06%)	2 (0.64%)
Sub Total	**1 (3.3%)**	**5 (8.77%)**	**40 (10.6%)**	**17 (5.44%)**
Congenital, familial and genetic disorders				
Atrial septal defect	1 (3.3%)	0	0	0
Cerebral palsy	1 (3.3%)	1 (1.75%)	0	0
Congenital anomaly	3 (10%)	0	0	0
Pulmonary hypoplasia	1 (3.3%)	0	0	0

SOC	Neonate 0-28 days N 30 Events	Infant 28 days-1 year N 57 Events	Child > 1 year-< 12 years N 374 Events	Adolescent 12 years-< 18 years N 312 Events
Renal aplasia	1 (3.3%)	0	0	0
Skull malformation	1 (3.3%)	0	0	0
Talipes	1 (3.3%)	0	0	0
Sub Total	**9 (30%)**	**1 (1.75%)**	**0**	**0**
Ear and labyrinth disorders				
Ear disorder	0	0	0	1 (0.26%)
Vertigo	0	0	0	3 (0.96%)
Sub Total	**0**	**0**	**0**	**4 (1.28%)**
Eye disorders				
Accomodation disorder	0	0	0	2 (0.64%)
Blindness	0	1 (1.75%)	0	0
Eye haemorrhage	0	1 (1.75%)	0	0
Eye pain	0	0	0	1 (0.32%)
Eyelid ptosis	0	0	0	1 (0.32%)
Mydriasis	0	0		1 (0.32%)
Oculogyric crisis	0	0	1 (0.26%)	0
Photophobia	0	0	1 (0.26%)	1 (0.32%)
Pupils unequal	0	1 (1.75%)	0	0
Saccadic eye movement	0	0	1 (0.26%)	0
Uveitis	0	0		1 (0.32%)
Vision blurred	0	0	2 (0.53%)	1 (0.32%)
Visual impairment	0	0	0	1 (0.32%)
Sub Total	**0**	**3 (5.26%)**	**5 (1.33%)**	**9 (2.88%)**
Gastrointestinal disorders				
Abdominal distension	0	2 (3.50%)	1 (0.26%)	0
Abdominal pain	0	0	2 (0.53%)	2 (0.64%)
Colitis	0	0	1 (0.26%)	0
Constipation	0	0	0	1 (0.32%)
Diarrhoea	0	0	2 (0.53%)	0
Dry mouth	0	0	2 (0.53%)	3 (0.96%)
Gastrointestinal motility disorder	0	0	1 (0.26%)	0
Gastrointestinal sounds abnormal	0	2 (3.50%)	0	0
Lip swelling	0	0	0	2 (0.64%)
Nausea	0	0	0	3 (0.96%)
Pancreatitis acute	0	0	0	2 (0.64%)
Paraesthesia oral	0	0	1 (0.26%)	0
Tooth discolouration	0	1 (1.75%)	0	1 (0.32%)
Vomiting	0	0	3 (0.80%)	0
Sub Total	**0**	**5 (8.77%)**	**13 (3.47%)**	**14 (4.48%)**
General disorders and administration site conditions				
Adverse event	0	0	0	1 (0.32%)
Asthenia	0	0	0	1 (0.32%)
Brain death	0	0	0	1 (0.32%)
Chest discomfort	0	0	1 (0.26%)	0
Chest pain	0	0	1 (0.26%)	2 (0.64%)
Crying	0	0	1 (0.26%)	0
Death	0	3 (5.26%)	5 (1.3%)	1 (0.32%)
Drug effect incomplete	0	0	0	1 (0.32%)
Drug ineffective	0	0	3 (0.80%)	2 (0.64%)
Drug interaction	0	0	3 (0.80%)	3 (0.96%)
Feeling abnormal	0	0	0	2 (0.64%)
Drug withdrawal syndrome	1 (3.3%)	0	1 (0.26%)	0
Facial pain	0	0	1 (0.26%)	0
Fatigue	0	0	3 (0.80%)	0
Feeling hot	0	0	1 (0.26%)	0
General symptom	0	0	3 (0.80%)	3 (0.96%)

SOC	Neonate 0-28 days N 30 Events	Infant 28 days-1 year N 57 Events	Child > 1 year-< 12 years N 374 Events	Adolescent 12 years-< 18 years N 312 Events
Irritability	0	0	1 (0.26%)	0
Malaise	0	0	0	1 (0.32%)
Mucosal dryness	0	0	0	2 (0.96%)
No adverse event	0	0	4 (1.06%)	0
Pyrexia	0	0	3 (0.80%)	2 (0.96%)
Sluggishness	0	0	0	1 (0.32%)
Therapeutic response unexpected	0	0	1 (0.26%)	0
Sub Total	**1 (3.3%)**	**3 (5.26%)**	**32 (8.55%)**	**23 (7.37%)**
Hepatobiliary disorders				
Cholelithiasis	0	0	1 (0.26%)	0
Hepatic function abnormal	0	0	0	1 (0.32%)
Hepatobiliary disorders	0	0	0	0
Hepatitis	0	0	0	1 (0.32%)
Hepatocellular injury	0	0	0	1 (0.32%)
Hyperbilirubinaemia	0	0	0	1 (0.32%)
Jaundice	1 (3.3%)	0	0	0
Sub Total	**1 (3.3%)**	**0**	**1 (0.26%)**	**4 (1.28%)**
Immune system disorders				
Hypersensitivity	0	0	0	1 (0.32%)
Sub Total	**0**	**0**	**0**	**1** (0.32%)
Infection and Infestations				
Appendicitis	0	0	0	1 (0.32%)
Nasopharyngitis	0	1 (1.75%)	0	1 (0.32%)
Pneumonia	0	1 (1.75%)	1 (0.26%)	1 (0.32%)
Pneumonia necrotising	0	0	1 (0.26%)	0
Sub Total	**0**	**2 (3.50%)**	**2 (0.53%)**	**3 (0.96%)**
Injury, poisoning and procedural complications				
Accidental exposure to product	0	2 (3.50%)	14 (3.74%)	0
Accidental exposure to product by child	0	0	2 (0.53%)	0
Accidental overdose	0	0	9 (2.40%)	1 (0.32%)
Drug administration error	0	2 (3.50%)	4 (1.06%)	0
Drug dispensing error	0	0	1 (0.26%)	0
Exposure during breast feeding	1 (3.3%)	3 (5.26%)	0	1 (0.32%)
Exposure during pregnancy	3 (10%)	0	0	1 (0.32%)
Foetal exposure during pregnancy	1 (3.3%)	0	0	0
Incorrect dose administered	0	0	1 (0.26%)	1 (0.32%)
Injury	0	0	0	1 (0.32%)
Intentional overdose	0	0	1 (0.26%)	1 (0.32%)
Maternal exposure timing unspecified	0	1 (1.75%)	0	1 (0.32%)
Overdose	0	9 (15.78%)	57 (15.24%)	56 (17.94%)
Poisoning deliberate	0	1 (1.75%)	0	0
Poisoning	0	0	1 (0.26%)	2 (0.64%)
Prescribed overdose	0	0	2 (0.53%)	0
Toxicity to various agents	0	0	26 (6.95%)	11 (3.52%)
Wrong technique in drug usage	0	0	1 (0.26%)	0
Sub Total	**5 (16.6%)**	**18 (31.5%)**	**119 (31.8%)**	**75 (24.03%)**
Investigations				
Aspartate aminotransferase increased	0	0	1 (0.26%)	0
Blood pressure increased	0	0	0	2 (0.64%)
Blood pressure decreased	0	1 (1.75%)	0	0
Blood prolactin increased	0	0	0	1 (0.32%)
Carbon dioxide increased	0	0	1 (0.26%)	0
Cardiac function test abnormal	0	0	1 (0.26%)	0
Drug level changed	0	1 (1.75%)	0	1 (0.32%)

SOC	Neonate 0-28 days N 30 Events	Infant 28 days-1 year N 57 Events	Child > 1 year-< 12 years N 374 Events	Adolescent 12 years-< 18 years N 312 Events
Drug screen positive	0	0	0	1 (0.32%)
Echocardiogram abnormal	0	0	1 (0.26%)	0
Electrocardiogram abnormal	0	0	1 (0.26%)	1 (0.32%)
Electrocardiogram change	0	0	1 (0.26%)	0
Electrocardiogram PR prolongation	0	0	1 (0.26%)	0
Electrocardiogram QT prolonged	0	0	2 (0.53%)	2 (0.64%)
Electrocardiogram ST-T change	0	0	0	4 (1.28%)
Platelet count decreased	0	0	1 (0.26%)	0
Weight decreased	0	0	0	1 (0.32%)
Weight increased				2 (0.64%)
Sub Total	**0**	**2 (3.50%)**	**10 (2.67%)**	**15 (4.80%)**
Metabolism and nutrition disorders				
Acidosis	0	0	0	1 (0.32%)
Decreased appetite	0	0	1 (0.26%)	1 (0.32%)
Dehydration	0	1 (1.75%)	0	1 (0.32%)
Feeding disorder neonatal	0	0	1 (0.26%)	0
Fluid retention	0	0	2 (0.53%)	0
Hyperglycaemia	0	0	0	1 (0.32%)
Hypoglycaemia	0	0	0	1 (0.32%)
Hypokalemia	0	0	0	1 (0.32%)
Metabolic acidosis	0	0	0	1 (0.32%)
Sub Total	0	1 (1.75%)	**4 (**1.06%)	**7 (2.24%)**
Musculoskeletal and connective tissue disorders				
Arthralgia	0	0	1 (0.26%)	0
Back Pain	0	0	1 (0.26%)	0
Hand deformity	1 (3.3%)	0	0	0
Joint effusion	0	0	1 (0.26%)	0
Muscle contracture	0	0	1 (0.26%)	0
Muscle spasms	0	0	0	1 (0.32%)
Muscular weakness	0	0	0	1 (0.32%)
Systemic lupus erythematosus			1 (0.26%)	0
Sub Total	1 (3.3%)	0	5 (1.33%)	2 (0.64%)
Neoplasms, benign, malignant and unspecified incl cysts and polyps)				
Brain neoplasm benign	1 (3.3%)	0	0	0
Sub Total	1 (3.3%)	0	0	0
Nervous system disorders				
Akathisia	0	0	0	1 (0.32%)
Altered state of consciousness	0	0	1 (0.26%)	0
Clonic convulsion	0	0	1 (0.26%)	0
Coma	0	2 (3.50%)	12 (5.08%)	17 (5.44%)
Convulsion	1 (3.3%)	2 (3.50%)	19 (5.08%)	4 (1.28%)
Convulsion neonatal	1 (3.3%)	0	0	0
Depressed level of consciousness	0	0	1 (0.26%)	2 (0.64%)
Disturbance in attention	0	0	2 (0.53%)	0
Dizziness	0	0	2 (0.53%)	4 (1.28%)
Dysarthria	0	0	0	1 (0.32%)
Dyskinesia	0	0	1 (0.26%)	1 (0.32%)
Encephalopathy	0	0	1 (0.26%)	0
Epilepsy	0	1 (1.75%)	0	0
Extrapyramidal disorder	0	0	0	1 (0.32%)
Grand mal convulsion	0	0	12 (3.20%)	2 (0.64%)
Headache	0	0	1 (0.26%)	3 (0.96%)
Hydrocephalus	1 (3.3%)	0	0	0
Hyperkinesia	0	0	1 (0.26%)	0
Hypersomnia	0	0	1 (0.26%)	0

SOC	Neonate 0-28 days N 30 Events	Infant 28 days-1 year N 57 Events	Child > 1 year-< 12 years N 374 Events	Adolescent 12 years-< 18 years N 312 Events
Hypertonia	0	1 (1.75%)	0	1 (0.32%)
Hypotonia	0	1 (1.75%)	1 (0.26%)	0
Lethargy	0	2 (3.50%)	2 (0.53%)	5 (1.60%)
Loss of consciousness	0	0	1 (0.26%)	0
Mental impairment	0	0	0	1 (0.32%)
Muscle spasticity	0	1 (1.75%)	0	0
Myoclonic epilepsy	0	0	1 (0.26%)	0
Nervous system disorder	0	0	1 (0.26%)	0
Nystagmus	1 (3.3%)	0	0	0
Paralysis	1 (3.3%)	0	0	0
Paraesthesia	0	0	0	2 (0.64%)
Psychomotor hyperactivity	0	0	2 (0.53%)	1 (0.32%)
Sedation	0	0	0	1 (0.32%)
Serontin syndrome	0	0	1 (0.26%)	0
Somnolence	1 (3.3%)	0	12	4 (1.28%)
Status epilepticus	0	1 (1.75%)	1 (0.26%)	0
Stupor	0	0	0	1 (0.32%)
Syncope	0	0	0	2 (0.64%)
Tremor	0	0	1 (0.26%)	0
Unresponsive to stimuli	0	0	0	1 (0.32%)
Visual field defect	0	0	0	1 (0.32%)
Sub Total	**6 (20%)**	**11 (19.2%)**	**78 (20.8%)**	**56 (17.9%)**
Pregnancy, puerperium and perinatal conditions				
Complication of pregnancy	0	0	0	1 (0.32%)
Neonatal disorder	2 (6.6%)	2 (3.50%)	0	
Normal newborn	0	0	0	1 (0.32%)
Premature baby	1 (3.3%)	0	0	2 (0.64%)
Sub Total	**3**	**2 (3.50%)**	**0**	**2 (0.64%)**
Psychiatric disorders				
Abnormal behaviour	0	0	1 (0.26%)	
Abnormal dreams	0	0	0	1 (0.32%)
Affect lability	0	0	0	1 (0.32%)
Agitation	0	0	0	1 (0.32%)
Bipolar I disorder	0	0	0	1 (0.32%)
Completed suicide	0	0	0	8 (2.56%)
Confusional state	0	0	0	5 (1.60%)
Depression	0	0	0	1 (0.32%)
Disorientation	0	0	0	1 (0.32%)
Drug abuse	0	0	1 (0.26%)	0
Drug dependence	0	0	1 (0.26%)	0
Eating disorder	1 (3.3%)	0	0	0
Insomnia		0	0	1 (0.32%)
Intentional drug misuse	0	0	0	1 (0.32%)
Mania	0	0	1 (0.26%)	0
Mental disorder	0	0	0	3 (0.96%)
Psychotic disorder due to a general medical condition	0	0	0	1 (0.32%)
Sleep disorder	0	0	0	1 (0.32%)
Suicide attempt	0	0	1 (0.26%)	13 (4.16%)
Tic	0	0	3	0
Withdrawal syndrome	0	0	2 (0.53%)	1 (0.32%)
Sub Total	**1 (3.3%)**	**0**	**10 (2.67%)**	**40 (12.8%)**
Renal and urinary disorders				
Dysuria	0	0	0	1 (0.32%)
Enuresis	0	0	1 (0.26%)	0
Pollakiuria	0	0	1 (0.26%)	0
Renal failure	0	1	0	1 (0.32%)

SOC	Neonate 0-28 days N 30 Events	Infant 28 days-1 year N 57 Events	Child > 1 year-< 12 years N 374 Events	Adolescent 12 years-< 18 years N 312 Events
Renal impairment	0	0	0	1 (0.32%)
Tubulointerstitial nephritis	0	0	0	1 (0.32%)
Urinary retention	0	0	1 (0.26%)	3 (0.96%)
Sub Total	0	1 (1.75%)	3 (0.80%)	7 (2.24%)
Reproductive system and breast disorders				
Amenorrhoea	0	0	0	1 (0.32%)
Breast cyst	0	0	0	1 (0.32%)
Menstrual disorder	0	0	1 (0.26%)	2 (0.64%)
Menstruation delayed	0	0	0	1 (0.32%)
Penile pain	0	0	1 (0.26%)	0
Vaginal discharge	0	0	0	1 (0.32%)
Sub Total	**0**	**0**	**2 (0.53%)**	**6 (1.92%)**
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome	0	0	0	1 (0.32%)
Apnoea	0	0	2 (0.53%)	0
Aspiration	0	0	1 (0.26%)	0
Choking sensation	0	0	1 (0.26%)	0
Dyspnoea	0	1 (1.75%)	3 (0.80%)	1 (0.32%)
Epistaxis	0	0	1 (0.26%)	0
Hyperventilation	0	0	1 (0.26%)	0
Hypopnoea	0	1 (1.75%)	1 (0.26%)	0
Hypoxia	0	0	1 (0.26%)	0
Neonatal respiratory distress syndrome	1 (3.3%)	0	0	0
Pneumothorax	0	0	1 (0.26%)	0
Pulmonary oedema	0	0	1 (0.26%)	0
Respiratory acidosis	0	0	1 (0.26%)	0
Respiratory arrest	0	0	2 (0.53%)	0
Respiratory depression	0	0	3 (0.80%)	1 (0.32%)
Respiratory distress	0	1 (1.75%)	1 (0.26%)	0
Respiratory failure	0	0	0	1 (0.32%)
Sleep apnoea syndrome	0	0	1 (0.26%)	0
Sub Total	**1 (3.3%)**	**3 (5.26%)**	**21 (5.61%)**	**4 (1.28%)**
Skin and subcutaneous tissue disorders				
Alopecia	0	0	0	1 (0.32%)
Drug eruption	0	0	1 (0.26%)	0
Eczema	0	0	1 (0.26%)	0
Erythema	0	0	2 (0.53%)	1 (0.32%)
Hyperhidrosis	0	0	1 (0.26%)	2
Nail discolouration	0	0	1 (0.26%)	0
Pigmentation disorder	0	0	0	1 (0.32%)
Pruritus	0	0	1 (0.26%)	1 (0.32%)
Rash	0	0	1 (0.26%)	0
Rash maculo-papular	0	0	1 (0.26%)	0
Sweling face	0	0	1 (0.26%)	1 (0.32%)
Sub Total	**0**	**0**	**10 (2.67%)**	**7 (2.24%)**
Social circumstances				
Victim of abuse	0	0	1 (0.26%)	0
Victim of child abuse	0	0	1 (0.26%)	0
Sub Total	0	0	**2** (0.53%)	0
Surgical and medical procedures				
Abortion induced	0	0	0	1 (0.32%)
Off label use	0	0	6 (1.60%)	1 (0.32%)
Sub Total	0	0	6 (1.60%)	2 (0.64%)
Vascular disorders				
Hypertension	0	0	1 (0.26%)	0

SOC	Neonate 0-28 days N 30 Events	Infant 28 days-1 year N 57 Events	Child > 1 year-< 12 years N 374 Events	Adolescent 12 years-< 18 years N 312 Events
Hypotension	0	0	5 (1.33%)	5 (1.60%)
Orthostatic hypotension	0	0	0	1 (0.32%)
Pallor	0	0	0	1 (0.32%)
Peripheral coldness	0	0	0	1 (0.32%)
Raynaud's phenomenon	0	0	3 (0.80%)	0
Sub Total	0	0	9 (0.80%)	8 (2.56%)
Total	**30**	**57**	**374**	**312**
Suicide Terms				
Suicide attempt	0	0	1	13
Suicidal behavior	0	0	0	0
Suicidal ideation	0	0	0	0
Completed Suicide	0	0	0	8
Total events	**0**	**0**	**1**	**21**

Rapporteur's comment
In response to a follow-up question from the Rapporteur, the MAH confirmed that all cases reported in their cumulative literature review (see section 6.1.2 below) and meeting minimum adverse event (AE) case criteria were included in the above Response table. Specified minimum AE criteria were: an identifiable source; a subject/patient or group of patients, even if not precisely identified by date of birth, age, group of age, gender, etc.; a suspect Merck product and an adverse event/ relevant safety information. The criteria may have changed over the years since this product was first licensed in 1961.

The applicant concludes that the review of cumulative serious and nonserious postmarketing AEs suggests that the pattern and distribution of events in the paediatric population is consistent with that of the overall population, notwithstanding terms specific to the paediatric age group (e.g., accidental drug intake by child). The SOCs with the highest frequency of AEs are injury/poisoning, followed by nervous system disorders, cardiac disorders, and psychiatric disorders.

The MAH notes that, as reported in several articles in the literature review, there are certain patterns by age that are reflected in their database. For example overdose in younger children is more likely to be due to accidental intake either by the child or as accidental or suspected malicious administration by a parent/guardian. On the other hand, in older children/adolescents, overdose is more likely to be in the context of suicide attempt.

The applicant notes that one confounding factor precluding full assessment of paediatric safety from postmarketing data is that cases typically report multiple AEs (e.g., overdose, coma, and convulsions). Therefore it is difficult to fully assess any difference in frequency of combinations of AEs. Given the overall exposure and experience with amitriptyline, it is unlikely that any clinically meaningful difference exists.

The MAH concluded that the review of more than 50 years of reports in their safety database confirmed both the known safety profile of amitriptyline and the adequacy of the product labelling.

Rapporteur's comment
<u>Paediatric cases of unknown age/additional cases:</u>

Following receipt of the company's response, the company was asked to explain why their safety review (as outlined in the table above) did not contain any paediatric cases of unknown age.

In response, the company updated their search using the search terms "neonate", "neonates", "neonatal", "infant", "baby", "fetal", "fetus", "child", "children", "adolescent", "pediatric" and "congenital". This new search identified one additional fatal case with two adverse events and 66 additional non-fatal cases with 122 adverse events. The additional cases are summarised in the Response table 2 below. They had not been included in the original response.

Given that the data are based on passive surveillance, an estimation of the true incidence of paediatric adverse effects, including fatalities, is not possible. The denominator is unknown. Underreporting is likely, particularly since amitriptyline has been licensed for decennia.

Response table 2: Additional adverse events identified by the company following the Rapporteur's query

SOC	Neonate 0-28 days	Infant 28 days-1 year	Child > 1 year- < 12 years	Adolescent 12 years - <18 years	Pediatric, unknown age
Blood and lymphatic system disorders					
Anaemia	0	0	0	0	1
Leukocytosis	0	0	0	0	1
Sub Total	0	0	0	0	2
Cardiac disorders					
Tachycardia	0	0	0	0	1
Sub Total	0	0	0	0	1
Congenital, familial and genetic disorders					
Anal atresia	0	0	1	0	0
Cleft palate	1	0	0	0	0
Coarctation of the aorta	1	0	0	0	0
Congenital anomaly	2	0	0	0	0
Cryptorchism	1	0	0	0	0
Genitalia external ambiguous	1	0	0	0	0

Heart disease congenital*	1	0	0	0	0
Hernia congenital	1	0	0	0	0
Microcephaly		0	0	0	2
Pulmonary malformation	1	0	0	0	0
Sub Total	9	0	1	0	2
Eye disorders					
Eyelid ptosis	1	0	0	0	0
Mydriasis	0	0	0	0	1
Pupillary reflex impaired	0	0	0	0	1
Sub Total	1	0	0	0	2
General					
Death neonatal*	1	0	0	0	0
Developmental delay	0	0	0	0	2
Drug withdrawal syndrome neonatal	0	0	0	0	1
Sub Total	1	0	0	0	3
Injury, poisoning and procedural complications					
Accidental exposure to product	0	0	0	0	42
Exposure during breastfeeding	0	1	0	0	1
Exposure during pregnancy	6	0	0	0	2
Maternal exposure timing unspecified	2	0	0	0	0
Poisoning	0	0	0	0	3
Toxicity to various agents	0	0	0	1	0
Sub Total	8	1	0	1	48
Investigations					
Activated partial thromboplastin time prolonged	0	0	0	0	1
Electrocardiogram abnormal	0	0	0	0	1
Electrocardiogram PR prolongation	0	0	0	0	1
Electrocardiogram QRS complex prolonged	0	0	0	0	1
Electrocardiogram QT prolonged	0	0	0	0	3
Electrocardiogram ST-T change	0	0	0	0	1
Prothrombin time prolonged	0	0	0	0	1
QRS axis abnormal	0	0	0	0	1
Transaminases increased	0	0	0	0	1
Sub Total	0	0	0	0	11
Metabolism					
Acidosis	0	0	0	0	1
Feeding disorder neonatal	1	0	0	0	0
Hyperglycaemia	0	0	0	0	1
Hypoglycaemia	0	0	0	0	1

Hyponatraemia	0	0	0	0	1
Sub Total	1	0	0	0	4
Musculoskeletal					
Muscle disorder	1	0	0	0	0
Spinal deformity	0	0	1	0	0
Sub Total	1	0	1	0	0
Nervous					
Areflexia	0	0	0	0	1
Extensor plantar response	0	0	0	0	1
Brain injury	1	0	0	0	0
Convulsion	0	0	0	0	1
Coma	0	0	0	0	2
Lethargy	0	0	0	0	1
Nystagmus	0	0	0	0	2
Somnolence	0	1	0	0	
Status epilepticus	0	0	0	0	2
Sub Total	1	1	0	0	10
Psych					
Agitation neonatal	1	0	0	0	0
Sub Total	1	0	0	0	0
Pregnancy, puerperium and perinatal conditions					
Large for dates baby	1	0	0	0	0
Neonatal disorder	1	1	0	0	1
Normal newborn	1	0	0	0	0
Premature baby	1	0	0	0	0
Sub Total	4	1	0	0	1
Renal					
Hydronephrosis	0	1	0	0	0
Sub Total	0	1	0	0	0
Respiratory					
Neonatal respiratory distress syndrome	1	0	0	0	0
Respiratory depression	0	0	0	0	2
Sub Total	1	0	0	0	2
Vascular					
Hypertension	0	0	0	0	1
Hypotension	0	0	0	0	1
Orthostatic hypotension	0	0	0	0	1
Sub Total	0	0	0	0	3
Total Events	28	4	2	1	89

*Fatal outcome

The company stated that 42 of these additional cases (all cases of accidental exposure), were derived from one single publication, cited as 'Cihangir Akgun et al Hum Exp Toxicol. 2006 Mar;25(3):107-10'). They did not provide the relevant publication. They did not discuss the outcomes of these cases. A search performed by the assessor identified the following abstract:

Caksen H et al, 1. Hum Exp Toxicol. 2006 Mar;25(3):107-10: *Acute amitriptyline intoxication: an analysis of 44 children. The tricyclic antidepressant agents, particularly amitriptyline and dothiepin, are recognized for their potentially lethal cardiovascular and neurological effects in poisoned patients. In this article, the clinical and laboratory findings of 44 children with amitriptyline intoxication are reviewed. Our purpose was to investigate amitriptyline intoxication in childhood. Of 44 patients, 21 (47.7%) were boys, 23 (52.3%) were girls, and the ages ranged from 12 months to 14 years (mean +/- SD; 4.09 +/- 2.9 years). All children except one who took an overdose of amitriptyline to decrease his pain accidentally ingested an overdose of amitriptyline. The amount of amitriptyline ingested was between 2 mg/kg and 97.5 mg/kg (mean +/- SD; 13.6 +/- 17.7 mg/kg per dose) (the drug dosage was not known in 13 children). The most commonly observed clinical and laboratory findings were lethargy, tachycardia, convulsion, hyperglycemia and leukocytosis. In all patients except for two children who died the abnormal clinical and laboratory findings returned to normal within a few days after admission and they were discharged from the hospital in good health within the fourth day of admission. One of the children ingested 97.5 mg/kg amitriptyline and probably died due to status epilepticus and another child who died ingested 36 mg/ kg amitriptyline and died due to cardiopulmonary arrest. In conclusion, our findings showed that initial symptoms and signs of acute amitriptyline intoxication appeared severe, but they disappeared with only*

supportive care required in most children except for cases that ingested high doses of drug within a few days. In contrast to adults, we infrequently noted respiratory insufficiency, arrhythmia and hypotension in children with acute amitriptyline intoxication.

The company stated that two cases reported in this publication had already been included in their original response document, but they did not specify which cases these were.

In addition, the company stated in their follow-up response: *'There were also 3 cases with 35 adverse events from a single literature article "Clinical, electrocardiographic, and laboratory findings in children with amitriptyline intoxication" by Hasim Olgun et al (Pediatr Emerg Care. 2009 Mar;25(3):170-3). The first case was a summary report listing 30 AEs. The two other reports contained a total of 5 AEs all of which were captured in the first summary case. This single article contributed all adverse events in the Investigations SOC to the above table.'*

A review of the cited publication indicates that far more than three cases were reported by Olgun et al. For example, the publication lists 40 cases of lethargy but the tabular summaries provided by the MAH contain only 10 cases. Hyponatremia is reported in 14 cases (versus n= 1 reported by MAH), etc.

TABLE 2. Clinical and Laboratory Findings of the Patients

Parameters	Group A (n = 41)		Group B (n = 11)		Total	
Symptoms and signs	n	%	N	%	n	%
Lethargy	32	78.0	8	72.7	40	76.9
Tachycardia	25	61.0	5	45.5	30	57.7
Coma	19	46.3	6	54.5	25	48.1
Babinski sign	12	29.3	3	27.3	15	28.8
Bilateral loss of deep tendon reflexes	11	26.8	2	18.2	13	25.0
Hypotension	7	17.1	4	36.4	11	21.2
Bilateral loss of light reflexes	8	19.5	1	9.1	9	17.3
Mydriasis	9	22.0	0	—	9	17.3
Flushing	6	14.6	0	—	6	11.5
Convulsion	3	7.3	1	9.1	4	7.7
Hypertension	0	—	1	9.1	1	1.9
Laboratory findings						
Hyponatremia (serum sodium level less than 130 mEq/dL)	10	24.4	4	36.4	14	26.9
Leukocytosis (blood leukocytes count more than 12,000/mL)	11	26.8	2	18.2	13	25.0
Hyperglycemia (blood glucose level more than 120 mg/dL)	9	22.0	2	18.2	11	21.2
Anemia (hemoglobin level less than 10 g/dL)	8	19.5	0	—	8	15.4
Increased transaminase level*	3	7.3	1	9.1	4	7.7
Prolonged prothrombin time (more than 15 seconds)	2	4.9	2	18.2	4	7.7
Acidosis of blood-gas analysis	4	9.8	0	—	4	7.7
Prolonged partial thromboplastin time (more than 35 seconds)	2	4.9	0	—	2	3.8
Hypoglycemia (blood glucose level less than 70 mg/dL)	2	4.9	0	—	2	3.8

*Both aspartate aminotransferase and alanine aminotransferase levels were elevated.

Frequencies of the clinical and laboratory findings were not different between the 2 groups ($P > 0.05$).

CIOMS report forms and line listings:

There are inconsistencies in the information reported in the tabular AE summaries, line listings and CIOMS reports. Response Table 1 contains 8 completed suicides and 14 suicide attempts, whilst the line listings contain 13 completed suicides and 9 suicide attempts.

CIOMS reports: 13 full CIOMS reports of completed suicide and 8 CIOMS reports of suicide attempts were submitted. An additional case of suicide attempt in an adolescent is contained in a CIOMS report. This is a case

of a 16-year-old girl treated with amitriptyline for acute depression. The patient took an overdose of fourteen, 50 mg tablets of amitriptyline hydrochloride but recovered. This case is not contained in the line listings.

In a large number of cases line listings state that the parenteral formulation of amitriptyline (verbatim: ELAVIL/Injection') was used, even when the method of administration was stated as 'ingestion'. It would appear that amitriptyline is available in a parenteral formulation outside the EU. No such information has been provided by the applicant. In some cases the parenteral formulation might have been ingested. In other cases the information appears incorrect. For example the narrative for a particular case states that the child was given three 50 mg *tablets* and was found unresponsive, yet the suspect drug is stated as 'amitriptyline hydrochloride *injection'*.

Some of the provided CIOMS reports are incomplete. For example, there is a report of '*Unintentional General'* that a 5-year-old girl died of. The assessor is unaware of a diagnosis or PT called 'unintentional general'.

4.7 Cumulative literature search

At request the applicant conducted a cumulative literature search of paediatric use of amitriptyline, primarily in Medline and Embase, as well as other local or regional journals and Reactions Weekly. The search was limited to human use and English publications only and returned 321 articles. Of these, 62 articles that met inclusion/exclusion criteria, the remainder was excluded for the following reasons: meeting abstracts, as the company did not consider these to be official, final publications; individual case reports; and small case series (fewer than ~10 patients).

Rapporteur's comment

The exclusion of meeting abstracts, individual case reports; and small case series from a safety review is not acceptable. Meeting abstracts and individual case reports might contain cases that would be eligible for inclusion in the safety database according to the company's specified minimum criteria. Case series of 'fewer than '10 patients' might contain case up to nine cases of fatal reports.

Although the company stated that all cases reported in their cumulative literature review and meeting minimum adverse event case criteria were included in their tabular safety summary, it would appear that not all reported cases were included (e.g. only 10 of 40 reported cases of lethargy included in the tabulated safety summary).

The MAH repeatedly states that '*intentional and unintentional poisonings, which are potentially fatal, are known issues with amitriptyline'*.

1. Otto AU. Jämförande undersökning av Preparyl, Tonfranil samt Tryptizol vid enuresis nocturna hos gravt utveeklingsstörda barn och ungdomar. Lakartidningen 1964:3894-901.
2. Krakowski AJ. Amitriptyline in treatment of hyperkinetic children a double-blind study, 1965.
3. Krakowski AJ. Outpatient treatment of the emotionally III child: A comparison of two psychotropic agents, 1965.
4. Kraft IA, Ardali C, Duffy J, Hart J, Pearce PR. Use of amitriptyline in childhood behavioral disturbances. Int J Neuropsychiatry 1966:611-4.
5. Krakowski AJ. Treatment of psychosomatic gastrointestinal reactions in children. Dis Nerv System 1966:403-8.

6. Poussaint AF. Study of amitriptyline in enuresis, 1964.

7. Steel CM, O'duffy J, Brown SS. Clinical effects and treatment of impramine and amitriptyline poisoning in children. Br Med Jour 1967:663-7.

8. Weinstein RA, Ruggieri G, Baldos CS. Treating anxiety and depression in high school students. J Med Soc 1968:11-5.

9. Kelly D, Guirguis W, Frommer E, Mitchell-Heggs N, Sargant W. Treatment of phobic states with antidepressants - a retrospective study of 246 patients. Br J Psychiatry 1970;116:387-98.

10. Brown TCK, Dwyer ME, Stocks JG. Antidepressant overdosage in children - a new menace. Med J Aust 1971;2:848-51.

11. Shah LP. Amitryptiline in the treatment of enuresis. Indian Pediatr 1971;8(11):767-9.

12. Brown TCK, Barker GA, Dunlop ME, Loughnan PM. The use of sodium bicarbonate in the treatment of tricyclic antidepressant-induced arrhythmias. Anaesth Intensive Care 1973;1(3):203-10.

13. Goel KM, Shanks RA. Amitriptyline and imipramine poisoning in children. Br Med Jour 1974;1:261-3.

14. Penttilä A, Lehti H, Lönnqvist J. Psychotropic drugs and impairment of psychomotor functions. Psychopharmacologia 1975;43(1):75-80.

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The MAH concludes that the publications reported safety issues that are well-known and labelled in the current CCDS. The types of adverse events were consistent across disease states evaluated in studies. No new safety

signals have been identified and the MAH considers the labelling for amitriptyline to adequately describe the safety profile.

4.8 Review of suicidality in children >6 years treated with amitriptyline for enuresis nocturna

The MAH was asked to assess the possibility of suicidality related to the use of amitriptyline for treatment of enuresis nocturna in children >6 years of age. They reviewed this possibility using the same literature and postmarketing data mentioned above.

The following summary was provided by the applicant:

Postmarketing Data Review

Suicidal behaviour, Suicidal ideation

There were no reports of suicidal behaviour or suicidal ideation in any age group.

Completed Suicide

There 8 reports of completed suicides in patients 12-18 years of age, and none in any of the younger age groups. Several of the 8 reports were from a single literature report. None of the 8 reported the indication, precluding assessment regarding use in enuresis.

Suicide Attempt

There was 1 report of suicide attempt in children 1 to 12 years of age. This was a literature report (see Citak, et al., 2006, above) that described a 9 year old girl taking amitriptyline for unknown indication, which precludes review and interpretation.

There were 13 suicide attempts in patients 12-18 years of age. The indication was unknown in 11 patients, depression in 1 patient, and possible depression in 1 patient. As none of these patients had an indication for enuresis, they are not eligible for review.

The MAH concludes that no meaningful conclusions can be drawn from the review of reports of suicidality due to lack of information regarding indication.

Literature Reports

Most postmarketing reports of suicidality came from literature reports rather than from spontaneous reports. The company states that those pertaining to enuresis generally enrolled children, who are at lower risk of suicide. In addition, most of the older publications do not contain the same level of detail as more recent publications, although one would expect AE as serious as suicidality to be reported.

The articles reporting suicidality were primarily toxicology-type reports and, thus, most did not report any indications with the exception of one that reported a vague history of psychiatric problems. Consistent with the postmarketing data, the literature reviews reported suicidality almost exclusively in older patients who, if treated with amitriptyline (as opposed to obtaining it elsewhere), are probably more likely to receive it for an indication other than enuresis.

Rapporteur's comment

The applicant has provided limited and inconsistent information regarding suicidality.

Cumulative Reports of All Serious and Nonserious AEs Through 1-MAY-2013:

Suicide Terms				
Suicide attempt	0	0	1	13
Suicidal behavior	0	0	0	0
Suicidal ideation	0	0	0	0
Completed Suicide	0	0	0	8
Total events	**0**	**0**	**1**	**21**

Line listings: These contain 13 completed suicides (adolescents only) and 9 suicide attempts (adolescents n=8, child n =1 with unknown outcome).

CIOMS reports: 13 CIOMS reports of completed suicide and 8 CIOMS reports of suicide attempts were submitted. An additional case of suicide attempt in an adolescent is contained in a CIOMS report. This is a case of a 16-year-old girl treated with amitriptyline for acute depression. The patient took an overdose of fourteen 50 mg tablets of amitriptyline hydrochloride but recovered. This case is not contained in the line listings.

Enuresis is not stated as indication in any of the available reports of suicidality, but the provided data cannot be taken as evidence of absence of suicidality risk in enuresis.

4.8.1 Discussion on safety data provided

The company was requested to submit a cumulative safety review including data from three sources: clinical trials, spontaneous reports and published literature. Two separate reviews were presented, one 'Postmarketing review', and one 'Literature review'. The new data are summarised in section 6.1 of the attached draft Rapporteur's Response Assessment Report. Please refer to Annex 2.

The presentation of the data makes the assessment difficult, as files have no names but only numbers. The data are somewhat unclear, inconsistent and incomplete:

1. The Postmarketing review '*could also include AE reports from company sponsored trials'*, but it is not clear if it actually did include any such reports.

2. As the company had stated that the Postmarketing review *'could also include data from literature'*, a confirmation was sought whether or not the cases reported in the 'Literature review' were included in the 'Postmarketing review'. The company affirmed that this was indeed the case. A comparison of case numbers indicates inconsistencies, with considerable underreporting in the 'Postmarketing review'. For example, Amitai reports 37 paediatric deaths, but the number of deaths stated in the company's report is 10 (Amitai 2006).

3. The search terms for the 'Literature review' were not provided. Less than 20% of publications identified by the applicant's search were included in the review. Individual case reports, case series with < 10 patients, and abstracts were specifically excluded from the review. Such exclusions from a safety review are not acceptable.

4. There are inconsistencies in the numbers of reports in tabular adverse event summaries, line listings and CIOMS reports. These inconsistencies include the numbers of suicides and suicide attempts.

5. The information provided in line listings and CIOMS reports appears to be incorrect in some cases and is incomplete in others.

6. A follow-up request to clarify why the entire dataset provided did not include any paediatric cases of unknown age resulted in the report of a large number of additional adverse events, including one fatal case.

7. Some redundant information has been provided, i.e. the results of database searches for suicide in neonates and infants.

All the above points might be considered to raise some concern regarding the pharmacovigilance procedures of the applicant.

The company concludes that no new safety signals were identified, but acknowledges that intentional and unintentional poisonings, which are potentially fatal, are known issues with amitriptyline.

Only limited conclusions can be drawn from the submitted data:

1. The data are in line with the known serious safety concerns for amitriptyline, a tricyclic antidepressant, primarily cardiotoxicity.

2. There are hundreds of published cases of amitriptyline overdose/poisoning in children, including fatal cases. For example, Bronstein et al report 531 exposures in children ≤5 years, 107 in children 6-12 years, 312 in adolescents 13-19 years, and 5 in children of unknown age, all reported within the year 2009 (Bronstein AC, et al. 2009).

3. Cases of suicide and suicide attempts have been reported. Enuresis is not stated as indication in any of the available reports of suicidality, but the provided data cannot be taken as evidence of absence of suicidality risk in enuresis.

4. Given the data limitations set out above, and given the fact that the data provided appear to be primarily based on passive surveillance, no robust conclusion can be drawn on the relative frequencies of adverse effects between paediatric age groups. For the same reasons, an estimation of the true incidence of paediatric adverse effects, including fatalities, is not possible. The denominator is unknown. Underreporting is likely, particularly since amitriptyline has been licensed for > 50 years.

5. A comparison of relative frequencies of adverse effects between the adult population and the paediatric population is not possible on the basis of the submitted data.

6. The balance of benefits and risks of tricyclics for the average case of bedwetting in childhood has been questioned as early as 1974 (Goel KM 1974).

Under the present Article 45 procedure, data were only submitted by one marketing authorisation holder. The relevant product, Tryptizol™, is nationally licensed in two European member states, Portugal and the Netherlands. The indication is '*Nocturnal enuresis where organic pathology has been excluded*'. Given the

safety and tolerability profile of amitriptyline and the available alternatives, such a wide indication which potentially includes first line treatment is not acceptable.

It might be questioned whether the use of a drug that is potentially life threatening in overdose is justified in a non-life threatening condition. Current recommendations by national and international groups such as the UK National Institute for Clinical Excellence (NICE) and the International Children's Continence Society (ICCS) limit the use of tricyclic antidepressant for enuresis to third line therapy. NICE guidelines state (1) that they were specifically concerned about the potential side effects of tricyclic antidepressants and their danger in overdose, and (2) if using a tricyclic, imipramine should be used (NICE 2010). The International Children's Continence Society (ICCS) also limit their recommendations to imipramine (Neveus T et al 2010).

Neither guideline provides a justification for the choice of imipramine over other tricyclics. Possible reasons might be for example a greater abundance of data or more robust data for imipramine or differences in the pharmacokinetic, efficacy and/or safety profiles. The company has not provided any relevant discussion. Worm stated that amitriptyline is by far the most frequently occurring cyclic antidepressant in fatal poisonings, adding that this is not surprising as amitriptyline is one of the most frequently prescribed antidepressants and one of the most toxic ones (Worm K. 1990). Amitai found that case fatality rates were higher for amitriptyline as compared to imipramine in children aged < 6 years but not in those older than 6 years (Amitai Y 2006). Litovitz reported a higher hazard factor in paediatric exposures for amitriptyline (22.8) than for imipramine (20.0). (Litovitz T 1992)

Trygge Neveus, the president of the ICCS, states that the potential cardiotoxicity of imipramine makes it a controversial subject and many experts actively discourage its use (Neveus T 2006). He concludes there is still a place for tricyclic antidepressant therapy, but only for children failing all relevant first and second-line therapies (alarm, urotherapy, desmopressin , anticholinergics) and only if adequate safety precautions are strictly observed (ECG to exclude long QT syndrome when indicated by history including family history, compliant well informed family who knows that drugs should be securely locked).

It is acknowledged that bedwetting is a widespread and distressing condition that can have a deep impact on the emotional, behavioural and social wellbeing of children and can be highly stressful for parents and carers. Nevertheless, it is not a life-threatening disease and pharmaceutical treatment options other than amitriptyline are available. Several new drugs are in clinical development for the treatment of enuresis. Once these are licensed, they may provide another alternative to tricyclic antidepressants.

Cardiotoxicity in overdose, potentially resulting in death, is a class effect of tricyclic antidepressants. The review of class effects however is not within the remit of an Article 45 procedure, nor is the deletion of an indication.

Therefore, for the products already containing the paediatric nocturnal enuresis indication, it was decided to recommend restriction to third line therapy and a strengthening of the warnings as outlined in section 2 below. Amitriptyline products that are not licensed for use in paediatric enuresis should remain unchanged.

5 MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Toxicity in overdose, potentially resulting in death, is a class effect of tricyclic antidepressants. It might be questioned whether the use of a drug that is potentially life threatening in overdose is justified in a non-life threatening, albeit distressing, condition. The review of class effects is however not within the remit of an Article 45 procedure, nor is the deletion of an indication.

The Member States therefore concluded that a restriction of the indication of amitriptyline to third line therapy of nocturnal enuresis and a strengthening of the warnings should be imposed.

It is noted that the proposed SmPC changes are only applicable to products that are already licensed for the paediatric indication of nocturnal enuresis. Amitriptyline products that are not licensed for use in paediatric enuresis should remain unchanged.

Section 4.1: The indication should be restricted as follows:

> Amitriptyline is indicated for the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology has been excluded and no response has been achieved to all other non-drug and drug treatments (used only as third line therapy). Amitriptyline should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

Section 4.2: The following text should be added to the posology section: Enuresis: An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome. The dose should be increased gradually. The initial treatment course is for 3 month. If repeated courses of amitriptyline are needed, a medical review should be conducted every 3 months. When stopping treatment, amitriptyline should be withdrawn gradually.

Section 4.3: A contraindication for use in children < 6 years should be added.

Section 4.4. The following warning statements should be added:

Enuresis:

- An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.
- Amitriptyline for enuresis should not be combined with an anticholinergic drug.
- Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis.

Section 4.5.:

The following statement should be added: Amitriptyline for enuresis should not be combined with an anticholinergic drug.