COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vesolox 1 mg/ml, solution for intravesical use

(oxybutynin hydrochloride)

NL/H/3909/001/DC

Date: 25 April 2019

This module reflects the scientific discussion for the approval of Vesolox 1 mg/ml, solution for intravesical use. The procedure was finalised at 25 July 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AABC	Age Adjusted Bladder Capacity
ABU	Asymptomatic Bacteriuria
AE	Adverse Event
BfArM	German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BW	Bodyweight
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CIC	Clean Intermittent Catheterisation
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	Central Nervous System
DEOB	N-Desethyl-Oxybutynin
EAU	European Association of Urology
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
K_{ow}	Octanol-Water partition coefficient
MAH	Marketing Authorisation Holder
MDP	Max Detrusor Pressure
NDO	Neurogenic Detrusor Overactivity
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UTI	Urinary Tract Infections

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vesolox 1 mg/ml (in some countries the registered brand name is Vesoxx 1 mg/ml), solution for intravesical use from Oxyton Pharma GmbH.

The product is indicated for the suppression of detrusor overactivity due to spinal cord injury or myelomeningocele (spina bifida) in children from six years of age and adults, who are managing bladder emptying by clean intermittent catheterisation, not adequately managed with oral anticholinergics.

A comprehensive description of the indications and posology is given in the SmPC.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Luxembourg, Poland, Portugal, Sweden and Slovakia.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

Intravesical use of oxybutynin hydrochloride (oxybutynin-HCl)
Oxybutynin-HCl has been administered orally for more than three decades and thus, comprehensive knowledge on its biochemistry, pharmacology, toxicology and clinical use exists. In addition to oral formulations, transdermal formulations are marketed.

Since 1991, oxybutynin-HCl has also been available in the EEA for intravesical use. The intravesical application of oxybutynin-HCl is supported by various publications from different countries of the EEA. Intravesical formulations have been used in adults and children most frequently in cases of neurogenic detrusor overactivity (NDO), in which clean intermittent catheterisation (CIC) is required.

Currently no intravesical form of oxybutynin is registered. The proposed medicinal product Vesolox 1 mg/ml intravesical solution comprises identical concentration and composition with a product which is prepared since 1999 by a pharmacy in Germany (Grachtenhaus-Apotheke, Hamburg) based on a medical prescription according to Article 3 of Directive 2001/83/EC, as amended, as well as Section 21(2) No. 1 of the German medicinal products act (Arzneimittelgesetz, AMG).

Scientific advice
A Scientific Advice meeting was held on 20 April 2016 at the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) covering the possibility to approve the proposed drug product Vesolox 1 mg/ml intravesical solution according to Article 10a of Directive 2001/83/EC, as amended (well-established use).

The BfArM viewed that the proposed drug product probably represented an effective and important medicinal product that could be approvable in accordance to Article 10a of Directive 2001/83/EC, as amended, if the MAH demonstrated the comparability of the proposed oxybutynin-HCl formulation with other formulations of the same active substance, which have been used in published clinical trials. Furthermore, prescription data of the proposed drug product should be presented to demonstrate systematic clinical use for at least ten years.

The MAH adequately presented and discussed these requirements. Information on children and elderly is also included during the procedure (see IV. Clinical aspects).

II. QUALITY ASPECTS

II.1 Introduction

Vesolox is a clear, colourless intravesical solution with a pH of 3.8 to 4.5.

10 ml solution is packed in a prefilled syringe (cyclo-olefin copolymer) with a plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber).

One scaled prefilled ready-to-use syringe with 10 ml solution contains 10 mg oxybutynin-HCl.

The excipients are hydrochloric acid, sodium chloride and water for injections.

II.2 Drug Substance

The active substance is oxybutynin-HCl, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Oxybutynin-HCl is a white or almost white, crystalline powder; freely soluble in water and ethanol 96%, soluble in acetone, and practically insoluble in cyclohexane.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore, no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additionally, a microbiological test is included. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

Stability of drug substance
The active substance is stable for four years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. A standard formulation of an acidified aqueous solution of oxybutynin-HCl is available in the DAC/NRF (German Pharmaceutical Codex/New Prescription Formulary).

Oxybutynin-HCl solution (ranging 0.01% to 0.25%) has been manufactured since 1999 by pharmacies as a formulation prepared in advance and delivered to individual patients by medical prescription. Since 2009 it is only manufactured in the concentration of 0.1%. To ease the handling at administration, the drug product of this application is provided in pre-filled break-resistant 10 ml single-use syringes made of cycloolefin copolymer.

The choice of excipients is justified, and their functions explained. Incompatibilities between oxybutynin-HCl and the excipients were not shown through pharmaceutical literature. Since the application has been submitted in accordance with Article 10a of Directive 2001/83/EC, no own studies have been conducted by the MAH. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is based on the manufacturing process described by the DAC monograph. It consists of dissolving the active substance and adjusting the pH. The solution is then filtered, filled in type I glass bottles and sterilised twice. The sterilisation process has been adequately justified. Even though the amount of active substance is below 2% the manufacturing process can be considered as a standard process. The homogeneity of the active substance is not considered to be critical since the drug product is dissolved. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipient hydrochloric acid, dilute (10%) is tested according to the Ph.Eur. monograph. Sodium chloride solution (0.9%) is used as prepared solution made from sodium chloride (Ph.Eur.). These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance of solution, identity, density, pH, particulate contamination of visible and sub-visible particles, extractable volume, uniformity of dosage units, assay, impurities, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from three full scaled from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three full scaled batches stored at 25°C/60% RH (6 months), 30°C/65% RH (18 months) and 40°C/75% RH (up to 18 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed final packaging.

Supporting stability data at 25°C/60% RH (up to 24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) are available from two earlier development studies. The main difference is, that the manufacturing process includes an additional sterilisation of the bulk solution for one study and for the other study syringes are sterilised and subsequently labelled, while in the earlier development study syringes have been labelled and subsequently sterilised. The composition, primary packaging and main manufacturing principle of the batches tested in the supporting studies are compliant with the dossier and correspond to those of the current study.

At all three stability conditions all parameters stayed well within the specification limits. Photostability study results show that the drug product is not light sensitive. On basis of the data submitted, a shelf life was granted of 24 months. There is no objection to the approved labelled storage conditions 'Keep the syringes in the outer carton in order to protect from light'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vesolox 1 mg/ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The active substance is a well-known substance. Since this a bibliographic application, the submitted non-clinical dossier consists of published literature references. Most aspects of efficacy and safety are covered by clinical data. This is accepted.

III.2 Pharmacology

The primary pharmacodynamics of oxybutynin is driven by its high affinity binding to muscarinic receptors throughout the body.[1,2,3] Muscarinic receptors relevant to the pharmacodynamics of oxybutynin were identified to be present in the urothelium, the detrusor muscle, and on peripheral and central nerve fibers involved in sensation of bladder filling and voiding.[4]
Oxybutynin suppresses involuntary contractions of the bladder's smooth muscle (spasms) by blocking the binding of acetylcholine to muscarinic receptors by competitive binding.[5] It has therefore anticholinergic properties. Furthermore, oxybutynin is also able to exert direct spasmolytic effect on the bladder's outer layer of muscle (the detrusor muscle) by local anaesthesia of the C-fibers in the urothelium.[6,7,8,9] In addition, a calcium-antagonistic effect was observed, requiring however higher concentrations.[10]

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[1] Nilvebrant, L., *On the muscarinic receptors in the urinary bladder and the putative subclassification of muscarinic receptors.* Acta Pharmacol Toxicol (Copenh), 1986. **59 Suppl 1**: p. 1-45.
[2] Chapple, C.R., T. Yamanishi, and R. Chess-Williams, *Muscarinic receptor subtypes and management of the overactive bladder.* Urology, 2002. **60**(5 Suppl 1): p. 82-8; discussion 88-9.
[3] Noronha-Blob, L. and J.F. Kachur, *Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2 and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs.* J Pharmacol Exp Ther, 1991. **256**(2): p. 562-7.
[4] Ito, Y., et al., *Muscarinic Receptor Binding in Rat Bladder Urothelium and Detrusor Muscle by Intravesical Solifenacin.* Biol Pharm Bull, 2016. **39**(7): p. 1167-71.
[5] Chapple, C.R., T. Yamanishi, and R. Chess-Williams, *Muscarinic receptor subtypes and management of the overactive bladder.* Urology, 2002. **60**(5 Suppl 1): p. 82-8; discussion 88-9.
[6] Yarker, Y.E., K.L. Goa, and A. Fitton, *Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability.* Drugs Aging, 1995. **6**(3): p. 243-62.
[7] Mohler, J.L., *Relaxation of intestinal bladders by intravesical oxybutynin chloride.* Neurourology and Urodynamics, 1990. **9**(2): p. 179-187.
[8] Kim, Y., et al., *Antimuscarinic agents exhibit local inhibitory effects on muscarinic receptors in bladder-afferent pathways.* Urology, 2005. **65**(2): p. 238-42.
[9] De Wachter, S. and J.J. Wyndaele, *Intravesical oxybutynin: a local anesthetic effect on bladder C afferents.* J Urol, 2003. **169**(5): p. 1892-5.
[10] Kachur, J.F., et al., *R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine.* J Pharmacol Exp Ther, 1988. **247**(3): p. 867-72.

Oxybutynin undergoes rapid (first pass) metabolism following oral administration. The resulting first-pass metabolite, N-Desethyl-Oxybutynin (DEOB), is comparable in anticholinergic activity and largely contributes to the overall pharmacodynamic effect.[11]
Following intravesical administration, oxybutynin can act locally at the level of the urothelium, where the local anaesthetic effect can be expected to be important. Following local diffusion, oxybutynin can be active at the level of the detrusor muscle, resulting in direct spasmolytic activity. This may be a muscarinic receptor mediated local drug effect, but the calcium antagonistic activity may contribute to the spasmolysis.
Oxybutynin is also systemically bioavailable following intravesical administration, and both, oxybutynin and its metabolite DEOB can interact with muscarinic receptors on central and peripheral nerves, and directly on the detrusor muscle. The exact contribution of the individual components to the overall pharmacology is not known.[12,13]
An additional secondary effect which may be of therapeutic advantage is an inhibition of smooth muscle cell proliferation in the urothelium, which may prevent or reduce the muscle hypertrophy following stretch-induced stress derived from increased bladder pressure.[14,15]
In addition, oxybutynin was found to increase bladder permeability, and this effect may contribute to the systemic bioavailability of oxybutynin following instillation.[16]

Secondary pharmacodynamic effects are directly related to systemic muscarinic receptor-mediated anticholinergic effects. These include reduced salivation (xerostomia), constipation, tachycardia, mydriasis, and resulting blurred vision.[17] In addition, an inhibition of stress-induced gastric secretion and ulcer formation can be also attributed to the anticholinergic activity.[18]
These secondary effects require systemic exposure to oxybutynin or its metabolite DEOB, which both contribute to the total effect. Since the systemic exposure to the sum of oxybutynin and DEOB is reduced following intravesical administration, it can be expected that systemic anticholinergic effects are reduced compared to oral administration.[19]

[11] Waldeck, K., B. Larsson, and K.E. Andersson, *Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland.* J Urol, 1997. **157**(3): p. 1093-7.
[12] Oki, T., et al., *Demonstration of bladder selective muscarinic receptor binding by intravesical oxybutynin to treat overactive bladder.* J Urol, 2004. **172**(5 Pt 1): p. 2059-64.
[13] Oki, T., A. Toma-Okura, and S. Yamada, *Advantages for transdermal over oral oxybutynin to treat overactive bladder: Muscarinic receptor binding, plasma drug concentration, and salivary secretion.* J Pharmacol Exp Ther, 2006. **316**(3): p. 1137-45.
[14] Park, J.M., et al., Oxybutynin chloride inhibits proliferation and suppresses gene expression in bladder smooth muscle cells. J Urol, 1999. 162(3 Pt 2): p. 1110-4.
[15] Bonney, W.W., R.A. Robinson, and R.J. Theobald, Jr., *Topical effect of intravesical oxybutynin.* J Urol, 1993. **150**(5 Pt 1): p. 1522-5.
[16] Ersay, A. and O.C. Demirtas, *Intravesical oxybutynin affects bladder permeability.* Int Urol Nephrol, 2001. **32**(3): p. 359-61.
[17] Yarker, Y.E., K.L. Goa, and A. Fitton, *Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability.* Drugs Aging, 1995. **6**(3): p. 243-62.
[18] Lish, P.M., et al., *Oxybutynin--a musculotropic antispasmodic drug with moderate anticholinergic action.* Arch Int Pharmacodyn Ther, 1965. **156**(2): p. 467-88.
[19] Oki, T., et al., *Demonstration of bladder selective muscarinic receptor binding by intravesical oxybutynin to treat overactive bladder.* J Urol, 2004. **172**(5 Pt 1): p. 2059-64.

Muscarinic receptor-mediated effects, affecting the gastrointestinal tract[20,21,22,23], the cardiovascular system[24,25,26], and the central nervous system (CNS)[27,28,29,30,31], also dominate the safety pharmacology of oxybutynin. All identified safety pharmacology findings represent exacerbated pharmacology effects.
Pharmacodynamic drug interactions were observed in animal experiments for cholinergic drugs used to augment learning and memory. The central effect of orally administered oxybutynin may reduce the positive effect of such cholinergic drugs. The relevance of these findings for the clinical use of intravesical instillation of oxybutynin is not known.[32]

From the non-clinical point of view, it can be summarised that intravesical instillation of oxybutynin effectively inhibits bladder contractions, improves bladder compliance and shows decreased secondary effects such as reduced influence on salivation compared to the oral administration. Xerostomia is more pronounced after oral administration due to the first-pass effect that metabolises oxybutynin to DEOB, which has higher affinity to the salivary gland than to the bladder. The pharmacodynamic effects seen following intravesical instillation in animal experiments can be compared with the clinical dose. In most patients, the effective dose for intravesical administration is 10 mg per dose. Assuming a body weight of 70 kg, this amounts to a dose of 143 µg/kg. It can be concluded that pharmacodynamic effects seen in animal experiments are achieved at doses which are well in line with the human dose of 10 mg.

[20] Kachur, J.F., et al., *R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine.* J Pharmacol Exp Ther, 1988. **247**(3): p. 867-72.
[21] Lish, P.M., et al., *Oxybutynin--a musculotropic antispasmodic drug with moderate anticholinergic action.* Arch Int Pharmacodyn Ther, 1965. **156**(2): p. 467-88.
[22] EMEA *Kentera oxybutynin European Public Assessment Report EPAR, Summary for the Public, Summary of Product Characteristis, Scientific Discussion. Accessed online, Dec. 9th 2016.* 2015.
[23] Martindale, *Oxybutynin*, in *Martindale. The Complete Drug Reference. 38 ed.*, S.S. (Editor), Editor. 2014, Pharmaceutical Press. pp. 2361-2362.
[24] Korol, B. and L.D. Miller, *Oxybutynin influence on autonomic measures in dogs.* J Pharm Sci, 1979. **68**(5): p. 643-5.
[25] Misawa, M., et al., *[Effects of oxybutynin on the cardiovascular system in dogs].* Nihon Yakurigaku Zasshi, 1984. **84**(4): p. 395-406.
[26] Yamamoto, T., et al., *General pharmacology of the new antimuscarinic compound vamicamide.* Arzneimittelforschung, 1995. **45**(12): p. 1274-84.
[27] Suzuki, M., et al., *Effect of antimuscarinic drugs used for overactive bladder on learning in a rat passive avoidance response test.* Eur J Pharmacol, 2007. **557**(2-3): p. 154-8.
[28] Sugiyama, T., Y.C. Park, and T. Kurita, *Oxybutynin disrupts learning and memory in the rat passive avoidance response.* Urol Res, 1999. **27**(5): p. 393-5.
[29] Oka, T., et al., *Effects of antimuscarinic drugs on both urinary frequency and cognitive impairment in conscious, nonrestrained rats.* Jpn J Pharmacol, 2001. **87**(1): p. 27-33.
[30] Wagg, A., et al., *Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study.* Eur Urol, 2013. **64**(1): p. 74-81.
[31] Kay, G.G., et al., *Cognitive effects of oxybutynin chloride topical gel in older healthy subjects: a 1-week, randomized, double-blind, placebo- and active-controlled study.* Clin Drug Investig, 2012. **32**(10): p. 707-14.
[32] Suzuki, M., et al., *Effect of antimuscarinic drugs used for overactive bladder on learning in a rat passive avoidance response test.* Eur J Pharmacol, 2007. **557**(2-3): p. 154-8.

III.3 Pharmacokinetics

Oxybutynin is well absorbed following oral administration and following transdermal and intravesical administration. Following oral administration, oxybutynin undergoes rapid first-pass metabolism, resulting in the formation of the active metabolite DEOB. Both, oxybutynin and DEOB contribute to the pharmacology and toxicology of muscarinic receptor medicated pharmacology, therefore the combined plasma exposure of both compounds is to be considered.[33] Following transdermal or intravesical administration, the metabolism of oxybutynin is reduced, resulting in reduced plasma levels of DEOB compared to the oral route.[34,35,36] The bioavailability of intravesical oxybutynin was not determined in animal experiments.

Oxybutynin and its metabolite DEOB are widely distributed in the body including the CNS. The main organs for distribution identified after oral treatment with 14C-oxybutynin in rats, were gastrointestinal tract, liver and kidney. Placental transfer of radioactivity could be demonstrated in rats after oral treatment with 14C-labelled oxybutynin on GD 11 and GD 18.[37] Generally, the plasma protein binding was comparable between human and rat blood (99% and 98%). In rats, the affinity of DEOB was slightly lower. However, this finding was not observed in human blood. The human alpha1-acid glycoprotein showed the highest affinity to oxybutynin and its main active metabolite.[38]

The primary metabolism is CYP3A4-mediated, and both, oxybutynin and DEOB are further metabolised.[39] Very low amounts of parent drug or DEOB are excreted as such; supporting that metabolism is the primary route of clearance. Metabolites are excreted involving both the urinary and the faecal route. There is some evidence from animal studies that oxybutynin or its metabolites are excreted into milk.[40]

Based on the metabolic pathway involving CYP3A4, pharmacokinetic drug interaction can be expected with inhibitors of CYP3A4, but no preclinical studies were reported. The antifungal itraconazole, a potent inhibitor or CYP3A4, however, had limited effects on the pharmacokinetics of oxybutynin and its metabolite DEOB. Further pharmacodynamic drug interactions may derive from the effect on gastric motility.

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[33] Waldeck, K., B. Larsson, and K.E. Andersson, *Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland.* J Urol, 1997. **157**(3): p. 1093-7.

[34] Oki, T., et al., *Demonstration of bladder selective muscarinic receptor binding by intravesical oxybutynin to treat overactive bladder.* J Urol, 2004. **172**(5 Pt 1): p. 2059-64.

[35] Buyse, G., et al., *Intravesical oxybutynin for neurogenic bladder dysfunction: less systemic side effects due to reduced first pass metabolism.* J Urol, 1998. **160**(3 Pt 1): p. 892-6.

[36] Oki, T., A. Toma-Okura, and S. Yamada, *Advantages for transdermal over oral oxybutynin to treat overactive bladder: Muscarinic receptor binding, plasma drug concentration, and salivary secretion.* J Pharmacol Exp Ther, 2006. **316**(3): p. 1137-45.

[37] Akimoto, Y., et al., *Studies on the metabolic fate of Oxybutynin hydrochloride. 1. Absorption, distribution, and excretion in rats and dogs.* Iyakuhin Kenkyu, 1984. **15**(4): p. 519-535.

[38] Mizushima, H., et al., *Stereoselective pharmacokinetics of oxybutynin and N-desethyloxybutynin in vitro and in vivo.* Xenobiotica, 2007. **37**(1): p. 59-73.

[39] Mizushima, H., et al., *Stereoselective pharmacokinetics of oxybutynin and N-desethyloxybutynin in vitro and in vivo.* Xenobiotica, 2007. **37**(1): p. 59-73.

[40] Akimoto, Y., et al., *Studies on the metabolic fate of Oxybutynin hydrochloride. 1. Absorption, distribution, and excretion in rats and dogs.* Iyakuhin Kenkyu, 1984. **15**(4): p. 519-535.

III.4 Toxicology

Oxybutynin is a well-known anticholinergic agent for which there is extensive experience in clinical use for the treatment of overactive bladder. The toxicological profile and common adverse effects are well known. The toxicological profile of oxybutynin is dominated by exacerbated pharmacology, i.e. by muscarinic receptor mediated effects, both, after single and multiple dose administration. Target organs are organs with muscarinic receptor expression, including the digestive tract (xerostomia, reduced gastro-enteral motility, obstipation), cardiovascular system (heart rate increase/tachycardia), CNS (mydriasis, hyperactivity), and the urinary tract (bladder distension). Unspecific toxicological findings, which are not related to the anticholinergic activity of oxybutynin, e.g. alterations in haematology or microscopic findings were only seen at doses well exceeding the doses inducing anticholinergic drug effects and well above the no observed adverse effect level (NOAEL) in the respective toxicity studies. The anticholinergic findings observed in toxicity studies well reflect the safety profile and the adverse effect spectrum of oxybutynin[41] following oral administration in man and also following transdermal application.[42]

Oxybutynin and its metabolites were not found to be genotoxic *in vitro* and *in vivo* in standard test systems. No evidence of carcinogenicity was found in a 24 month study in rats. Additionally, no increased tumour incidence was reported from clinically use.[43,44,45]
The reproduction toxicity of oxybutynin was evaluated in rats and rabbits. Oxybutynin caused indications for teratogenic potential resulting in increased rates of visceral and skeletal abnormalities were observed, albeit only at maternal toxic doses. There is some evidence for milk transfer for oxybutynin or its metabolite. Some retardation of development of the offspring was observed in a pre- and post-natal development study. While based on these data oxybutynin exposure is not recommended during pregnancy and nursing, no reports of foetal or embryo toxicity are known from long-standing clinical use.[46,47]

The local tolerance of intravesical administered oxybutynin was evaluated in a rat study with repeated instillation of a concentration which is about 25 times as high as the highest local tissue concentration for human use (1 mg/ml) and in rabbits administering the concentration

[41] Janssen-Ortho, *Product Monograph: Ditropan XL, accessed online, December 23, 2016,* https://www.janssen.com/canada/sites/www_janssen_com_canada/files/product/pdf/dxl12192014cpm_nc.pdf, G.B.D. Janssen Ortho Inc, Toronto, Ontario M3C 1L9, Editor. 2014.
[42] EMEA *Kentera oxybutynin European Public Assessment Report EPAR, Summary for the Public, Summary of Product Characteristis, Scientific Discussion. Accessed online, Dec. 9th 2016.* 2015.
[43] EMEA *Kentera oxybutynin European Public Assessment Report EPAR, Summary for the Public, Summary of Product Characteristis, Scientific Discussion. Accessed online, Dec. 9th 2016.* 2015.
[44] Janssen-Ortho, *Product Monograph: Ditropan XL, accessed online, December 23, 2016,* https://www.janssen.com/canada/sites/www_janssen_com_canada/files/product/pdf/dxl12192014cpm_nc.pdf, G.B.D. Janssen Ortho Inc, Toronto, Ontario M3C 1L9, Editor. 2014.
[45] Iwata, T., et al., *Mutagenicity tests of oxybutynin hydrochloride.* Yakuri to Chiryo, 1985. **13**: p. 6637-6643.
[46] Edwards, J.A., Y.J. Reid, and D.D. Cozens, *Reproductive toxicity studies with oxybutynin hydrochloride.* Toxicology, 1986. **40**(1): p. 31-44.
[47] EMEA *Kentera oxybutynin European Public Assessment Report EPAR, Summary for the Public, Summary of Product Characteristis, Scientific Discussion. Accessed online, Dec. 9th 2016.* 2015.

of 1 mg/ml. From both studies, it can be concluded that oxybutynin has no local irritant potential.[48,49] The lack or local irritation is also supported by a clinical study testing the safety and efficacy of the pertinent oxybutynin formulation and by the long-standing clinical use of intravesical administration of oxybutynin.[50,51]

III.5 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results

Table 1: Overview of main study results

Substance (INN/Invented Name): oxybutynin-HCl			
CAS-number (if available): 1508-65-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	4.56 (ion corrected D_{ow})	Potential PBT Y
PBT-statement :	pending		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, refined	0.0091	µg/L	>0.01 threshold N
Other concerns (e.g. chemical class)			N

Conclusions on studies:

The extrapolated log K_{ow} exceeds the PBT screening criterion of 4.5, and therefore a PBT assessment is warranted. The MAH has committed to perform a ready biodegradability study according to OECD TG 301 and to determine is oxybutynin meets the P screening criterion. If the substance is not readily biodegradable, higher tier PBT studies will be required, i.e. simulation, bioaccumulation and possibly aquatic toxicity testing. Since oxybutynin is extensively metabolised in mammalian cells, and since the chemical stability of oxybutynin in aqueous solutions is limited especially at alkaline pH with significant degradation within 48 hours, it is expected that the biodegradability test will demonstrate biodegradability. The results will be reported as soon as they are available.

Since the PEC is below the action limit, a Phase II assessment is not warranted.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of oxybutynin are well known. As oxybutynin is a widely used, well-known active substance, no further studies are

[48] Bonney, W.W., R.A. Robinson, and R.J. Theobald, Jr., *Topical effect of intravesical oxybutynin.* J Urol, 1993. **150**(5 Pt 1): p. 1522-5.
[49] Landau, E.H., et al., *Histologic studies of intravesical oxybutynin in the rabbit.* J Urol, 1995. **153**(6): p. 2022-4.
[50] Krause, P., et al., *Pharmacokinetics of intravesical versus oral oxybutynin in healthy adults: results of an open label, randomized, prospective clinical study.* J Urol, 2013. **190**(5): p. 1791-7.
[51] Schroder, A., et al., *Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomized, prospective, controlled multi-center trial.* Neurourol Urodyn, 2016. **35**(5): p. 582-8.

required. An overview based on literature review is appropriate and has been provided by the MAH.
The intravesical administration is demonstrated in pharmacodynamic studies to result in better separation of pharmacodynamic effects from adverse drug reactions. Both, local drug effects and systemic effects may contribute to the intended pharmacology. The intravesical administration was shown in animals to result in reduced muscarinic receptor occupancy while maintaining local drug effects. The combination of local drug effects with the reduced systemic exposure enables an improved therapeutic activity while at the same time reducing systemic toxicity.
The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.
The MAH committed to perform a ready biodegradability study according to OECD TG 301 and to determine if oxybutynin meets the P screening criterion.

IV. CLINICAL ASPECTS

IV.1 Introduction

Oxybutynin-HCl is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The MAH aimed to demonstrate the comparability of the proposed oxybutynin-HCl formulation with other formulations of the same active substance, which have been used in published clinical trials. Furthermore, prescription data of the proposed drug product has been presented to demonstrate systematic clinical use for at least ten years.

IV.2 Pharmacokinetics

Absorption
The pharmacokinetics of intravesically administered oxybutynin-HCl have been described in three publications by Krause et al., 2013[52], Lehtoranta et al., 2002[53] and Buyse et al., 1998[54]. Based on the publication of Krause et al., 2013, intravesical oxybutynin is well absorbed through the bladder wall into systemic circulation. An absolute bioavailability of about 20% might be estimated for the parent compound after intravesical instillation. Bypassing pre-systemic metabolism in the gut wall and liver by bladder instillation results in significant differences, i.e. total exposure of the parent drug was considerably higher after intravesical

[52] Krause P, Fuhr U, Schnitker J, Albrecht U, Stein R, Rubenwolf P. Pharmacokinetics of intravesical versus oral oxybutynin in healthy adults: results of an open label, randomized, prospective clinical study. 2013;190:1791-1797.
[53] Lehtoranta K, Tainio H, Lukkari-Lax E, Hakonen T, Tammela TLJ. Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. 2002;36:18-24.
[54] 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. 1998;160:1084-1087.

application (~three times higher for both R- and S-oxybutynin) while exposure of the metabolite was considerably lower for both enantiomers. These results were supported by three additional publications.[55,56,57]

Distribution

Oxybutynin is widely distributed in body tissues following systemic absorption. Based on oral and intravenous data the apparent volume of distribution of oxybutynin after intravenous administration of 1 mg and 5 mg oxybutynin was 89 L and 193 L, respectively.

Excretion and Metabolism

Oxybutynin is rapidly excreted from the body after oral and intravesical administration. However, after intravesical administration oxybutynin exhibits a prolonged elimination compared to oral administration with reported elimination half-lives of 2.56 h and 1.48 h, respectively. Oxybutynin administered orally is metabolised primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Metabolites include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and DEOB, which is pharmacologically active. The potential of interactions with CYP3A4 is decreased after intravesical administration and not expected to exert clinically relevant significant effects. Intravesical administration of oxybutynin mainly circumvents the first-pass gastrointestinal and hepatic metabolism, resulting in higher systemic exposure to the parent drug and lower exposure to the active DEOB metabolite.

Special populations

No pharmacokinetic data regarding hepatic or renal impairment is available and therefore a proposed appropriate wording on the lack of such data in these special populations is acceptable. In addition, due to limited data on gender, race and age, no scientifically sound conclusions can be made. The MAH provided pharmacokinetic data in children (n=11, aged between 3.5 and 15.7 years) derived from one pharmacokinetic study in children, where lower dose than what is recommend, especially in children above 12 years, was used. However, efficacy studies have been conducted with higher doses in paediatric population.

IV.3 Pharmacodynamics

Because of its antimuscarinic activity, oxybutynin exerts a direct effect on the detrusor muscle followed by a decrease of detrusor pressure and increase of maximum bladder capacity. Thus, keeping the detrusor pressure during the filling and the voiding phases within safe limits reduces the mortality from urological causes in these patients.[58,59]

[55] Lehtoranta K, Tainio H, Lukkari-Lax E, Hakonen T, Tammela TLJ. Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. 2002;36:18-24.

[56] 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. 1998;160:1084-1087.

[57] Stolze T. Pharmakokinetische Studie einer intravesikalen Applikation von Oxybutynin-Hydrochlorid zur Therapie der Detrusorüberaktivität, Dissertation. 2011.

[58] Frankel HL, Coll JR, Charlifue SW, Whiteneck GG, Gardner BP, Jamous MA, et al. Long-term survival in spinal cord injury: a fifty year investigation. Spinal Cord 1998;36:266-274.

It can be concluded from human as well as animal data that intravesically applied oxybutynine exerts its anticholinergic activity via both a systemic and local action on muscarinic receptors. Further, it has been shown that intravesically administered oxybutynin exerts a temporary anaesthetic effect.

The secondary pharmacodynamic effects consist of other systemic anticholinergic effects such as decrease salvia production and possible cognitive disturbances. Oxybutynin is a lipophilic substance and thus, able to access the CNS by passing the blood brain barrier (BBB). It may bind to muscarinic receptors in the CNS and thus, cause disturbances of the cognitive function.

IV.4 Clinical efficacy

From 1989 up to date, numerous studies have been published investigating the efficacy of intravesical oxybutynine in NDO patients as outlined in Table 2. This study set comprises randomised, controlled studies as well as a number of small cohort studies and case series. The study parameters vary with respect to the oxybutynin doses used, the treatment duration, outcome parameters, the concentration of the instilled oxybutynin solution as well as the retention time in the bladder. The number of patients enrolled is limited in most of the studies.
Overall, the efficacy of intravesical oxybutynin treatment of NDO has been investigated in 25 clinical studies comprising about 470 patients. Although the results within each study were highly variable, an effect of intravesical oxybutynin on urodynamic parameters can be assumed in both short-term and long-term use up to 15 years. Some effects on urodynamic parameters could be demonstrated with different formulations and preparations from dissolved crushed tablets up to pharmacy-manufactured sterile solutions in prefilled syringes. Moreover, these studies also showed that intravesical treatment using prefilled sterile syringes is more convenient resulting in an increased patient compliance.[60,61,62] The applied doses ranged from 0.14 mg/kg to 0.9 mg/kg bw. A recent meta-analysis has confirmed the clinical and urodynamic efficacy of antimuscarinic therapy compared to placebo in adult NDO. Limited information on patient reported outcomes (micturition and incontinence episodes) was available in the submitted publications. The information available indicates a reduction in micturition and incontinence episodes.

[59] Jamil F. Towards a catheter free status in neurogenic bladder dysfunction: a review of bladder management options in spinal cord injury (SCI). Spinal Cord 2001;39:355-361.
[60] Buyse G, Waldeck K, Verpoorten C, Björk H, Casaer P, Andersson KE. Intravesical oxybutynin for neurogenic bladder dysfunction: less systemic side effects due to reduced first pass metabolism. The Journal of urology 1998;160:892-896.
[61] 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. The Journal of Urology 1998;160:1084-1087; discussion 92.
[62] 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 opitmized intravesical oxybuynin hydrochloride therapy. Eur J Pediatr Surg 1995;6:31-34.

At least 18 clinical trials included paediatric patients from three months up to 18 years - in the EU, nine clinical studies involving children have been published in which approximately 175 children were treated with oxybutynin-HCl intravesically. The MAH has shown that in published data in children between six and 12 years of age, between 3 mg and 40 mg oxybutynin-HCl were applied daily. In adolescents ranging from 12 to 18 years of age, doses between 6 mg and 64 mg oxybutynin-HCl have been given intravesically. In addition, daily doses of 10 to 20 mg without any weight adjustment have been applied in several studies in children and adolescents from 1 to 18 years of age.
One publication describes a randomised, multicentre trial investigating the efficacy of intravesical oxybutynin treatment in adult patients with NDO (Schröder et al., 2016[63]). This study has been conducted using an oxybutynin intravesical solution prepared by Grachtenhaus-Apotheke, Hamburg, Germany. The study results show a statistical significant effect on maximum bladder capacity, maximum detrusor pressure and detrusor compliance. GCP issues with this study have been brought to attention which affect mainly the comparison with the oral formulation. Whilst this data is not relied on for the present application, neither the study documentation nor inspection reports are available to verify the extent of the GCP issues therefore the study should be viewed with caution.

The overall effect of treatment was estimated in a meta-analysis both including the study by Schröder et al. in 2016 as well as excluding this study. For the mid-term (>4 weeks to 6 months) and long term (>6 months) treatment period the study had no substantial impact on the estimated overall efficacy results, while for the short-term treatment (1 to 4 weeks) the study substantial influenced the estimated overall effect. Considering both mid and long-term treatment, a relevant effect is shown on cystometric bladder capacity as well as end-filling pressure in several studies.
Therefore, it can be concluded that studies investigating the effect of intravesical oxybutynin on the detrusor pressure showed that the bladder pressure decreased upon instillation of oxybutynin. In many cases, the bladder pressure decreased below the threshold of 40 cm H_2O[64] (threshold for increased risk of kidney damage).

Table 2 Key results of efficacy studies on intravesical treatment with oxybutynin-HCl

Author, year	Study results	Conclusions
Pivotal Studies		
Schröder et al., 2016	• Increase in maximum bladder capacity of 116.6 ± 27.5 ml with intravesical application (p = 0.0002) versus 18.1 ± 27.5 ml with the oral application (p = 0.5141). • Statistically significant difference of 98.5 ± 39.1 ml (p = 0.0086) between the two treatments. • No statistically significant difference between the two treatments for secondary efficacy variable.	Intravesical 0.1% oxybutynin hydrochloride is safe and efficient in the treatment of NDO.

[63] Schröder A, Albrecht U, Schnitker J, Reitz A, Stein R. Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: a randomized, prospective, controlled multi-center trial. 2015; Wiley online library: DOI 10.1002/nau.22755.
[64] P. Madhuvrata, et al. Anticholinergic Drugs for Adult Neurogenic Detrusor Overactivity: A Systematic Review and Meta-analysis. European Urology. 2012;62:816 -830.

Author, year	Study results	Conclusions
Humblet et al., 2015[65]	• At follow-up, cystometric bladder capacity (CBC) increased to the 25-50% percentiles for age, from the 5% percentile. • Mean end-filling pressure, 24.5 ± 14.4 cm H_2O, returned to the safe zone. • Statistically significant increase of bladder compliance expressed as a fraction of normal compliance for age (Wahl units). • Prevalence of renal scars of 30% (95% CI: 6-65%) at follow-up. • Kidney lengths correlated with scarring at DMSA-scintigraphy, (51)Cr-EDTA-clearance did not.	More than adequate suppression of detrusor activity over a period of 15 years.
Supportive Studies		
Lehnert et al., 2012[66]	• Two drop-outs in group II. • Bladder capacity increased from 173 (± 99) to 371 (± 115) ml in group I and from 245 (± 133) to 370 (± 156) ml in group II. • Six of the ten patients in group I and six of the nine patients in group II reached normal EBV. Three of the ten subjects in group I and six of the nine in group II had bladder compliance values >10 ml/cm H_2O. • At final follow-up, the overall rate of urinary tract infections was equal. Social continence was achieved in six of the ten in group I and seven of the nine in group II.	Conservative medical treatment combined with CIC feasible; Improved pattern of bladder function may avoiding bladder surgery in children with NDO.
George et al., 2007[67]	• 33% of the patients showed improvement with respect to cystometric bladder capacity and leak point pressure after instillation with oxybutynin. No clinical urinary tract infections were observed.	Intravesical agents may be used as effective adjuvants in the management of incontinence.
Lehtoranta et al., 2002	• The mean number of toilet visits/day decreased from the baseline value of 6.9 to 5.7 during oxybutynin treatment, whereas during the placebo period the value increased to 7.4 (p=0.022). • Mean number of toilet visits/day remained at the same decreased level during the one-year follow-up period.	Significant decrease in mean number of daily toilet visits.
Ferrara et al., 2001[68]	• No significant differences between patient groups • Urodynamic bladder capacity increased in 70% • Detrusor LLP decreased in 64% • Overall decrease in UTI incidence in 69% • CIC frequency decreased	Safe and effective treatment; attention on central AEs.

[65] Humblet M, Verpoorten C, Christiaens, Hirche H, Jansen K, Buyse G, van Gool JD. Long-term outcome of intravesical oxybutynin in children with detrusor-sphincter dyssynergia: with special reference to age-dependent parameters. 2014; Wiley online library: DOI 10.1002/nau.22560.
[66] Lehnert T, Weisser M, Till H, Rolle U. The effects of long-term medical treatment combined with clean intermittent catheterization in children with neurogenic detrusor overactivity. 2011;44:335-341.
[67] George J, Tharion G, Richard J, Macaden AS, Thomas R, Bhattacharji S. The effectiveness of intravesical oxybutynin, propantheline, and capsaicin in the management of neuropathic bladder following spinal cord injury. 2007;7:1683-1690.
[68] Ferrara P, D'Aleo CM, Tarquini E, Salvatore S, Salvaggio E. Side-effects of oral or intravesical oxybutynin chloride in children with spinida bifida. 2001;87:674-678.

Author, year	Study results	Conclusions
Haferkamp et al., 2000[69]	• Significant (p<0.01) decrease in the median max detrusor pressure (MDP) and a significant (p<0.01) increase in the median compliance and the median age adjusted bladder capacity (AABC). • Eleven out of 32 patients remained incontinent under a dosage of 0.3 mg/kg bodyweight (bw) per day. Median MDP, median compliance and median AABC remained nearly unchanged. • Seven out of eleven incontinent patients under a dosage of 0.3 mg/kg bw per day were treated efficiently with the higher dosages of up to 0.9 mg/kg bw per day. • Median necessary dosage escalation to achieve treatment success was 0.7 mg/kg bw per day (range 0.5 to 0.9 mg/kg bw per day). • Median MDP was significantly (p<0.05) decreased and median compliance and median AABC were significantly (p<0.05) increased. • Four out of eleven patients remained incontinent and showed only little improvement in urodynamic data. • Two out of eleven patients with the dosage escalation (B) showed side effects at a dosage of 0.9 mg/kg bw per day.	Intravesical application of oxybutynin was well-tolerated and efficacious. Topical oxybutynin therapy dosage of 0.3 mg/kg bw per day was efficient in 66% of the selected patients. Escalating dosage titration of up to 0.9 mg/kg bw per day increased the efficiency to 87%.
Pannek et al., 2000[70]	• Increase in bladder storage volume from 349 to 420 ml. • Mean maximum storage pressure was significantly reduced from 54 to 26.5 cm H_2O. • Detrusor storage pressures returned to values less than 40 cm H_2O in 21 of 25 patients. • Dysreflexia was treated successfully in three of five patients.	Safe and effective treatment option for detrusor hyperreflexia in adults.
Amark et al., 1998a[71]	• Continence was clearly promoted and urodynamic parameters improved whereas an increased occurrence of asymptomatic bacteriuria and lower tract infections was noted. • Compliance was good, adverse reactions rare, and in some cases vesicoureteral reflux resolved. • Infants and very young children were treated without complications.	Intravesical oxybutynin is effective to diminish bladder pathophysiology and promote continence in this patient group.
Amark et al., 1998b[72]	• Considerable improvement of continence in all patients, except one. • Bladder pressures reduced in most patients.	Safe and effective treatment option to improve incontinence and diminish bladder pathophysiology.

[69] Haferkamp A, Staehler G, Gerner HJ, Dörsam J. Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. 2000;38:250-254.
[70] Pannek J, Sommerfeld HJ, Bötel U, Senge T. Combined intravesical and oral oxybutynin chloride in adult patients with spinal cord injury. 2000;55:358-362.
[71] Åmark P, Bussman G, Eksborg S. Follow-up of long-time treatment with intravesical oxybutynin for neurogenic bladder in children. 1998;34:148-153.
[72] Åmark P, Eksborg S, Juneskans O, Bussman G, Palm C. Pharmacokinetics and effects of intravesical oxybutynin on the paediatric neurogenic bladder. 1998;82:859-864.

Author, year	Study results	Conclusions
Buyse et al., 1998	• In 13 of the 15 children therapeutic compliance was excellent. • Detrusor hyperactivity decreased and systemic side effects were absent or minimal. • After four and 24 months, mean cystometric bladder capacity plus or minus standard error of mean increased from 114 ± 15.2 to 161 ± 26.6 and 214 ± 21.7 ml (p<0.01). • Mean ratio of cystometric-to-expected bladder capacity increased from 0.88 ± 0.12 to 1.18 ± 0.14 and 1.24 ± 0.16 (p<0.01), and end filling bladder pressure decreased from 57.0 ± 7.1 to 25.6 ± 4.4 and 30.8 ± 4.4 cm. water (p<0.01), respectively	Specially prepared oxybutynin solution is safe and reliable in children with persistent NDO. Eliminating the complex crushing preparation has made this therapy easy to use and acceptable in the long term.
Vaidyananthan et al., 1998[73]	• Patients noted a remarkable improvement in the quality of life. • All patients were able to discard penile sheaths and leg bags during day and night. • High degree of continence was achieved.	Socially acceptable continence and improved quality of life and enhanced sexuality.
Holland et al., 1997[74]	• Two out of seven patients became continent and one patient had an improvement in upper tract dilatation. • One patient had a limited improvement with oxybutynin alone but became continent with the addition of ephedrine. • Three patients had no response to treatment.	Adequate treatment option for children with intolerable AEs due to oral treatment.
Szollar and Lee, 1996[75]	• Mean bladder capacity improved from a mean 344 ± 36.2 cc to 400 ± 56.32. • Mean DLPP decreased from 65 ± 6.55 to 47 ± 7.17 cm H_2O (significant, no p value given). • Mean volume at first contraction increased from 167 ± 24.17 to 184 ± 25.45 cc.	Improvement of urodynamic parameters with statistically significant decrease of bladder pressure.
Painter et al., 1996[76]	• 43% of patients had improvement in all three urodynamic parameters. • Mean total capacity increased from 192 ± 94 to 322 ± 107 ml. • Mean safe capacity increased from 140 ± 99 to 287 ± 107 ml. • Mean end filling pressure decreased from 61 ± 20 to 38 ± 18 cm.	Viable option for patients with neurogenic bladder dysfunction secondary to myelodysplasia.

[73] Vaidyananthan S, Soni BM, Brown E, Sett P, Krishnan KR, Bingley J, Markey S. Effect of intermittent urethral catherization and oxybutynin bladder instillation on urinary continence status and quality of life in a selected group of spinal cord injury patients with neuropathic bladder dysfunction. 1998;36:409-414.
[74] Holland AJA, King PA, Chauvel PJ, O'Neill MK, McKnight DL, Barker AP. Intravesical therapy for the treatment of neurogenic bladder in children. 1997;67:731-733.
[75] Szollar SM and Lee SM. Intravesical oxybutynin for spinal cord injury patients. 1996;34:284-287.
[76] Painter KA, Vates TS, Bukowski TP, Fleming P, Freedman AL, Smith CA, Gonzalez R, Perlmutter AD. Long-term intravesical oxybutynin chloride therapy in children with myelodysplasia. 1996;156:1459-1462.

Author, year	Study results	Conclusions
Kaplinsky et al., 1996[77]	• Seven patients (25%) could not tolerate intravesical oxybutynin • Remaining 21 children have been followed on intravesical oxybutynin for a mean of 35 months (range 3 to 67). • Twelve children (57%) became completely dry day and night • Five (24%) achieved daytime continence between catheterizations and four (19%) remained clinically unchanged with two in diapers. • 21 patients had increased bladder capacity of up to 1.150% (mean 237%, p<0.0001) and decreased mean maximum filling pressures	Significant improvement in urodynamic parameters and continence; Response appears to be durable.
Madersbacher and Knoll, 1995[78]	• In three patients with reflex bladder, cystometric bladder capacity increased by 20% 20 min after instillation. • Slight decrease in maximal detrusor pressure by 15%. • After two hours, mean increase in cystometric bladder capacity in the reflex bladders was 60%. • Peak plasma levels of oxybutynin after instillation appear later, are lower and stay longer.	Well-tolerated and efficacious treatment.
Buyse et al., 1995	• Intravesical oxybutynin efficiently suppressed detrusor hyperreflexia and hypertonicity. • Mean cystometric bladder capacity increased from 114.2 to 127.4 ml after 1.5 h (p>0.05) and to 161.1 ml after four months (p=0.0091)	Previously reported problems using crushed oxybutynin tablets can be resolved using an optimized drug preparation for intravesical oxybutynin therapy.
Weese et al., 1993[79]	• 33 patients followed the protocol. • 55% of patients (n=18) reported at least a moderate subjective improvement. • Nine of patients reporting improvement experienced complete resolution of their symptoms.	Confirms the utility of intravesical oxybutynin treatment of NDO.
Greenfield and Fera, 1991[80]	• 50% became completely dry day and night. • 30% achieved daytime continence alone. • Two patients showed no improvement. • Increases in bladder capacity up to 335% over baseline and decreases of maximum filling pressures to 63%. • Surgical bladder augmentation was avoided in those who clinically responded to this therapy.	Efficient treatment option after failed oral therapy or in patients who did not tolerate oral oxybutynin.

[77] Kaplinsky R, Greenfield S, Wan J, Fera M. Expanded followup of intravesical oxybutynin chloride use in children with neurogenic bladder. 1996;156:753-756.
[78] Madersbacher H and Knoll M. Intravesical application of oxybutynin: mode of action in controlling detrusor hyperreflexia. 1995;28:340-344.
[79] Weese DL, Roskamp DA, Leacch GE, Zimmern PE. Intravesical oxybutynin chloride experience with 42 patients. 1993;41:527-530.
[80] Greenfield SP and Fera M. The use of intravesical oxybutynin chloride in children with neurogenic bladder. 1991;146:532-534.

Author, year	Study results	Conclusions
Madersbacher and Jilg, 1991[81]	• Ten of 13 patients showed a decrease of the MDP six hours after instillation of oxybutynin, ranging between 125 and 10 cm H_20 with a mean decrease of 36 cm H_20. • Statistically highly significant differences in the cystometric bladder capacity and in the MDP before and after intravesical instillation of oxybutynin with a PR> T of 0.0005 for bladder capacity and 0.0043 for MDP.	Intravesical instillation of oxybutynin is especially suitable for patients already on CIC but still incontinent in between due to persisting NDO.
Brendler et al. 1989[82]	• Ten patients reported subjective improvement following treatment and all became totally continent. • Mean bladder capacity increased from 224 to 360 ml ($p<0.01$), mean max. Filling pressure decreased from 33 to 24 cm H_2O ($p=0.17$).	Effective alternative in case of unresponsiveness or intolerable side effects on oral medications.

A starting dose of 2 mg daily for children between the ages of 6 and 12, and of 10 mg daily for the adolescents and adults aged 12 and older is proposed. Following this the MAH recommends that the dose should be increased using a step-wise approach until neurogenic detrusor overactivity is sufficiently controlled to allow close monitoring of both efficacy and safety. This reflects the need of individualised treatment. Intravesical oxybutynin-HCl can be assumed of benefit at these dose ranges based upon the submitted literature.

IV.5 Clinical safety

Safety and tolerability of intravesically administered oxybutynin has been investigated in various studies with different study design, with short or long-term observation, using different dosages and different preparations (see Table 2). The studies are published from 1989 to 2016.

The profile of adverse events (AEs) observed in the published clinical trials is in line with what is known for the pharmacological class of anticholinergic drugs. Most AEs described in clinical studies were non-serious and fatal cases have not been reported. In some cases, AEs led to discontinuation of therapy, especially in paediatric patients. As oxybutynin is able to cross the BBB and to stimulate muscarinic receptors in the brain, AEs affecting the CNS may occur, particularly upon oral administration. It has been shown that intravesical administration of oxybutynin is accompanied by a reduced first-pass metabolism and therefore, systemic AEs such as dry mouth, constipation or dizziness may occur less frequently.
An increased incidence of asymptomatic bacteriuria (ABU) und urinary tract infections (UTI) has been reported. To avoid the occurrence of ABU and UTI due to application errors, oxybutynin-HCl 0.1% intravesical solution should only be used in cases where CIC has already been established.
Due to insufficient clinical data on the safety of intravesical oxybutynin in pregnant women and an abnormal embryo-foetal development observed in animal studies, the proposed

[81] Madersbacher H and Jilg G. Control of detrusor hyperreflexia by the intravesical instillation of oxybutynin hydrochloride. 1991;29:84-90.
[82] Brendler CB, Radebaugh LC, Mohler JL. Topical oxybutynin chloride for relaxation of dysfunctional bladders. 1989;141:1350-1352.

medicinal product should not be used unless clearly necessary. Furthermore, the use of the proposed medicinal product is not recommended during breast-feeding and lactation.
In children and elderly patients, some of the clinical data suggest a higher prevalence of systemic AEs affecting the CNS such as hallucinations and disturbance in attention. Discontinuation of intravesical oxybutynin resulted rapidly in recovery without any additional treatment. New safety concerns could not be identified. The proposed drug product should be used with particular caution in these special populations.
In several studies, patients were switched from oral anticholinergics therapy due to either intolerable systemic adverse reactions and/or insufficient response to the oral treatment. In a considerable number of patients, intravesical treatment with oxybutynin-HCl was shown to be well tolerated compared to treatment with oral anticholinergics.

Overall, based on safety information from literature publications and post-marketing data of other approved oxybutynin preparations, new safety issues have not been identified for intravesical oxybutynine. Non-serious local reactions such as administration site pain may occur. Intravesical oxybutynin showed an acceptable safety profile in both, short-term as well as long-term clinical use. All systemic AEs, which are reported in the literature, resulted from an exacerbated pharmacology, also in case of overdose. It is noted that AEs concerning the CNS, including psychiatric AEs, might be more common in children and elderly patients compared to adults. In general, patients should closely be monitored for the occurrence of systemic anticholinergic AEs, particularly when high doses are indicated.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Vesolox 1 mg/ml.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Psychiatric and CNS anticholinergic events especially in elderly patients and children
Important potential risks	• Exacerbation of cardiac disorders
Missing information	• Use in pregnant or breastfeeding women • Use in fertile women or men

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

The first publication on intravesical use of oxybutynin dates from 1989 and articles appear in literature since. The latest study was published in 2017. Within the EU, publications go back

to 1991. The MAH has provided evidence of well-established use within the EU for at least ten years with doses as recommended in the SmPC. It is estimated that approximately 15,000 patients were treated with intravesical oxybutynin-HCl within the EU in 2014.
Of the submitted publications, 18 studies included paediatric patients from three months up to 18 years of age. In total, since 1989, clinical use of intravesical oxybutynin-HCl in about 296 children has been demonstrated in public literature. In the EEA, about 175 children were treated with oxybutynin-HCl intravesically in the course of published clinical trials since 1995.
Currently no EMA guidelines dedicated to NDO are available although the guideline on incontinence (CPMP/EWP/18/01/Rev. 1) discussed NDO in children and makes some recommendations on the parameters to be studied. According to this guidance, the patient reported outcome should be the primary endpoint (micturition and incontinence episodes). In children with NDO, the treatment aim should be to maintain a low bladder pressure (below 40 cm H_2O) as assessed by cystometry.
Although the results within each study were highly variable, some effect of intravesical oxybutynin on urodynamic parameters can be assumed in short, mid and long-term use. Some effects on urodynamic parameters could be demonstrated with different formulations and preparations from dissolved crushed tablets up to pharmacy-manufactured sterile solutions in prefilled syringes. Moreover, these studies also showed that intravesical treatment using prefilled sterile syringes is more convenient than the previously used solutions of crushed tablets resulting in an increased patient compliance. The applied doses ranged from 0.14 to 0.9 mg/kg bw.
Studies investigating the effect of intravesical oxybutynin on the detrusor pressure showed that the bladder pressure decreased upon instillation of oxybutynin. In many cases, the bladder pressure decreased below the threshold of 40 cm H_2O (above this threshold there is an increased risk of kidney damage).
Limited information on patient reported outcomes (micturition and incontinence episodes) was available in the submitted publications. The information available indicated a reduction in micturition and incontinence episodes.

The profile of AEs observed in the publications is in line with what is known for the pharmacological class of anticholinergic drugs. To avoid the occurrence of ABU and UTI due to application errors, oxybutynin-HCl 0.1% intravesical solution should only be used in cases where CIC has already been established. Compared to oral oxybutynin treatment the safety profile appears somewhat mitigated however, no scientific proof for a beneficial safety profile for the intravesical administration compared to the oral formulation exists.

The results reported in the various studies, together with the advice given in various guidelines, indicate that intravesical instillation with oxybutynin is an effective and safe technique in the treatment of neurogenic bladder and that intravesical oxybutynin seems to be effective in treating incontinence and may have some protective effect on the lower urinary tract by reducing detrusor pressure below 40 cm H_2O.

Taken together the use of this intravesical oxybutynin product as a last resort treatment is positive. The MAH demonstrated comparability of Vesolox with other formulations of the

same active substance, which have been used in published clinical trials. Furthermore, prescription data of the proposed drug product demonstrated systematic clinical use for at least ten years.

Children
Whereas the efficacy and safety of intravesical oxybutynin-HCl can be concluded in children, adolescents and adults over the age of six years, clinical data on intravesical treatment with oxybutynin-HCl in children below the age of six years is limited and juvenile toxicology data are not available at all. Therefore, a reliable conclusion on the efficacy and safety in children below the age of six years cannot be drawn. As potential risks cannot be sufficiently assessed in this age group, treatment with the proposed medicinal product is not recommended in children below the age of six years.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with five participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The member states, on the basis of the data submitted, considered that Vesolox 1 mg/ml, solution for intravesical use demonstrated a satisfactory risk/benefit profile in the indication *suppression of detrusor overactivity due to spinal cord injury or myelomeningocele (spina bifida) in children from six years of age and adults, who are managing bladder emptying by clean intermittent catheterisation, not adequately managed with oral anticholinergics*.

The product has a proven chemical-pharmaceutical quality. The non-clinical and clinical data in support of the application are sufficient.

In the Board meeting of 29 June 2017, the GMP status of the finished product manufacturer with respect to the sterilisation process of the drug product, the comparison of the product applied for with products described in literature, and whether the use of the product was well-established, was discussed. Following the meeting, the issues have been adequately justified.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted,

considered that adequate evidence of efficacy and safety has been demonstrated for the approved indication and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 25 July 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse