

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

OXYBUTYNIN HYDROCHLORIDE

**Ditropan, Dridase, and Cystrin
Oral formulations**

UK/W/017/pdWS/001

**Marketing Authorisation Holder: SANOFI-AVENTIS,
AVENTIS PHARMA LTD UK, MYLAN AB.**

Rapporteur:	UK
Start of the procedure:	28 December 2009
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Date of the Final report (Day 120):	6 September 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Ditropan, Dridase, and Cystrin
INN (or common name) of the active substance(s):	Oxybutynin hydrochloride
MAH:	SANOFI-AVENTIS, AVENTIS PHARMA LTD UK, MYLAN AB
Currently approved Indication(s)	<p><u>Adults</u></p> <ul style="list-style-type: none"> - Urgency and frequency in unstable bladder conditions due either to idiopathic detrusor instability or neurogenic bladder disorders (detrusor hyperreflexia) in conditions such as spina bifida and multiple sclerosis with the following symptoms: pollakiuria, nocturia, urgency and urge incontinence, - In the control of vesical hyperactivity seen after surgery of the bladder or prostate, or accompanying cystitis, - Increased nocturnal urination (nycturia), - Imperative urge to urinate, - Involuntary incontinence with and without urge to urinate (urge incontinence), <p><u>Children</u></p> <ul style="list-style-type: none"> - Neurogenic bladder disorders - Enuresis
Pharmaco-therapeutic group (ATC Code):	Drugs for urinary frequency, enuresis and incontinence
Pharmaceutical form(s) and strength(s):	<p>ORAL FORMULATIONS 2.5 mg, 3mg, 5mg and 10mg tablets (film-coated or prolonged release tablets) 5mg/5ml syrup 2.5mg/5ml oral solution</p>

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EXECUTIVE SUMMARY

In November 2009, one MAH (Sanofi-Aventis) submitted data regarding the paediatric use of Oxybutynin hydrochloride, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

Oxybutynin acts on bladder contraction mainly through an antimuscarinic action. It is a synthetic tertiary amine which, similar to atropine, antagonizes the muscarinic actions of acetylcholine. Also has a direct spasmolytic effect on the detrusor muscle and the small intestine, as well as local anaesthetic action.

The paediatric approved indications for oral formulations of Oxybutynin are Neurogenic bladder disorders and Enuresis. It is noted that the use of oxybutynin in children under 5 years of age is not currently recommended.

Based on the paediatric evidence submitted, the MAH concludes that "*the benefit risk ratio of Oxybutynin favourable for the treatment of children over 5 years in the currently approved indications, such as neurogenic bladder disorders and enuresis*". Therefore no amendment in the currently approved SmPCs/PILs of the oral formulations containing Oxybutynin is proposed.

Reviewing the data submitted, it is concluded that the efficacy of oral oxybutynin at the recommended doses of 5 mg bid in the treatment of neurogenic bladder in children over 5 years of age has been demonstrated. It is noted that enuresis is already included as an indication in the approved SmPCs. However the majority of the placebo-controlled studies in paediatric patients with enuresis did not demonstrate a clear therapeutic beneficial effect from Oxybutynin. Its use in such patients should be therefore recommended with caution and only after other measures have failed.

It is noted that although children below the age of 5 years have been included in some of the efficacy clinical studies, there is not sufficiently robust evidence which would support the use of oral oxybutynin formulations in patients with neurogenic bladder or enuresis in paediatric patients under the age of 5 years.

The current approved posology in children over 5 years reflects the current standards of treatment and the rapporteur agrees with the MAH that there is currently no need for any changes in the dosage recommendations for neurogenic bladder disorders and enuresis.

From the data submitted by the MAH, there is not enough scientific evidence to support the use of intravesical or transdermal oxybutynin in the paediatric population, regardless of the condition. However there appear to be significant data in published literature supporting a role of intravesical Oxybutynin in selected paediatric patients. The rapporteur is of the view that the treatment of paediatric patients with intravesical Oxybutynin might represent a safe alternative to oral formulations and therefore strongly supports the development of appropriate paediatric intravesical Oxybutynin formulations and the investigation of the safety and efficacy of this method of treatment in paediatric clinical studies.

Based on the analyzed data, including safety information from literature publications and post-marketing data, no new safety issues have been identified regarding the use of oxybutynin in the paediatric population. However it is noted that the CNS/psychiatric AEs appear to be very common in children, possibly even more common than in adults.

The response from the MAH regarding the recommended wording for sections 4.1 and 4.4 was received in June 2010. In summary the MAH fully endorse the proposed wording regarding the paediatric use of Oxybutynin oral preparations. Furthermore the MAH proposed paediatric

wording which should be included in the PIL of all oxybutynin containing oral preparations.

RECOMMENDATION

Based on the review of the presented paediatric data the rapporteur considers that:

For all oral products (tablets, syrup and oral solution) containing Oxybutynin across the EU, it is recommended that SmPCs and PILs contain the following statements:

4.1 Therapeutic indications

Paediatric population

Oxybutynin hydrochloride is indicated in children over 5 years of age for:

- *Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor overactivity).*
- *Nocturnal enuresis associated with detrusor overactivity, in conjunction with non-drug therapy, when other treatment has failed.*

4.4 Special warnings and precautions for use

Paediatric population

Oxybutynin hydrochloride is not recommended for use in children below age 5 years due to insufficient data on safety and efficacy.

There is limited evidence supporting the use of Oxybutynin in children with monosymptomatic nocturnal enuresis (not related to detrusor overactivity).

In children over 5 years of age, Oxybutynin hydrochloride should be used with caution as they may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

PIL Wording :

“What X is used for:

X can be used in children 5 years or older to treat:

- *Loss of control in passing urine (urinary incontinence)*
- *Increased need or urgency to pass urine*
- *Night time bedwetting, when other treatments have not worked”*

“Take special care with X:

Check with your doctor or pharmacist before taking your medicine if:

- *The person taking the medicine is a child (use is not recommended under 5 years of age)”*

I. INTRODUCTION

On 16 November 2009, the MAH (Sanofi-Aventis) submitted the following documents for Oxybutynin hydrochloride, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use:

- A critical expert overview of Oxybutynin hydrochloride
- A list of 114 references which included one non clinical study, an extensive number of published and unpublished clinical trials associated with the use of oxybutynin in bladder syndromes and 3 additional MAH internal documents on clinical aspects of Ditropan use.

The MAH has reviewed the clinically relevant information on efficacy and safety available on the paediatric use of Oxybutynin and concluded that *“Based on the available clinical studies and the long experience with this product, the MAH considers the benefit risk ratio of Oxybutynin favourable for the treatment of children over 5 years in the currently approved indications, such as neurogenic bladder disorders and enuresis.”* Furthermore the MAH stated that no changes in the dosage recommendations are thought to be needed for the oral formulations of Oxybutynin containing products.

Assessor’s Comment

Oxybutynin is a commonly used drug across Europe and USA, a fact that is reflected by the extended list of literature references provided by the MAH. It is noticed that the SmPCs for the currently authorised preparations has not been provided by the MAH, although available information has been summarized in the critical overview document. It would have been interesting to identify variations in the paediatric indications and posology as well as the safety warnings between member states and different products. It is also noted that in the provided reference list it is very difficult to identify the studies sponsored by the MAH, which have not previously been assessed by a regulatory authority.

II. SCIENTIFIC DISCUSSION

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

Oxybutynin acts on bladder contraction mainly through an antimuscarinic action. It is a synthetic tertiary amine which, similar to atropine, antagonizes the muscarinic actions of acetylcholine. Also has a direct spasmolytic effect on the detrusor muscle and the small intestine, as well as local anaesthetic action.

Oxybutynin hydrochloride was first approved in Greece in 1979 as a 5 mg tablet formulation. In Europe, it has been approved and currently marketed in 19 EU countries and in Iceland and Switzerland. The European available products (Ditropan, Dridase, Cystrin) are marketed in various oral formulations: 2.5 mg, 3 mg, 5 mg and 10 mg film-coated or prolonged release tablets, 5 mg/5 ml syrup and 2.5 mg/5 ml oral solution. Pharmaceutical forms suitable for a paediatric use (oral solutions and syrup) are available in the following 4 EU countries: BE, IE, LU and UK.

Beside oral administration, intravesical Oxybutynin has been used in adults most frequently in cases of neurogenic detrusor overactivity (NDO) in which self-catheterization is required but this method of administration is not licensed in children. Additionally, oxybutynin has also been developed in other formulations such as suppository form or adhesive patch but those formulations are not marketed by the MAH. Although some of the data submitted include these unlicensed preparations, this paediatric assessment report addresses predominately the issues regarding the paediatric use of oral formulations Oxybutynin.

Oxybutynin is used in the following indications in adults:

- Urgency and frequency in unstable bladder conditions due either to idiopathic detrusor instability or neurogenic bladder disorders (detrusor hyperreflexia) in conditions such as spina bifida and multiple sclerosis with the following symptoms: pollakiuria, nocturia, urgency and urge incontinence,
- In the control of vesical hyperactivity seen after surgery of the bladder or prostate, or accompanying cystitis,
- Increased nocturnal urination (nycturia),
- Imperative urge to urinate,
- Involuntary incontinence with and without urge to urinate (urge incontinence),

The paediatric approved indications are:

- Neurogenic bladder disorders
- Enuresis.

The use of oxybutynin in children under 5 years of age is currently not recommended. The recommended dosage in children over 5 years of age is:

- Neurogenic bladder disorders: The usual dose is 2.5 mg twice a day. This dose may be titrated upwards to 5 mg two or three times a day to obtain a clinical response provided that the side effects are well tolerated.
- Enuresis: The usual dose is 2.5 mg twice a day. This dose may be titrated upwards to 5mg two or three times a day to obtain a clinical response provided that the side effects are well tolerated. The last dose should be given before bedtime.

Assessor's Comment

Oxybutynin was among the first generation of antimuscarinic drugs for the treatment of incontinence in children. As it is one of the most widely used drugs for the treatment of overactive bladder symptoms and detrusor overactivity, it is accepted that there is long standing experience with this product. The well-known anticholinergic side effects limit its use, affecting particularly long-term compliance. It is noted that the UK authorised SmPC includes a warning in section 4.4 relevant to paediatric use: "Oxybutynin should be used with caution in the frail elderly and children who may be more sensitive to the effects of the product".

II.2 Non-clinical aspects

2.1 Introduction

One non-clinical study has been provided by the MAH on Oxybutynin. An additional literature review conducted by the MAH based on several databases (Medline, Embase and Chemical Abstract) did not provide any non-clinical information relevant for the paediatric assessment.

Assessor's Comment

The MAH has not provided detailed information regarding the methods used for the review of literature. It is noted that no pre-clinical information of therapeutic relevance is available at the currently approved UK SmPCs in section 5.3.

2.2 Non clinical study

➤ Description

Acute toxicity in mice, rats and dogs.

➤ **Methods**

Objectives

The study was conducted to determine the LD₅₀ (dosage of a substance that will kill 50% of the animals given) of Oxybutynin in mice and rats when administered orally, intraperitoneally and/or intravenously as well as the approximate minimum lethal dose (MLD) in dogs when administered orally and intravenously.

Study design

This was a single-dose acute toxicity study using mice, rats, including 10 newborn rats (5 days old) and dogs. The animals were observed for up to 10 days or until death. The newborn rats group received Oxybutynin orally.

➤ **Results**

From the oral administration to new born rats, it was determined that the LD₅₀ of Oxybutynin was 560 mg/kg [95%C.L. 528-594mg/kg]. It is noted that in the oral acute toxicity test of adult rats, the LD₅₀ was 1600mg/kg [95%C.L 1176-2176mg/kg]. When reviewing the toxic symptoms in the group of newborn rats, labored respiration and decreased activity were the only symptoms noted. In comparison, in the adult rat group, exophthalmos, CNS stimulation, ataxia and salivation were common findings; convulsion were noted in some dosage levels and female animals appeared to be more susceptible to toxic symptoms and mortality than males. The newborn rats mostly died on day 2 compared to the adult animals were most of the deaths occurred within the first 24 hours.

➤ **Conclusions**

The MAH concluded that “This study did not show any conclusion on juvenile animals.”

Assessor’s Comment

The MAH provide a brief synopsis of a single-dose acute toxicity study that included juvenile animals. The exact date of this study is not provided. Currently in drug development, the LD₅₀ test is controversial because the results have limited, if any, significance when applied to humans and this type of animal study is not used as it was in the 1980s and 1990s. The rapporteur agrees with the MAH conclusion that this study does not offer any additional information regarding the paediatric use of Oxybutynin.

2.3 Discussion of non-clinical aspects.

Based on information from published literature, one of the main concerns associated with the use of antimuscarinics is the risk of cognitive impairment as well as other CNS side effects. In published preclinical studies, significant binding of brain muscarinic receptors in mice was observed by the oral administration of oxybutynin and to a lesser extend by newer antimuscarinics. Although the impact of oxybutynin on cognitive function is associated with old age, the MAH didn’t provide any information on juvenile animal studies, which could have clarified this issue. Furthermore as muscarinic receptors are also present in smooth muscle of the bowel, salivary glands, eyes and the heart, the effects of blocking these receptors in the developing child have not been adequately investigated.

II.3 Clinical pharmacogy

3.1 Pharmacodynamics

Oxybutynin acts on bladder contraction mainly through an antimuscarinic action. Bladder contraction is predominantly under the control of the parasympathetic nervous system via muscarinic receptors. Five muscarinic receptors (M1-M5) have been identified so far in the human bladder. The M3 receptor is considered to be primarily responsible for detrusor contraction while M2 receptor is thought to oppose sympathetically mediated detrusor relaxation. Oxybutynin has a high affinity for these muscarinic receptors, especially the M1, M2 and M3 subtypes. It also has a direct anesthetic and smooth muscle relaxant effect.

Assessor's Comment

The mode of action of Oxybutynin is well established. The MAH provided information regarding the effects of the drug on the bladder through its antimuscarinic action; these effects have not been reported to be different in paediatric population. However muscarinic receptors are widespread also in the central nervous system, especially post-synaptic M1 and M2 receptors. Oxybutynin acts primarily on M1 receptors and crosses the blood-brain barrier and thus electroencephalographic abnormalities have been reported in healthy volunteers (Peitzko et al 1994). The MAH did not provide any information regarding unwanted central nervous system effects either in adults and in children.

3.2 Pharmacokinetics

The MAH summarized the PK findings from 3 published articles, 2 of which included paediatric patients:

1. Massad C.A., Kogan B.A, Trigo-Rocha F.E. (1992) **The Pharmacokinetics in intravesical and oral oxybutynin chloride.** J Urol148: 595-597.
2. Douchamps J, Derenne F, Stocks A, Gangji D, Juvent M, Herchuelz A. (1988) **The pharmacokinetics of Oxybutynin in man.** Eur J Clin Pharmacol, 35: 515-520
3. Autret E, Jonville AP, Dutertre JP, Bertiere MC, Robert M, Averous M. Couet W. (1994) **Plasma levels of Oxybutynin chloride in children.** Eur J Clin Pharmacol 46 :83-85.

Oxybutynin pharmacokinetics is characterized by a rapid oral absorption (t_{max} between 1 and 2 hours) and an extensive oxidative metabolism to N-desethyloxybutynin which possesses a pharmacological activity comparable to the intact drug. This extensive metabolism is responsible for the rather low (6%) and variable bioavailability of the drug due to the first pass hepatic metabolism after oral intake. The amount of parent drug found in the urine is negligible. Oxybutynin has a short half-life which justifies the administration of the drug twice a day **(1)**.

Clinical studies conducted in children above 5 years of age showed pharmacokinetic profiles comparable to those seen in adults. The mean C_{max} observed in children was not very different from that observed in adults. On average, after a 5 mg dose i.e. 0.08 mg/kg, in adults, the C_{max} was around 8 ng/ml **(2)**. In children aged 6-9 years, the average C_{max} was 9 ng/ml +/- 6.6 ng/ml for a mean dose of 0.11 mg/kg/day **(3)**.

Assessor's Comment

The findings from the Autret et al paper should be reviewed with caution. The authors noted that "The most important finding was extreme inter-individual variability of the peak plasma concentrations." This could possibly lead to an unpredicted risk of developing atropine-like symptoms even within the proposed doses. To confirm that the anticholinergic adverse-effects are directly related to the plasma concentration of the drug, it would be necessary to measure the C_{max} at the time of appearance of these adverse-effects, because of the very rapid excretion half-life of the drug. The authors conclude that in children, dosage adapted to the child's weight could be advisable.

II.4 Clinical aspects

4.1 Introduction

The MAH has provided a comprehensive overview of the available information on the clinical efficacy of Oxybutynin in children with neurogenic bladder, day-time lower urinary tract conditions and enuresis. A significant number of paediatric clinical trials (79) were listed and are analysed in this assessment report.

The safety of Oxybutynin was assessed by the MAH from data included is selected paediatric clinical trials reviewing the efficacy of the treatment in different paediatric indications. Furthermore a specific literature search was performed on the key terms "oxybutynin" and

“adverse effects” in the paediatric population (0-18 years) through external medical literature databases such ADIS Reactions, Derwent Drug File, Embase and Medline, up to 12 October 2009. Overall an addition 35 published articles were identified and reviewed in this assessment report. The two sanofi-aventis postmarketing pharmacovigilance databases were also searched for worldwide paediatric medically confirmed cases up to 30 September 2009.

4.2 Overview of efficacy

The report from the MAH is a summary of the available data from Oxybutynin studies in the paediatric population. A literature search was performed on Oxybutynin in clinical trials in association with the recommended indications through external medical literature databases such Medline, up to October 2009. The findings from studies sponsored by the MAH were also reviewed.

Assessor’s Comment

Following the new terminology document by the International Children’s Continence Society, daytime lower urinary tract conditions is the new term used to group together functional incontinence problems in children. After any possible underlying uropathy or neuropathy has been excluded, a problem of incontinence in children is grouped into the category of daytime lower urinary tract conditions. Night-time wetting is known as enuresis which according to the European Society for Paediatric Urology (ESPU)/European Association of Urology (EAU) guidelines is synonymous to the previously used term of “intermittent nocturnal incontinence”. As part of the group of daytime lower urinary tract conditions, there are two main groups of voiding dysfunction, namely, filling-phase dysfunctions and voiding-phase dysfunctions. In filling-phase dysfunctions, the detrusor can be overactive, as in overactive bladder (OAB) and urge syndrome, or underactive, as in underactive or highly compliant bladder. In voiding-phase (emptying) dysfunctions, interference with the sphincter and pelvic floor during detrusor contraction is the main pathogenic mechanism.

4.2.1 Oxybutynin and neurogenic bladder in children

The MAH has provided an overview of 22 studies conducted in paediatric patients with various patterns of detrusor-sphincter dysfunction (such as neurogenic detrusor overactivity [NDO]), including an MAH sponsored clinical investigation previously submitted in 1981 as part of the new drug application. (Please note that in the text of section 4.2.1, the studies are referenced by the numbers in the list below).

1. Hehir M, Fitzpatrick JM. **Oxybutynin and the prevention of urinary incontinence in spina bifida.** Eur Urol. 1985;11(4):254-6.
2. Bono AV, Marconi AM, Gianneo E. **Oxybutynin chloride on the pure instable bladder. Preliminary controlled study versus placebo.** 1982. Urologia 49:764-8.
3. Marion Laboratories. **Internal reports on efficacy and safety of DITROPAN to placebo in treating signs and symptoms associated with reflex or uninhibited neurogenic bladder.** Extract of New Drug Application. 1981
4. Madersbacher H, Mürtz G, et al. **Propiverine vs oxybutynin for treating neurogenic detrusor overactivity in children and adolescents: results of a multicentre observational cohort study.** BJU Int.2009 Mar;103(6) :776-81.
5. Bouchot O, Buzelin JM, Labat JJ. **Long-term efficacy of anticholinergenic and alphablocking drugs on the detrusor of children with myelomeningocele.** J Urol. 1988; 94(2):83-6.
6. Franco I, Horowitz M, Grady R, et al. **Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction.** J Urol 2005; 173 (1):221-5.
7. Youdim K, Kogan BA. **Preliminary study of the safety and efficacy of extended-release oxybutynin in children.** Urology. 2002 Mar;59(3):428-32.

8. Aubert D, Cencig P, Royer M. **Treatment with oxybutynin hydrochloride of urinary incontinence and hyperactive bladder conditions in children.** Ann Pediatr (Paris). 1986 Sep;33(7):629-34.
9. Goessl C, Knispel HH et al. **Urodynamic effects of oral oxybutynin chloride in children with myelomeningocele and detrusor hyperreflexia.** Urology. 1998 Jan;51(1):94-8.
10. De Castro R, Casolari E, Ricci S. **Combination of oxybutynin chloride (Ditropan) with intermittent catheterization in the treatment of neurogenic bladder in childhood: results on continence.** Pediatr Med Chir. 1984 Nov-Dec;6(6):795-803.
11. Cartwright PC, Coplen DE, Kogan BA, Volinn W, Finan E, Hoel G. **Efficacy and safety of transdermal and oral oxybutynin in children with neurogenic detrusor overactivity.** J Urol. 2009 Oct;182(4):1548-54.
12. Ferrara P, D'Aleo CM, Tarquini E, Salvatore S, Salvaggio E. **Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida.** BJU Int. 2001 May;87(7):674-8.
13. Haferkamp A, Staehler G, Gerner HJ, Dörsam J. **Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients.** Spinal Cord. 2000 Apr;38(4):250-4.
14. Painter KA, Vates TS, Bukowski TP, Fleming P, Freedman AL, Smith CA: **Long-term intravesical oxybutynin chloride therapy in children with myelodysplasia.** J Urol. 1996. 156(4):1459-62
15. Buyse G, Verpoorten C, Vereecken R, Casaer P. **Intravesical application of a stable oxybutynin solution improves therapeutic compliance and acceptance in children with neurogenic bladder dysfunction.** J Urol. 1998 Sep;160(3 Pt 2):1084-7; discussion 1092.
16. Amark P, Bussman G, Eksborg S. **Follow-up of long-time treatment with intravesical oxybutynin for neurogenic bladder in children.** Eur Urol. 1998 Aug;34(2):148-53.
17. Kaplinsky R, Greenfield S, Wan J, Fera M. **Expanded followup of intravesical oxybutynin chloride use in children with neurogenic bladder.** J Urol. 1996 Aug;156(2 Pt 2):753-6.
18. Buyse G, Verpoorten C, Vereecken R, Casaer P **Treatment of neurogenic bladder dysfunction in infants and children with neurospinal dysraphism with clean intermittent (self) catheterisation and optimized intravesical oxybutynin hydrochloride therapy.** Eur J Pediatr Surg. 1995 Dec ;5 Suppl 1 :31-4.
19. Connor JP, Betrus G, Perlmutter AD and Reitelman C: **Early cystometograms can predict the response to intravesical instillation of oxybutynin chloride in myelomeningocele patients.** J Urol. 1994. 151(4):1045-7.
20. Kasabian NG, Vlachiots JD, Lais A, Klumpp B, Kelly MD, Siroky MB et al. **The use of intravesical oxybutynin chloride in patients with detrusor hypertonicity and detrusor hyperreflexia.** J Urol. 1994. 151(4):944-5.
21. Greenfield SP and Fera M. **The use of intravesical oxybutynin in children with neurogenic bladder.** J Urol. 1991. 146(2):532-4.
22. Guerra LA, Moher D, Sampson M, Barrowman N, Pike J, Leonard M. **Intravesical oxybutynin for children with poorly compliant neurogenic bladder: a systematic review.** J Urol. 2008 Sep;180(3):1091-7.

Oral Oxybutynin was investigated versus placebo in 2 published randomized controlled studies (1, 2) conducted on children over 10 years of age (40 in total). The main outcomes studied were urinary frequency, urodynamic parameters such as bladder volume and bladder maximum filling pressure and those appear to be improved in the treatment group versus the placebo.

Similar findings were reported in 5 double-blind randomized controlled applicant sponsored studies conducted on 18 children aged 5 to 13 years as summarised in the new drug application document (3). Each study was designed as a two-way, double-blind randomized crossover study

to compare the safety and efficacy of 5 mg bid oxybutynin for 30 days in treating the signs and symptoms associated with reflex or uninhibited neurogenic bladder. The studies and the findings are summarised in the table below:

TABLE OF SPONCORED STUDIES INCLUDED IN NEW DRUG APPLICATION DOCUMENT

Author	Study design	Oxybutynin	Control	Duration	Number of patients total/analysed	Age (years)	Diagnosis	Outcomes	Authors' conclusion
Internal report									
Marion Lb N°012-019 (30)	DB R CO	5 mg bid	P	30 d	9	5-13	Reflex or inhibited neurogenic bladder	Vesical capacity, vesical volume, daytime and nocturnal frequency and accidents, incontinence	Oxy>P
Marion Lb N°012-022 (30)	DB R CO	5 mg bid	P	ns	4/2	5-11	Reflex or inhibited neurogenic bladder	Daytime and nocturnal frequency and accidents, incontinence	Oxy>P
Marion Lb N°012-031 (30)	DB R CO	5 mg bid	P	ns	1	6	Uninhibited neurogenic bladder, bilateral hydronephrosis and recurrent infections	Enuresis and urinary frequency	Oxy=P
Marion Lb N°012-059 (30)	DB R CO	5 mg bid	P	30 d	4/3	11-13	Uninhibited neurogenic bladder	Nocturia and urinary frequency	Oxy≥P
Marion Lb N°012-069 (30)	DB R CO	5 mg bid	P	26 to 35 d	3	5-10	Uninhibited neurogenic bladder	Daytime and nocturnal frequency and accidents, incontinence	Oxy>P

CIC: Clean-intermittent catheterization CO: cross-over, d: day, DB: double-blind, ER: extended-release, IR: immediate release, m: month, ns: not specified, O: opened, Oxy: oxybutynin, P: placebo, Pros: prospective, PG: parallel group, R: randomized, Retro: retrospective, UC: uncontrolled, yr: year, wk: week.

Assessor's Comment

It is noted from the information from the new drug application document that the number of paediatric patients in applicant sponsored studies is very limited. There is a significant number of participants (5/18) that did not completed the two arm-crossover periods of the investigations either due to side effects, lack of therapeutic effect or loss in follow up. Only in the first of the studies (N°012-019) statistical significant improvement in cystometric parameters were reported. In study N°012-022 only 2 out of the 4 patients completed the 2 crossover phases and the results reported in the remaining 2 show some improvements of the symptoms, without any other information. In the 3rd study of the document (N°012-031) treatment with Oxybutynin of 6 year old boy did not improve his symptoms of enuresis and urinary frequency and the investigator rated the therapeutic effectiveness of Oxybutynin as poor. In study N°012-05) the results were also poor as in 2 out of 3 children treatment didn't improve the incidence of nocturia and frequency. And finally the last study (N°012-069) demonstrated improvement of symptoms that was reported to be statistically significant, although the number of participants was very limited (n=3). In the assessor's opinion these studies fail to demonstrate a clearly positive effect of the Oxybutynin treatment in paediatric patients with NDO.

Oral Oxybutynin has been investigated in these patients versus other treatments. In 1 multi-centre retrospective observational cohort study (4) in 255 children and adolescents aged 1-18 years with NDO (the majority with myelomeningocele), the efficacy of propiverine and oxybutynin was assessed with urodynamic and clinical variables before and after at least 12 months of treatment. The results of this study demonstrated that comparing the efficacy, tolerability and safety of the 2 antimuscarinics, propiverine was at least as effective as oxybutynin, but better tolerated, resulting in superior clinical effectiveness than for oxybutynin. In a long-term study (5) including 54 patients, the efficacy of anticholinergic drugs (oxybutynin and hexocyclium methylsulphate) and alpha-blocking drugs in children with myelomeningocele aged 5 to 20 years was studied. The anticholinergics were found to be as effective as alpha-blocking drugs after 3 to 12 months of therapy. Of the anticholinergic drugs, oxybutynin was found to act more rapidly than hexocyclium methylsulphate but after 2 years, no difference in efficacy remained.

Assessor's Comment

As Oxybutynin is one of the first drugs used in NDO, in many comparative trials, it is chosen as a reference drug to assess the efficacy and safety of the other treatments. The assessor found a significant number of such studies published in the literature that have not been included in the review provided by the MAH. However, it is not easy to assess if those comparisons provide new relevant information regarding the efficacy of Oxybutynin.

Franco et al in 2005 **(6)** reported the results of 2 prospective open-label multicenter studies, involving 132 children aged 1 to 15 years old (including 16 children under 5 years old). The first study was designed to examine the efficacy and safety of oxybutynin tablets, syrup and extended release tablets in children 6 to 15 years old. The second study explored the use of oxybutynin therapy at least 2 weeks in duration in children 1 to 5 years old. In these studies oxybutynin improved bladder function with all the formulations tested, which were considered to be roughly equivalent after 2 to 24 weeks of treatment.

In a retrospective study **(7)** including 25 children treated with extended-release oxybutynin (dose 0.3 mg/kg daily), patients and families were asked to assess the effects of the medication on efficacy, as well as side effects and compliance with medication schedules. Fourteen had neurogenic bladder dysfunction and 11 had urinary frequency and urgency and urge incontinence but no neurologic abnormalities. All 25 patients had improvement in incontinence and/or voiding dysfunction on extended-release oxybutynin; only 12 patients (48%) experienced no side effects. It was concluded that of patients previously treated with oxybutynin (immediate release tablets 0.1 mg/kg three times daily), the extended-release oxybutynin was equally or more efficacious and had the same or fewer side effects, especially less dry mouth. Families reported much better patient compliance with the medication regimen.

Another retrospective uncontrolled study **(8)** which analysed the findings from 162 patients aged 3 to 17 years with all forms of bladder hyperactivity, including 19 cases of NDO, reported that the efficacy of oral Oxybutynin was demonstrated in all conditions apart from the cases with isolated enuresis.

In a prospective uncontrolled study **(9)** 41 children with detrusor hyperreflexia (aged 2 months to 15 years; mean 4.9 years) were evaluated urodynamically before and within 3 months after initiation of oral Oxybutynin (0.2 to 0.3 mg/kg/day), always combined with clean intermittent catheterization (CIC). It was found that treatment caused an increase in bladder capacity, a decrease in detrusor pressure at maximal capacity and an increase in detrusor compliance from baseline and these improvements in urodynamic measures correlated with continence. After a follow-up of at least 2 years, effective protection of renal function was achieved in 38 of the 41 children (93%) with conservative therapy alone. Adverse effects resulted in discontinuation of oral Oxybutynin treatment in only 2 cases.

Finally in a retrospective uncontrolled study **(10)** of 34 children (aged 4 months to 17 years) the authors concluded that there was an improvement of the urinary control from the combination of oral Oxybutynin and CIC.

Assessor's Comment

These studies investigate the effect of oral Oxybutynin in children with NDO with somewhat inconsistent results. However the quality of these uncontrolled studies is very variable with respect to providing robust evidence regarding the cystometric or symptomatic improvements of the treatment with oral Oxybutynin. It is noted that only 5 of the studies presented above included patients below the age of 5 years. The design of those studies is variable but none is a randomized double-blind controlled trial. The number of patients under the age of 5 years is very limited; more importantly the results on the efficacy outcomes or the safety findings are not presented separately for the youngest subsets to allow assessment of the effect of the oxybutynin treatment in the children less than 5 years.

The MAH summarized the findings from paediatric studies using other formulations of Oxybutynin including transdermal (OXY-TDS) and intravesical administration.

In 1 open randomized parallel-group study (11) the efficacy of transdermal and oral oxybutynin in 49 children 6 to 15 years old with NDO was evaluated after 12 months. Treatment with OXY-TDS resulted in significant improvement in all measured urodynamic parameters. Similar trends and a significant increase in maximal cystometric bladder capacity were observed in the oral oxybutynin group. It was also noted that the ratio of N-desethyloxybutynin-to-oxybutynin plasma concentrations was substantially lower with OXY-TDS than with oral (1.4 vs. 6.7).

In a 3 years retrospective study (12), 101 children (mean age 4.2 years, range 0.25-10 years) with uncoordinated detrusor-sphincter function and low compliance were treated with either oral or intravesical oxybutynin and CIC. Oral and intravesical oxybutynin both proved to be equally effective for managing neurogenic bladder dysfunction, but the authors considered that intravesical administration was safer and better tolerated than oral oxybutynin.

In a prospective study (13), the authors analyzed the dose dependent outcome of 27 NDO patients aged 1 to 18 years (including 4 children under 5 years) with intravesical application of oxybutynin. Clinical outcome, continence situation, side effects and urodynamic data of patients with standard dosages of intravesical oxybutynin (0.3 mg/kg/d) and with increasing dosages in steps of 0.2 up to 0.9 mg/kg/d were registered. The intravesical application of oxybutynin was found to be an efficacious therapy as the escalating dosage titration of oral oxybutynin could increase the efficiency to 87%

Assessor's Comment

It is noted that these formulations are not currently approved in any EU MS. In the 2 intravesical versus oral Oxybutynin studies (12, 13) crushed tablets or Oxybutynin powder were dissolved in NaCl or sterile water prior administration, a method of administration highly unacceptable for day-to-day paediatric practice.

The MAH also summarized the results from 1 retrospective (14) and 7 prospective studies (15-21) including 176 children (154 analyzed) with overactive bladder (the majority with neurogenic bladder) aged 0.5 to 18 years. The results demonstrated that intravesical oxybutynin (crushed tablets dissolved in water or saline solution, or sterile stable solutions in 2 studies at doses 10 mg to 20 mg/d and 0.1 to 0.2 mg/kg bid respectively) administered for various periods of time (from 2 to 67 months) significantly improved urodynamic parameters and continence, suggesting that intravesical oxybutynin could be an alternative treatment for children refractory to oral therapy.

However, in a recent systematic review (22) investigating intravesical oxybutynin for poorly compliant neurogenic bladder, the authors underline that the level of evidence is low, due to the poor design of these studies. For that reason, they consider that based on the current information, there is insufficient evidence to recommend this therapy.

Assessor's Comment

The rapporteur agrees with the MAH that based on the currently available information, the treatment of NDO with intravesical oxybutynin, although it might represent a safe alternative to oral formulations, is currently not recommended in the paediatric population.

4.2.2 Oxybutynin and day-time lower urinary tract conditions in children

The MAH has provided an overview of 7 studies conducted in paediatric patients with functional incontinence problems (known as day-time lower urinary tract conditions) such as filling-phase or voiding-phase dysfunctions. (Please note that the studies are referenced in the text of section 4.2.2 by the numbers in the list below).

1. Van Gool JD, de Jong TPVM, Winkler-Seinstra P, et al. **Comparison of standard therapy, bladder rehabilitation with biofeedback, and pharmacotherapy in children with nontherapeutic bladder-sphincter dysfunction** Abstract NeuroUrol 1999;18(4):261-62.

2. Reinberg Y, Crocker J, Wolpert J, Vandersteen D. **Therapeutic efficacy of extended release oxybutynin chloride, and immediate release and long acting tolterodine tartrate in children with diurnal urinary incontinence.** J Urol. 2003 Jan;169(1):317-9. Comment in: J Urol. 2003 Sep;170(3):928; author reply 928.
3. Scholtmeijer RJ, van Mastrigt R. **The effect of oxyphenonium bromide and oxybutynin hydrochloride on detrusor contractility and reflux in children with vesicoureteral reflux and detrusor instability.** J Urol. 1991 Aug;146(2 (Pt 2)):660-2.
4. Koff SA, Murtagh DS. **The uninhibited bladder in children: effect of treatment on recurrence of urinary infection and on vesicoureteral reflux resolution.** J Urol. 1983 Dec;130(6):1138-41.
5. Homsy YL, Nsouli I, Hamburger B, Laberge I, Schick E. **Effects of oxybutynin on vesicoureteral reflux in children.** J Urol. 1985 Dec;134(6):1168-71.
6. Casolari E. **Treatment of the so-called "minor" pediatric incontinence problems accompanied by mictional retraining with oxybutynin chloride.** Medicina Rivista dell'Enciclopedia Medica Italiana.1984 ; 1 :78-80.
7. Sureshkumar P, Bower W, Craig JC, Knight JF. **Treatment of daytime urinary incontinence in children: a systematic review of randomized controlled trials.** J Urol. 2003 Jul;170(1):196- 200; discussion 200.

The European Bladder Dysfunction Study (EBDS) **(1)**, a multi-centre prospective study, compared treatment plans for neurologically normal children with bladder-sphincter dysfunction. In Branch I of the EBDS, children with urodynamically proven urge syndrome were randomly allocated to either bladder rehabilitation with biofeedback or pharmacotherapy. In Branch II, children with urodynamically proven dysfunctional voiding were randomly allocated to either standard therapy or bladder rehabilitation with biofeedback. In both branches, all children received standard therapy, which consisted of low-dose chemoprophylaxis and treatment of constipation whenever indicated, complemented with elaborately standardized sets for explanation of the bladder-sphincter dysfunction problem and for instructions how to cope with it. Pharmacotherapy was double-blinded, either oxybutynin (0,3 mg/kg) or placebo. 216 children were enrolled in the study, 97 aged 6-12 years old in Branch I, 104 in Branch II, and 15 with non-groupable bladder-sphincter dysfunction. Clinical outcome was expressed as "cured", "same" or "worse". After 6 months, no statistically difference in outcome emerged between bladder rehabilitation and pharmacotherapy in Branch I, neither between the outcome of standard therapy and bladder rehabilitation in Branch II. The authors concluded that adding pharmacotherapy or bladder rehabilitation with biofeedback to standard therapy did not significantly improve the outcome. With standard therapy alone, approximately 65% of neurologically normal children with bladder-sphincter dysfunction could be cured.

One open label, parallel group, retrospective study **(2)** compared the efficacy of extended release oxybutynin chloride, and immediate release and long acting tolterodine tartrate in 132 children (5 to 18 years) with non-neurogenic diurnal urinary incontinence and symptoms of overactive bladder. The dose was titrated until effective. Extended release oxybutynin and long acting tolterodine were significantly more effective at reducing daytime urinary incontinence than immediate release tolterodine ($p<0.01$ and $p<0.05$, respectively). Extended release oxybutynin was significantly more effective than long acting tolterodine for complete resolution of diurnal incontinence ($p<0.05$).

The effects of the anticholinergic drugs oxyphenonium bromide and Oxybutynin hydrochloride were reviewed in a prospective study **(3)** which included 12 children aged 4.5 to 12 years old for 3 to 12 months. The results demonstrated that in this study only Oxybutynin proved to decrease detrusor contractility and the degree of reflux.

In a prospective study **(4)**, the authors treated 62 neurologically normal children aged 2 to 14 years with vesico-ureteral reflux using urodynamic techniques to identify uninhibited bladder contractions with voluntary sphincteric obstruction (dyssynergia). All children received antibiotic prophylaxis and anticholinergic drugs (including Oxybutynin). During 6 years of follow-up,

treatment of uninhibited contractions produced a 4-fold reduction in the incidence of recurrent urinary infection and tripled the rate of reflux resolution compared to controls. The authors concluded that these data suggest that uninhibited contractions with voluntary sphincter obstruction are an important prognostic finding in children with reflux, which when treated successfully can alter the disease course and may limit the need for surgical interventions.

In a retrospective uncontrolled study (5), involving 40 neurologically normal children aged 4-11 years old with vesico-ureteral reflux, 37 received Oxybutynin therapy (plus prophylactic antibiotics) for bladder hyperreflexia for 3 to 18 months. Reflux disappeared or became grade I in 62.3% of the ureters. Of the children manifesting urinary incontinence at the time of urodynamic study, reflux disappeared or became grade I in 78.6%. Reflux resolved or became grade I in 20 % of the children with no urinary incontinence. Of those patients with recurrent reflux at the onset of urinary incontinence and bladder instability, reflux resolved or became grade I in 80%. Oxybutynin therapy for hyperreflexic bladder resulted in an average increase in bladder capacity of 54.2%, which was maintained after cessation of treatment.

In another study (6), 60 patients aged 5-14 years old with obvious symptoms of unstable bladder were given 5 mg oxybutynin bid, increased to 5 mg tid after 15-20 days in patients above 6 years of age for at least 4 months. A low dose urinary disinfectant was also administered and accompanied by mictional retraining. Urge incontinence was the symptom on which the best results were achieved within the shortest period of time (by the first month of treatment) while the disappearance of bacteriuria required a greater period of time (> 3 months).

In a systematic review (7) of randomized controlled trials, investigating the treatment of daytime urinary incontinence in 5 studies, the authors identified only one trial of relevance to the current clinical care of children with daytime wetting (incomplete trial of oxybutynin versus biofeedback versus placebo) and concluded that it was not possible to identify proof of any intervention that is effective.

Assessor's Comment

The rapporteur agrees with the MAH that Oxybutynin is currently one of the most widely used antimuscarinic agents for the treatment of OAB symptoms and detrusor overactivity. In addition to its antimuscarinic activity, oxybutynin has a direct relaxing effect and paralyzing effect on smooth muscle, which could prove beneficial for the treatment of patients with vesico-ureteral reflux. However the evidence is not robust to include this indication for paediatric use of Oxybutynin.

4.2.3 Oxybutynin and enuresis in children

The MAH has provided an overview of 25 studies, including an MAH sponsored clinical investigation, conducted in paediatric patients with intermittent nocturnal incontinence (otherwise defined as enuresis). It is noted that drug therapy is usually proposed after conservative measures have not improved the disorder as detrusor hyperactivity is regarded as a pathogenic factor in nocturnal enuresis. (Please note that the studies are referenced in the text of section 4.2.3 by the numbers in the list below).

1. Van Hoeck KJ, Bael A, Van Dessel E et al. **Do holding exercises or antimuscarinics increase maximum voided volume in monosymptomatic nocturnal enuresis? A randomized controlled trial in children.** J Urol 2007 ; 178 : 2132-2136
2. Laboratoires DEBAT **Internal report – DITROPAN. Clinical investigation – enuresis with diurnal micturitional trouble in children.** January 1983.
3. Thompson IM, Lauvetz R. **Oxybutynin in bladder spasm, neurogenic bladder and enuresis.** Urol. 1976 Nov;3(5):452-4.
4. Lovering JS, Tallett SE, McKendry JB. **Oxybutynin efficacy in the treatment of primary enuresis.** Pediatrics. 1988 Jul;82(1):104-6.
5. Sehgal R, Paul P, Mohanty NK. **Urodynamic evaluation in primary enuresis: an investigative and treatment outcome correlation.**J Trop Pediatr.2007 Aug;53(4):259-63.

6. Kilic N, Balkan E, Akgoz S, et al. **Comparison of the effectiveness and side-effects of tolterodine and oxybutynin in children with detrusor instability.** *Int J Urol* 2006;13(2): 105-8.
7. Varan B, Saatçi U, Ozen S, Bakkaloğlu A, Beşbaş N. **Efficacy of oxybutynin, pseudoephedrine and indomethacin in the treatment of primary nocturnal enuresis.** *Turk J Pediatr.* 1996 Apr-Jun;38(2):155-9.
8. Marconi AM, Bocciardi A, Roggia A, Fava C. **Oxybutynin chloride in enuresis. Randomized controlled study.** *Urol.* 1984. 51(2):262-3.
9. Marconi AM, Felici E, Roggia A, Torelli F. **[Anticholinergic treatment in the therapy of primary enuresis. Effectiveness of oxybutynin chloride in a controlled clinical study of 58 patients]** *Pediatr Med Chir.* 1985 Jul-Aug;7(4):573-6.
10. Yuksek MS, Erdem AF, Atalay C, Demirel A. **Acupressure versus oxybutynin in the treatment of enuresis.** *J Int Med Res.* 2003 Nov-Dec;31(6):552-6.
11. Koşar A, Arikan N, Dinçel C. **Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna—a clinical and urodynamic study.** *Scand J Urol Nephrol.* 1999 Apr ;33(2) :115-8.
12. Grasseti F. et al. **Enuresis: an aetiopathogenic study with oxybutynin chloride.** *Ped oggi.* 1986. 6(1):47-51.
13. De Castro R, Casolari E, Ricci S. **Use of oxybutynin chloride (Ditropan) in treatment of enuresis.** *Riv Ital Ped.*1985;11:208-11.
14. Buttarazzi PJ. **Oxybutynin chloride (Ditropan) in enuresis.** *J Urol.* 1977 Jul;118(1 Pt 1):46.
15. Esmaeili M, Esmaeili M. **Combined treatment with oxybutynin and imipramine in enuresis.** *Iran J Med Sci* 2008; 33 (1): 12-16
16. Chertin B, Koulikov D, Abu-Arafeh W et al. **Treatment of nocturnal enuresis in children with attention deficit hyperactivity disorder.** *J Urol* 2007 ; 178 : 1744-1747
17. Lee T, Suh HJ, Lee HJ, et al. **Comparison of effects of treatment of primary nocturnal enuresis with oxybutynin plus desmopressin, desmopressin alone or imipramine alone: a randomized controlled clinical trial.** *J Urol* 2005; 174 (3): 1084-7.
18. Tahmaz L, Kibar Y, Yildirim I, Ceylan S, Dayanç M. **Combination therapy of imipramine with oxybutynin in children with enuresis nocturna.** *Urol Int.* 2000;65(3):135-9.
19. Caione P, Arena F, Biraghi M et al. **Nocturnal enuresis and daytime wetting: a multicentric trial with oxybutynin and desmopressin.** *Eur Urol.* 1997;31(4):459-63.
20. Neveus T. **Oxybutynin, desmopressin and enuresis.** *J Urol* 2001; 166 (6): 2459-62.
21. Casolari E. **Treatment of the so-called “minor” pediatric incontinence problems accompanied by mictional retraining with oxybutyninc chloride.** *Medicina Rivista dell'Enciclopedia Medica Italiana.* 1984 ; 1 :78-80.
22. Laurenti C, de Dominicis C, Dal Forno S, Iori F, Franco G, Bellino M. **Medical treatment of essential enuresis with oxybutynin hydrochloride and imipramine.** *Minerva Urol Nefrol.* 1987 Jul-Sep;39(3):195-200.
23. Azhir A, Gheissari A, Fragzadegan Z et al. **New treatment protocol for primary nocturnal enuresis in children according to ultrasound bladder measurements.** *Saudi Med J* 2008; 29 (10): 1475-1479
24. Vermandel A, de Wachter S, Wyndaele JJ. **Refractory monosymptomatic nocturnal enuresis: a combined stepwise approach in childhood and follow-up into adolescence, with attention to the clinical value of normalizing bladder capacity.** *BJU Int.* 2005 Sep ;96(4) :629-33.
25. Rodríguez do Forno A, Ariceta Iraola G. **Results of a therapeutic strategy against monosymptomatic nocturnal enuresis.** *An Esp Pediatr.* 2001 Jan;54(1):38-43.

In a published double-blind randomized controlled study (1) the efficacy of holding exercises and/or antimuscarinics (oxybutynin vs. placebo) for increasing maximum voided volume in

prepubertal children with monosymptomatic nocturnal enuresis was investigated. 149 children ranging in age from 5.9 to 12.7 years were randomly allocated to 5 groups, namely holding exercises with placebo (group A), holding exercises with oxybutynin (group B), placebo alone (group C), oxybutynin alone (group D) and alarm treatment (controls, group E). Study medication, holding exercise procedures and alarm treatment were administered for 12 weeks. The authors concluded that in the treatment of children with monosymptomatic nocturnal enuresis, maximum voided volume can be increased significantly through holding exercises, but not with oxybutynin alone. Compared to controls, increasing maximum voided volume had a minimal effect on monosymptomatic nocturnal enuresis.

The MAH provided the internal report of sponsored clinical investigation on “Enuresis with micturitional trouble in children” **(2)**. This study was designed to be a double-blind crossover study comparing one month of treatment with Oxybutynin 5mg twice a day vs. one month placebo in children older than 4 years of age. The primary inclusion criterion was primary enuresis with or without diurnal micturitional trouble (pollakiuria, urgency or incontinence) of 2 or more episodes per week. The study’s efficacy outcomes were the number of nocturnal urinary leakage episodes per week and the frequency of micturations and diurnal incontinence; adverse reactions and tolerance were also documented. The trial was conducted in 2 locations; however after the inclusion and analysis of 18 cases in one centre, with the exception with only one case, there was no difference between placebo and Oxybutynin and the investigator terminated the study as the results did not demonstrate that in primary enuresis the drug is not indicated. The other study however included 61 patients and demonstrated that treatment with Oxybutynin reduces the number of enuretic episodes and micturations as well as diurnal incontinence. Both investigators concluded that “Oxybutynin is not the drug of choice for the treatment of primary enuresis, but that it is very effective in the treatment of enuresis with diurnal mictional trouble due to an immature bladder function”.

In a double-blind placebo controlled crossover study **(3)**, 30 enuretic children (ages not defined) with no neurological disease were administered 5 mg oxybutynin twice daily for 4 months. Oxybutynin markedly increased the vesical volume at the onset of the first reflex contraction, whereas there was no significant difference between the mean baseline and placebo values. Besides, oxybutynin was obviously superior to placebo in diminishing frequency, nocturia and urge incontinence.

On the contrary, the effectiveness of oxybutynin in the treatment of primary enuresis was not demonstrated in a double-blind randomized crossover study **(4)** involving 30 children 6 years to 14 years of age, with primary enuresis and no daytime incontinence. The patients were treated with 10 mg of oxybutynin for 28 days. Before or after the treatment period, all children received placebo for 4 weeks. There were no differences in findings between boys and girls or between children who had previously taken imipramine and those who had not. The study showed no evidence that oxybutynin is effective in treating primary enuresis considering the frequency of bed-wetting episodes.

Six randomized controlled studies involving more than 300 enuretic children evaluated the efficacy of oxybutynin compared to other treatments: other antimuscarinic agents (flavoxate, dicyclomine), antidepressants (imipramine, indomethacin), a sympathomimetic amine (pseudoephedrine), or other therapies (behavioural therapy, acupuncture).

A prospective randomized study **(5)** included 119 patients age 5–14 years to evaluate the role of urodynamics in the management of primary enuresis and to compare the effectiveness of multidimensional behavioural therapy with pharmacological therapy. In patients with normal urodynamics, with behavioural therapy, complete remission was more common and with lesser relapse rate as compared to pharmacological therapy. Although this difference was statistically not significant probably due to small numbers, a trend was noted. In those with abnormal urodynamics, oxybutynin at doses 5mg bid to 5 mg tid was found to be superior to multidimensional behavioural therapy, flavoxate 3 mg tid and imipramine 0.9 to 1.5 mg/kg after 3 months of treatment and one month of tapering over.

In another prospective randomized study **(6)** with 60 patients 3 to 13 years old, oxybutynin at

doses of 0.4 mg/kg/d divided into 3 doses and administered for 6 to 31 months to children with detrusor instability and enuresis associated with daytime incontinence, was found to be equally effective as oral tolterodine 0.1/mg/kg/d (children < 5 years) or 1 mg bid (children > 5 years) but side-effects were more common with oxybutynin.

In a third randomized study **(7)**, the efficacy of oxybutynin (0.5 mg/kg), pseudoephedrine (2mg/kg) and indomethacin (2mg/kg) treatment was investigated in 29 patients aged 6-15 years old with primary nocturnal enuresis. After 4 weeks, oxybutynin and indomethacin did not cause a statistically significant difference in the number of dry nights but patients treated with pseudoephedrine had a significant increase in the number of dry nights.

In the two more randomized studies **(8, 9)**, a total of 92 enuretic children aged 5 to 16 years received oxybutynin 5 mg tid versus dicyclomine 20 mg tid for 8 weeks. Oxybutynin proved to be superior to dicyclomin in both studies considering the number of wet nights as primary outcome.

Finally, the efficacy of oral oxybutynin (0.4 mg/kg/d) in the treatment of enuresis was also compared to acupressure in one randomized study **(10)** involving 24 children aged 4 to 13 years (one child being under 5 years). After 6 months of treatment, complete and partial responses (evaluated in terms of number of wet nights per week) were seen in 83.3% and 16.7%, respectively, of patients treated with acupressure, and in 58.3% and 33.3% respectively of children who received oxybutynin; but even if the percentage was higher in the group treated with acupressure, there was no statistical significant difference.

In one uncontrolled open-label study **(11)** from 36 patients with enuresis non-responsive to imipramine, 17 were subsequently treated with oxybutynin hydrochloride after been urodynamically assessed. It was shown that the majority of the patients (88.2%) with inadequate bladder storage function were responsive to a minimum of 1-month regimen of 15 mg daily oxybutynin. The treatment in patients with normal bladder function at the same dosage was generally unsuccessful.

In another uncontrolled open-label study **(12)** the effect of Oxybutynin was evaluated in 35 enuretic patients aged 5-18 years. Oxybutynin (tablets or syrup depending on age, 5-30mg/day) proved to be effective, particularly in the treatment of cases characterized by disinhibited contractions and unstable bladder. Similarly in a study **(13)** of 30 enuretic patients aged 6-15 years which were treated with 5mg of Oxybutynin bid to tid and toilet training, a total or partial success of the treatment based on the number of dry night was demonstrated in 73% of the patients. Finally Buttarazzi in 1977**(14)** demonstrated that of 39 enuretic patients aged 5-28 years who were non-responsive to imipramine, 31 achieved significant nocturnal control with oral Oxybutynin (> 12 yr: 5 mg tid decreased by 5 mg daily each month, < 12 yr: 5 mg bid decreased by 5 mg daily each month).

In 5 randomized controlled trials (in total 515/471 analyzed enuretic children aged 5 to 15 years), the efficacy of oxybutynin in combination with other drugs (either anticholinergic or antidepressant) was evaluated after different treatment durations (from 1 to several months). All the studies demonstrated that oxybutynin used in combination with imipramin or desmopressin was more effective than each drug used alone **(15, 16, 17, 18, 19)**.

In a non-randomized study **(20)** (5-group, 2-week period, mean age of patients 10.6±3.2 years), renal concentrating capacity and functional bladder capacity were compared between 55 dry children who served as controls, and children with monosymptomatic enuresis who responded to desmopressin only (n=27), oxybutynin only (n=11), combination of desmopressin and oxybutynin (n=7), or were resistant to all treatment alternatives (n=23). The author's conclusion was that children responding to oxybutynin have small bladders and probably hyperactive detrusors, whereas those responding to desmopressin or who need both drugs to achieve dryness have polyuria.

In a second study **(21)**, the authors report their experience in treating 64 children 5 to 15 years with essential enuresis using a combination of imipramine with oxybutynin chloride (5 mg tablet twice daily for 30 days followed by another 20 to 30 day cycle in responders (cessation of imipramine and evening dose of oxybutynin chloride only). The results obtained in 50 analyzed

children were particularly encouraging both during and after cessation of the treatment. In 74% of children a positive response was obtained with over 90% of dry nights, and in 18% a partially positive result (60-90% of dry nights). No long-term recurrence of enuresis (after 4-6 months) was observed in 88% of the children showing a positive result.

Four more studies using combined approaches (including oxybutynin) were also included in the literature review provided by the MAH.

In a first study (22), 30 enuretic patients aged 5-15 years were administered oxybutynin for 3 months and miction retraining. One month after the suspension of treatment, a complete success was achieved in 60% of the cases and 20% had good results with a reduction by at least 60% of the enuretic episodes. The authors underlined however the preeminent role of toilet training to maintain the good results obtained.

The objective of the second study (23) including 52 children (31 analyzed children, aged 6-12 years old, treated for 3 months) was to evaluate the response rate of various modalities of therapy in primary nocturnal enuretic children according to the ultrasound bladder volume and wall thickness index (BVWI) measurements. Based on BVWI they were divided into 3 groups: one was treated with oral desmopressin (0.1 mg/d) and oxybutynin (5 mg/d); another with oral desmopressin and the last one with oral desmopressin (0.1 mg/d) accompanied by double-voiding technique and scheduled voiding. Significant reductions in mean bed-wetting frequency before and after first treatment cycle were observed in all groups. The best response rates were obtained in the group treated with oral desmopressin and oxybutynin. The authors concluded that the proposed treatment representation according to ultrasound BVWI measurements achieves favourable response rates in children with primary nocturnal enuresis.

The objective of the third study (24) was to assess the importance of normalizing bladder capacity to the age-expected capacity in children with refractory monosymptomatic nocturnal enuresis, and to evaluate the long-term results when these children grow into adolescence. The study included 34 children aged 6-15 years (mean age of 9.5) with refractory monosymptomatic nocturnal enuresis; all were treated for more than 5 years earlier for their monosymptomatic nocturnal enuresis using a combined stepwise approach, consisting of retention control training, oxybutynin and an enuresis alarm. Data of 27 analyzed children were obtained on their enuretic state, night-time voiding behaviour and bladder capacity. This combined stepwise approach improved enuresis, but normal night-time bladder behaviour in adolescence and adulthood was only achieved in some. Furthermore, about a fifth still had some enuretic episodes.

The aim of fourth study (25) was to evaluate several therapies introduced progressively to treat monosymptomatic nocturnal enuresis in 117 included children. Eighty-four patients, aged 6 to 14 years old, were studied. The 6 to 7 year old were treated with desmopressin, and oxybutynin was added in nonresponders (n=13). If enuresis persisted, a bladder alarm was given. Children over 7 years of age were randomly divided and treated with alarm or alarm plus desmopressin. Non-responders were treated with desmopressin alone. In children aged 6-7 years the cumulative response was 72%. Those who wetted themselves less responded to desmopressin. In children over 7 years of age, response to alarm was 73.3% and response to alarm plus desmopressin was 58.6%. In non-responders the cumulative response after desmopressin treatment increased to 80% and 62% respectively. In the group of 6 to 7 year old, desmopressin was indicated as first line therapy. Treatment efficacy was increased by adding oxybutynin especially in the children who wetted themselves the most. In children over 7 years of age alarm was the most effective treatment and relapses were fewer. No advantages were observed with the combination of alarm and desmopressin.

Assessor's Comment

In the studies provided by the applicant conflicting evidence verifies that in enuretic children the effect of treatment with Oxybutynin depends on the symptomatology of the condition. This is highlighted particularly in the recent randomized double-blind controlled study (1) in prepubertal children with monosymptomatic nocturnal enuresis which demonstrated that treatment with Oxybutynin without holding exercises did not increase holding exercise volume or maximum

voided volume after 12 weeks of treatment. Data for the literature actually suggest that Oxybutynin is more active in selected children, possibly as second line therapy for nocturnal enuresis related to detrusor overactivity, which would be expected to result in daytime as well as night-time wetting.

4.3 Discussion of clinical efficacy

The management of neurogenic bladder sphincter dysfunction in children has undergone major changes over the years. The introduction of clean intermittent catheterisation (CIC) has revolutionised the management of children with neurogenic bladder. Pharmacologic therapy plays an integral role in the treatment of patients with neurogenic bladder dysfunction. Treatment usually centres around 3 major elements: the use of antibiotics to prevent infection, the use of anticholinergic medications to relax the bladder and to increase storage capacity, and the use of alpha agonists to attempt to improve continence. At present, oxybutynin, tolterodine, trospium and propiverine are the most frequently used drugs. The efficacy of oral Oxybutynin has been demonstrated in several studies by reducing the incidence of uninhibited bladder contractions. The other forms of administration have not been investigated in the studies submitted under this European work-sharing procedure and therefore extension of their use in the neurogenic paediatric OAB population is not currently recommended. The rapporteur agrees with the MAH that from the data provided oral oxybutynin at the usual dosages is effective in neurogenic bladder in children over 5 years.

Regarding the use of Oxybutynin in daytime lower urinary tract conditions, the paediatric studies provided by the MAH are of variable design quality and limited in terms of the number of patients investigated. The rapporteur agrees with the comments that “there is a need to prove exactly which groups of children with this type of functional incontinence problems can or must not be treated with antimuscarinic drugs.”

Considering the data submitted by the MAH, the efficacy of Oxybutynin in paediatric patients with enuresis remains controversial. In one Cochrane report (Glazener et al 2003), the authors reviewed the efficacy of drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) including oxybutynin (4 studies were included and 8 excluded). They concluded that there was insufficient evidence to judge if these drugs (including oxybutynin) were effective in enuresis. The rapporteur concludes that treatment with Oxybutynin could be proven beneficial in selected paediatric patients with enuresis due to detrusor overactivity, if other conservative therapeutic interventions have failed.

4.4 Overview of safety

The list of additional references in Oxybutynin paediatric clinical trials used for reviewing the safety of the treatment in children with different low urinary tract dysfunctions can be found below. As part of this list, 7 published case-reports associated with adverse reactions to Oxybutynin treatment are also included. (Please note that the studies are referenced in the text of this section 4.4 by the numbers on the list below. The studies which have been listed in previous sections are referenced by the author’s name and original number and page).

1. Giramonti K.M., Kogan B.A., Halpern L.F. **The Effects of Anticholinergic Drugs on Attention Span and Short-Term Memory Skills in Children.** *Neurourology and Urodynamics* 2008; 27:315–318.
2. Hill LA. **Pharmacokinetics and safety of transdermal oxybutynin for treatment of neurogenic bladder in adults and children.**(Conference abstract 2008)
3. Um JM, Kim KM. **Efficacy and Tolerability of Extended-release Oxybutynin in Children with a Neurogenic Bladder.** *Korean J Urol.* 2007 Oct;48(10):1064-1068 (Korean)

4. Van Arendonk KJ. **Frequency of wetting is predictive of response to anticholinergic treatment in children with overactive bladder.** Urology. 2006 May;67(5):1049-53; discussion 1053-4.
5. Van Arendonk KJ. **Improved efficacy of extended release oxybutynin in children with persistent daytime urinary incontinence converted from regular oxybutynin.** Urology. 2006 Oct;68(4):862-5.
6. Myung KK, Wook LS **Efficacy and tolerability of tolterodine compared to oxybutynin in children with a neurogenic bladder.** Korean J Urol. 2005 Jun;46(6): 598-603 (Korean)
7. Sommer B, O'Hara R, Askari N, Kraemer H and Kennedy W. **The effects of oxybutynin treatment on cognition in children with diurnal incontinence.** J Urol. Jun 2005;Vol. 173, 2125–2127.
8. Mueller D, Roehr CC, Eggert P **Comparative tolerability of drug treatment for nocturnal enuresis in children.** Drug Saf. 2004;27(10):717-27. (abstract)
9. Saito M, Watanabe T, Tabuchi F, Otsubo K, Satoh K, Miyagawa I. **Urodynamic effects and safety of modified intravesical oxybutynin chloride in patients with neurogenic detrusor overactivity: 3 years experience.** Int J Urol. 2004 Aug;11(8):592-6.
10. Bolduc S, Upadhyay J, et al **The use of tolterodine in children after oxybutynin failure.** BJU International 91, 2003; 398 – 401.
11. Miller D. **High dose intravesical oxybutynin: is it more efficacious?** (Conference abstract 1998)
12. Palmer L, Zebold K, Firlit C, Kaplan W. **Complications of intravesical oxybutynin chloride therapy in the pediatric myelomeningocele population.** J Urol.1997; 157:638-640.
13. Von Zweigbergk M, Nordin B, Jonsson S. **Intravesical oxybutynin in children with meningocele. Efficient treatment with few side effects.** Lakartidningen. 1996 Oct 9;93(41):3573-6. (Swedish)
14. Madersbacher H, Stöhrer M, Richter R, Burgdörfer H, Hachen HJ, Mürtz G. **Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyperreflexia.** Br J Urol. 1995 Apr;75(4):452-6. (abstract)
15. Dursun E et al **The evaluation of the side-effects of oral oxybutynin chloride.** (Abstract 1994)
16. Jonville AP, Dutertre JP, Autret E, Barbellion M. **(Adverse effects of oxybutynin chloride (Ditropan). Evaluation of the official survey of regional pharmacovigilance centers).** Therapie. 1992 Sep-Oct;47(5):389-92. (French)
17. Jonville AP, Dutertre JP, Barbellion M, Autret E. **(Adverse effects of oxybutynin chloride (Ditropan) in pediatrics.)** Arch Fr Pediatr. 1993 Jan;50(1):27-9. (French).
18. Malone-Lee J. **The clinical efficacy of oxybutynin.** Rev Contemp. Pharmacother. 1994; 5:195-202.
19. Kasabian N, Bauer SB, Dyro FM, Colodny AH, Mandell J, Retik AB. **The prophylactic value of clean intermittent catheterization and anticholinergic medication in newborns and infants with myelodysplasia at risk of developing urinary tract deterioration.** Am J Dis Child. 1992 Jul;146(7):840-3.
20. Massad C, Kogan BA, Trico-Rocha FE. **The Pharmacokinetics of intravesical and oral oxybutin chloride.** J Urol.1992; 148: 595-597.
21. Persson-Jünemann C, Seemann O, Köhrmann KU, Jünemann KP, Alken P. **Comparison of Urodynamic findings and response to Oxybutynin in Nocturnal enuresis.** Eur Urol 1993; 24(1):92-96.
22. Appell RA, Deutsch JS et al **Retrospective evaluation of the efficacy and safety of oxybutynin.** South Med J 1990 ; 83(9) 2S-87 (Abstract)
23. Yokoyama E et al **Clinical effect of oxybutynin hydrochloride (1 mg / tablet).** Acta urologica Japonica 1990; 36(7); 869-76, (Japanese)

24. Baigrie R., Kelleher J, Fawcett D and Pengelly W. **Oxybutynin: is it safe?** BJU 1988; 62: 319-322.
25. Purcell MH, Gregory JG. **Intermittent catheterization: evaluation of complete dryness and independence in children with myelomeningocele.** J Urol. 1984 Sep;132(3):518-20. (abstract)
26. Brooks ME, Braf ZF **Oxybutybib Chloride (Ditropan) –clinical uses and limitations.** Paraplegia. 1980 Feb;18(1):64-8.
27. Gulsun M, Pinar M, Sabanci U. **Psychotic disorder induced by oxybutynin presentation of two cases.** Clin Drug Invest. 2006;26(10): 603-6.
28. Swana HS, Youmans SL, Kogan BA, Bogetz MS. **Hallucinations after hypospadias repair.** J Pediatr Surg. 2006 Mar ;41(3) : E33-E35.
29. Valsecia ME, Malgor LA, Espindola JH, Carauni DH. **New adverse effect of oxybutynin: “night terror”.** Ann Pharmacother. 1998 Apr;32(4): 506.
30. Hamdan AG, Nixon M. **Anticholinergic psychosis in children: A case report.** Hosp Community Psychiatry. 1991 Feb;42(2):191-3.
31. Choulot JJ, Mensire A, Saint Martin J. **Surdosage en atropiniques et syndrome confusionnel. (Overdose of anticholinergic agents and confusional syndrome).** Ann Pediatr Paris. 1989 Dec;36(10):714.
32. Coskun S, Yüksel H, Onag A. **Is attempting suicide an adverse effect of oxybutynin in a child with enuresis nocturna ?** Pediatr Emerg Care. 2001;17(5) :398
33. Autret E, Jonville AP, Furet Y, Breteau M. **Beware of atropinic drugs in pediatrics!** Arch Fr Pediatr. 1987 Nov;44(9):820-22. (French)
34. Gish P, Mosholder AD, Truffa M, Johann-Liang R. **Spectrum of central anticholinergic adverse effects associated with oxybutynin: comparison of pediatric and adult cases.** J Pediatr. 2009 Sep;155(3):432-4.
35. t’Veld BA, Kwee-Zuiderwijk WJ, van-Puijenbroek EP, Stricker BH. **(Neuropsychiatric adverse effects attributed to use of oxybutynin).** Ned Tijdschr Geneesk. 1998 Mar 14;142(11):590-2. (Dutch).

Assessor’s Comment

It is noted that a number to the publications summarized by the MAH are conference abstracts and some are articles in a language other than English for which only the abstract is provided. Therefore there are limitations on the amount of information which could be assessed from those types of publications.

4.4.1 Adverse events in clinical trials

Adverse events (AEs) in the oxybutynin studies included: constipation, nausea, dry mouth, dizziness, headache, drowsiness, hallucinations, blurred vision, facial flushing, dry skin and skin reaction. Epistaxis was also identified in 3 published studies for which the authors suggested that it was related to drying of the nasal mucosa due to the anticholinergic effect. Withdrawal from the studies has been very variable and some authors suggest that apart from the severity of the anticholinergic side effects of treatment, the number of drop-out patients is associated with the lack of a therapeutic effect of the treatment. The MAH concluded that “Analysis of adverse events by age did not show a difference in frequency among the age groups by treatment group.” No deaths were reported in the clinical trials performed in the pediatric population in different indications with oxybutynin oral, transdermal or intravesical. No overdose was reported in any study.

Some of the available information is summarized individually below.

Minimal side effects were noted with prophylactic use over 5 years of clean intermittent catheterization and oxybutynin in newborn and infants at risk of urinary tract deterioration, and

no adverse effects of clean intermittent catheterization were detected. However it is noted that 3(28%) stopped the instillation and were removed from the study due to side effect i.e. facial flushing, dry mouth and haematuria with febrile urinary tract infection **(19)**

A retrospective review of patients with daytime wetting who switched from oxybutynin to oxybutynin extended-release (ER) included 27 patients (age range: 3.5-16.7 years). Seven children developed a new side effect after switching to oxybutynin (ER), with flushing occurring in 3, new onset of constipation occurring in 2, fatigue in 1, and dry mouth in 1. Nine patients had no side effects with either medication, two had no change in their side effects, and three had a change in side effects. **(4)**

Regarding cognitive development, results from 14 children (5 to 11 years) in a double blinded cross-over trial **(1)** suggested that long-acting oxybutynin and tolterodine do not have a deleterious effect on children's attention and memory. Similarly results of a study designed to assess the effect of oxybutynin on cognitive function in children (n=25) showed no evidence that oxybutynin was associated with cognitive impairment in the treatment group evaluated. **(7)**

The side effects of oxybutynin often include atropinic and allergic reactions. All the side effects of Ditropan reported to the French Regional ADR monitoring centers and to the pharmaceutical firm Debat between January 1985 and June 1990 were analyzed in 2 published papers **(16, 17)**. The side effects were 4 times more frequent in children (1/4,000 prescriptions) than in adults. The authors concluded that the higher frequency of atropinic reactions in children may be due to the higher dosage of the drug used and/or to differences in hydroxylation metabolism that is genetically determined in adults.

Oxybutynin has been compared to other drugs in the published and the MAH provided comparison data with tolterodine from 5 published papers. In a prospective study, safety data of tolterodine and oxybutynin from 60 children (3-13 years) with detrusor instability followed for at least 6 months were reviewed. Adverse events were significantly lower in the tolterodine group (13 events in 13 patients) compared to the oxybutynin group (27 events in 20 patients; $P = 0.027$) **(Kilic, Reference 6 at page 17)**.

In another study **(6)**, the adverse effect of oral oxybutynin compared to tolterodine in children was investigated. Of the 16 patients (3-11 years), side effects developed in 12 (75%) during the oxybutynin treatment with mainly diarrhea, nausea, hallucination and hot flush whereas only 2 (13%) developed side effects during the tolterodine treatment ($p=0.001$).

The side-effects with oxybutynin and tolterodine were also compared in a crossover study **(10)**. The incidence of side-effects including dry mouth ($P<0.001$), constipation, blurred vision, mood swings, dizziness, headache, flushing and fatigue was decreased by 50–75% when patients were crossed-over to tolterodine. Side-effects were graded as moderate or severe in 89% (62/70) in the oxybutynin group, compared with 31% (eight of 26) in the tolterodine group.

The tolerability of immediate and ER oxybutynin, and long acting tolterodine tartrate in children with nonneurogenic diurnal urinary incontinence and symptoms of overactive bladder was investigated in 86 girls and 46 boys (5-18 years). This study found no statistically significant differences among the 3 treatment groups regarding the presence of peripheral anticholinergic side effects (dry mouth, dry skin, skin flushing and constipation) and central nervous system effects (mood changes, irritability, sleepiness, sleeplessness and confusion). **(Reinberg, reference 2 at page 15)**

Finally a systematic review of randomized controlled trials including tolterodine (2 studies), days time alarms (1 study), imipramine (1 study) and one prospective controlled study comparing biofeedback and oxybutynin or placebo. Adverse events occurred more frequently with tolterodine treatment than with oxybutynin. Side effects included stomach pain, insomnia, bad temper, dizziness and nausea. **(Sureshkumar, reference 7 at page 15)**

46 children with myelomeningocele were managed by nonsterile intermittent catheterization to

achieve continence **(25)**. All were given maximum therapeutic doses of supplemental medication (oxybutynin chloride, propantheline bromide, pseudoephedrine) to improve dryness. 9 children experienced side effects from supplemental medication severe enough to warrant discontinuation; these were mainly on oxybutynin and included drowsiness, hyperactivity, vomiting, mood changes, flushing and decreased sweating in summer months.

In a randomized, double-blind, multicentre trial **(14)**, comparing trospium chloride versus oxybutynin, 95 patients with spinal cord injuries and detrusor hyperreflexia were studied. The percentage of patients who reported severe dryness of the mouth was considerably lower (4%) in those receiving trospium 2 x 20 mg/day than in those receiving oxybutynin 3 x 5 mg/day. Withdrawal from treatment was also less frequent in those receiving trospium (6%) than in those receiving Oxybutynin (16%).

Other formulations of oxybutynin delivery have also been reviewed.

In a pharmacokinetics and safety study, 56 patients with neurogenic bladder who were treated with transdermal oxybutynin had low ratios of N-desethyloxybutynin to oxybutynin in plasma and experienced a low incidence of anticholinergic adverse events. **(2)**

Safety data from 55 patients (6-15 years) with neurogenic bladder treated by oxybutynin transdermal and oxybutynin oral were reviewed **(Cartwright, reference 11 at page 11)**. Mild vasodilatation was the only related AE observed among 13 patients receiving oxybutynin oral. Most of the AEs (n=12/42) related to transdermal application were mild skin reactions but none result in study withdrawal. No treatment effects on the central nervous system were observed.

8 children (5-18 years) with marked systemic side effects previously reported to oral oxybutynin were investigated by receiving intravesical instillation and compared the pharmacokinetics of both routes of delivery. Only 2 patients underwent this method of instillation result in side effects i.e transient diarrhea, facial flushing in one patient and mild dizziness and blurred vision in the second patient. The authors reported that this lack of significant systemic side effects despite high plasma concentrations suggests that the metabolite generated after oral administration may be mainly responsible for the side effects, and that intravesical instillation results in minimal side effects. **(20)**

In 39 children (0.5-18 years) with myelodysplasia and neurogenic bladder disturbance, intravesical oxybutynin 0.1 mg/kg twice daily was administered as a sterile pharmacy-produced solution. Anticholinergic side effects were reported by 2 patients. In 1 of them dose reduction by half maintained a good effect on incontinence but abolished side effects. The follow-up period was 0.66-5 years (mean 2.25). Seven children under 2 years of age were started on oxybutynin therapy. One patient was later lost to follow-up while the rest have been followed for 1.5–3.5 years without side effects. **(Amark, reference 16 at page 11)**

Intravesical oxybutynin was found to cause significantly less systemic side effect than oral oxybutynin in a prospective study in 15 children (0.6-13.8 years) with neurogenic bladder. Of the 7/15 children included in the trial due to the intolerable side effects of oral oxybutynin therapy, 3 reported no side effect and 4 had only minimal side effects (facial flushing and dry mouth). In 1 child transient supraventricular tachycardia noted shortly after starting intravesical therapy but did not recur after the reintroduction of intravesical oxybutynin. The significantly lower AUC ratio of the Ndesethyl metabolite over Oxybutynin, due to a reduced first pass metabolism, was the explanation the clinically relevant reduction of side effects that characterizes intravesical compared with oral oxybutynin therapy. **(Buyse, reference 18 at page 11)**

23 children (5-11 years) with myelodysplasia were treated with intravesical oxybutynin **(12)**. In 7/23 patients (28%) treatment was discontinued and oral formulations were resumed or other therapy was required due to side effects including agoraphobia, hyperactivity, dizziness, flushing, dry mouth, insomnia, rash, nausea, headache and bladder pain at instillation.

One case of ileus in a 14 year old child participating in 3-year follow-up study to assess side-effects of modified intravesical oxybutynin with hydroxypropylcellulose has been reported **(9)**.

4.4.2 Other published articles on Oxybutynin's safety

In all 7 of the published case-reports articles (27-33) the development of psychiatric disorders in children after administration of Oxybutynin in various doses is reported. In all patients discontinuation of the treatment resulted in total recovery.

Finally 2 safety review studies were identified by the MAH.

The objective of one publication (34) was to identify and characterize cases of anticholinergic central nervous system (CNS) effects in pediatric patients as compared with adult patients treated with oxybutynin. The authors reviewed Food and Drug Administration (FDA) postmarketing reports of CNS anticholinergic effects in association with oxybutynin. Pediatric (n = 37) and adult (n = 143) patients in whom anticholinergic CNS symptoms developed during treatment with oxybutynin were identified from the FDA's database as of January 2007. A significant portion of all AE reports for oxybutynin involve a CNS adverse event (31% of pediatric reports and 11% of adult reports). The most common indication reported for pediatric use was treatment of enuresis followed by treatment of neurogenic bladder. The median age was 6 years (range 15 months to 16 years). 30% (excluding accidental exposures) of patients were prescribed oxybutynin under the age of 5 years. In most cases the dose was 10 mg/d, and the events occurred within 1 month of beginning oxybutynin treatment. Hallucination was the most common CNS event reported among pediatric patients, followed by agitation, sedation, confusion, amnesia, and abnormal dreams (ie, nightmares). The authors concluded that CNS stimulation during an oxybutynin treatment was prominent in the paediatric cases.

In the second publication (35) from the Netherlands, since 1988, the Pharmacovigilance Foundation Lareb and the Inspectorate for Health Care have received 17 reports of patients with neuropsychiatric AEs attributed to the use of oxybutynin. These concerned 6 males and 11 females and 6 out of the 17 patients were children under the age of 13. In all cases patients had been treated according to a normal dosage regimen. Complaints included hallucinations, psychosis, concentration and orientation problems, apathy, listlessness, agitation, drowsiness and sleepiness. Symptoms improved or disappeared in all patients after dose reduction or withdrawal of oxybutynin.

4.4.3 Postmarketing paediatric experience

The two sanofi-aventis postmarketing pharmacovigilance databases were searched for worldwide medically confirmed cases up to 30 September 2009, reported in pediatric population (0-18 years) exposed to oxybutynin. All captured cases are divided into 3 age groups. First group is included children over 5 years of age (5 -17 years included). Second group is composed by the children with unspecified age: the patient's age in these cases was reported as child. Third group is included children under 5 years of age (0-4 years included).

Overall, 188 spontaneous medically confirmed cases were reported in pediatric population. Among 188 spontaneous cases involving a total of 341 reactions, 59 cases were serious and 129 cases were non-serious. All cases distributed by age range and seriousness are tabulated below:

	Serious cases	Non serious cases	Total cases
0 – 4 years	5	18	23
5 – 17 years	53	103	156
Unspecified age	1	8	9
Total cases	59	129	188

In children aged 5 to 17, the most frequent ADRs were Psychiatric disorders (40 cases and 66 reactions), Nervous system disorders (26 cases and 50 reactions), Skin and subcutaneous

tissue disorders (19 cases and 28 reactions), Eye disorders (13 cases and 25 reactions), and Gastrointestinal disorders (10 cases and 20 reactions). The psychiatric disorders commonly included hallucinations (19 reactions), nightmare (7 reactions), aggression (5 reactions), and anxiety (5 reactions), while the Nervous system disorders were mainly headache (10 reactions), convulsion (7 reactions), somnolence (5 reactions).

In children 0-5 years, although the use of oxybutynin in children, under 5 years of age is not recommended, Twenty three (23) case reports with 54 reactions (18 non-serious cases [35 reactions] and 5 serious cases [19 reactions]) were identified. The most frequent ADRs were Psychiatric disorders (8 cases and 17 reactions), Gastrointestinal disorders (3 cases and 10 reactions), and Nervous system disorders (2 cases and 6 reactions). The psychiatric disorders commonly included hallucinations (4 reactions), insomnia (3 reactions), while convulsions were also reported in this age group (3 reactions).

One SAE reported in an 11-year old girl who experienced a medically important serious palpitation while on a clinical study was described. The patient experienced palpitations shortly after starting the medication; finally the treatment was discontinued. Cardiac tests were normal.

Among the 188 medically confirmed cases, an overdose of oxybutynin was reported in 7 cases. In 4 cases, no adverse reactions were reported after an overdose.

Also among the 188 medically-confirmed cases, 1 case was fatal (A01200602056). However, the patient death was attributed to a concomitant treatment (dothiepin), because of a toxic drug level was detected in the patient's blood.

4.5 Discussion of clinical safety

Oxybutynin is an antimuscarinic medication, which crosses the blood-brain barrier. Apart from common anticholinergic peripheral side-effects (constipation, nausea, dry mouth, facial flushing and dry skin), CNS effects are reported to be very common in the paediatric population. The most frequently reported ADRs were hallucinations, headache, convulsions, somnolence and nightmares. These adverse reactions restrict the use of oxybutynin as they affect the compliance with treatment particularly in patients with chronic conditions such as neurogenic OAB. However in the great majority of the cases discontinuation of oxybutynin resulted rapidly in recovery without any treatment.

The reactions reported in the paediatric population under 5 years of age revealed no new or specific safety concerns that could be different with children over 5 years of age. However, the safety experience of oxybutynin treatment in the paediatric group less than 5 years of age is limited, and no definitive conclusion on the safety profile in this age group can be established.

Similarly from the data provided by the MAH during this Article 45 procedure, there isn't enough robust evidence to support the use of the transdermal or intravesical oxybutynin in the paediatric population, regardless of the indication. However the rapporteur acknowledges that these modes of administration might represent a safer and better tolerated alternative and further research is needed to establish their use in children 0-18 years.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION ON DAY 89

The efficacy of oral oxybutynin at the recommended doses of 5 mg bid in the treatment of neurogenic bladder in children over 5 years of age has been demonstrated. It is noted that enuresis is already included as an indication in the approved SmPCs. However the majority of the placebo-controlled studies in paediatric patients with enuresis did not demonstrate a clear therapeutic beneficial effect from Oxybutynin. Its use in such patients should be therefore recommended with caution and only after other measures have failed.

The rapporteur noted that although children below the age of 5 years have been included in some of the efficacy clinical studies, there is not sufficiently robust evidence which would

support the use of oral oxybutynin formulations in patients with neurogenic bladder or enuresis in paediatric patients under the age of 5 years; therefore the use of Oxybutynin should not be recommended in paediatric patients younger than 5 years. The current approved posology in children over 5 years reflects the current standards of treatment and the rapporteur agrees with the MAH that there is currently no need for any changes in the dosage recommendations for neurogenic bladder disorders and enuresis.

Based on the analyzed data, including safety information from literature publications and post-marketing data, no new safety issues have been identified regarding the use of oxybutynin in the paediatric population. However it is noted that the CNS/psychiatric AEs appear to be very common in children, possibly even more common than in adults. The rapporteur is of the view that a warning regarding the CNS effects in children to be included in the SmPC/PIL.

From the data submitted by the MAH, there is not enough scientific evidence to support the use of intravesical or transdermal oxybutynin in the paediatric population, regardless of the condition. However there appear to be significant data in published literature supporting a role of intravesical Oxybutynin in selected paediatric patients. The rapporteur is of the view that the treatment of paediatric patients with intravesical Oxybutynin might represent a safe alternative to oral formulations and therefore strongly supports the development of appropriate paediatric intravesical Oxybutynin formulations and the investigation of the safety and efficacy of this method of treatment in paediatric clinical studies.

Based on the review of the presented paediatric data on Oxybutynin and the currently used nomenclature for lower urinary tract disorders, the rapporteur considers that all the oxybutynin containing oral preparations (tablets, syrup and oral solution) should include the following wording in the SmPC/PIL:

4.1 Therapeutic indications

Paediatric population

Oxybutynin hydrochloride is indicated in children over 5 years of age for:

- *Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor overactivity).*
- *Nocturnal enuresis associated with detrusor overactivity in conjunction with non-drug therapy where this alone or in conjunction with other drug treatment, has failed.*

Additionally the rapporteur is of the view that in section 4.4 all relevant paediatric information should be clearly provided under separate heading as follows:

4.4 Special warnings

Paediatric population

Oxybutynin hydrochloride is not recommended for use in children below age 5 years due to insufficient data on safety and efficacy.

In children over 5 years of age, Oxybutynin hydrochloride should be used with caution as they may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

IV. MAH RESPONSE TO THE PRELIMINARY PDAR DAY 89

The MAH submitted a response to the Preliminary PdAR, dated 3/06/2010. In the submitted document the MAH accepts the proposed wording for sections 4.1 and 4.4 . Based on the points raised, the MAH also proposed the following wording for the PIL.

“What X is used for:

X can be used in children 5 years or older to treat:

- Loss of control in passing urine (urinary incontinence)
- Increased need or urgency to pass urine

- Night time bedwetting, when other treatments have not worked”

“Take special care with X:

Check with your doctor or pharmacist before taking your medicine if:

- The person taking the medicine is a child (use is not recommended under 5 years of age)”

Assessor’s Comment

The MAH overall accepted the rapporteur’s opinion that the available data is insufficient to support the efficacy and safety of oxybutynin in children younger than 5 years of age. It is accepted that the wording as proposed for section 4.1 better reflects the paediatric use of the drug. Furthermore the MAH accepted the need for a specific wording in section 4.4 regarding the CNS adverse reactions which are associated with the paediatric use of the oral preparations of oxybutynin. The proposed wording for PIL is considered acceptable.

V. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION

Overall the proposed changes in the SmPC and PIL of Oxybutynin should reflect the existing paediatric information available. Based on the review of the presented paediatric data the rapporteur considers that:

For all oral products (tablets, syrup and oral solution) containing Oxybutynin across the EU, it is recommended that SmPCs and PILs contain the following statements:

4.1 Therapeutic indications

Paediatric population

Oxybutynin hydrochloride is indicated in children over 5 years of age for:

- *Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor overactivity).*
- *Nocturnal enuresis associated with detrusor overactivity, in conjunction with non-drug therapy, when other treatment has failed.*

4.4 Special warnings and precautions for use

Paediatric population

Oxybutynin hydrochloride is not recommended for use in children below age 5 years due to insufficient data on safety and efficacy.

There is limited evidence supporting the use of Oxybutynin in children with monosymptomatic nocturnal enuresis (not related to detrusor overactivity).

In children over 5 years of age, Oxybutynin hydrochloride should be used with caution as they may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

PIL Wording :

“What X is used for:

X can be used in children 5 years or older to treat:

- *Loss of control in passing urine (urinary incontinence)*
- *Increased need or urgency to pass urine*
- *Night time bedwetting, when other treatments have not worked”*

PIL Wording :

"Take special care with X:

Check with your doctor or pharmacist before taking your medicine if:

- The person taking the medicine is a child (use is not recommended under 5 years of age)"*

VI. ADDITIONAL CLARIFICATIONS REQUESTED

None