COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Velariq 1 mg/ml intravesical solution

(oxybutynin hydrochloride)

NL/H/5240/001/DC

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This module reflects the scientific discussion for the approval of Velariq 1 mg/ml intravesical solution. The procedure was finalised at 15 September 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ABU	Asymptomatic Bacteriuria
ASMF	Active Substance Master File
BBB	Blood Brain Barrier
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
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
DEO	N-Desethyl-Oxybutynin
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
INN	International Nonproprietary Name
MAH	Marketing Authorisation Holder
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
SCI	Spinal Cord Injury
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UTI	Urinary Tract Infections
vPvB	very Persistent and very Bioaccumulative

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Velariq 1 mg/ml intravesical solution, from Medice Arzneimittel Pütter GmbH & Co. KG.

The product solution is indicated for the suppression of detrusor overactivity due to spinal cord injury or myelomeningocele (spina bifida) in children from 6 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 (CMSs) 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.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of oxybutynin. The marketing authorisation holder (MAH) should demonstrate that the active substance of the medicinal product has been in use within the Community for at least ten years for the condition indicated. Further, the results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. To use the results from literature, Velariq should be bridged to products most commonly studied in the scientific literature.

Assessment of the WEU

The active substance oxybutynin hydrochloride was first approved in Greece in 1979 as a 5 mg tablet formulation. Currently various intravesical formulations of oxybutynin are registered within the EU.

Data form national registries in Germany, Sweden, and the Netherlands suggest that approximately 1.4% – 3.3% of patients with Neurogenic Detrusor Overactivity (NDO) resulting from spinal cord injury (SCI) are currently treated with licensed instillation liquids containing oxybutynin in these countries. This should be considered a considerable portion of the patients. Therefore it is shown that oxybutynin is in use since 1975 (over 10 years) and is currently still in use for the treatment of NDO.

II. QUALITY ASPECTS

II.1 Introduction

Velariq is a clear, colourless solution with a pH of 3.8 to 4.2 and an osmolality of 280 – 300 mOsmol/kg. It contains as active substance 1 mg oxybutynin hydrochloride per ml solution.

The solution is supplied in sterile, prefilled ready-to-use syringes of 10 ml each. The syringes are made of cycloolefin copolymer and are closed with a plunger stopper and tip cap, both of synthetic bromobutyl rubber. The prefilled syringes are single dose containers, any unused product must be discarded immediately.

The excipients are hydrochloric acid (dilute) and sodium chloride solution (0.9 %).

II.2 Drug Substance

The active substance is oxybutynin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a white or almost white crystalline powder and is freely soluble in water.

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. and with the additional requirements described on the CEP. In addition, a test for bacterial endotoxins is performed. All tests are performed according to compendial methods, which are considered validated. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for four years when stored in a container consisting of double polyethylene bags placed in a HDPE drum. 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. The following aspects have been taken into consideration: stability of the active substance, physico-chemical and microbiological properties and sterility of the drug product.

The choice of excipients has been justified and their functions have been explained. The choices of the manufacturing process and packaging are sufficiently justified.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. It involves the filtration of a bulk solution of the drug product, which is then filled in the syringe and sterilised. Sufficient details are provided and in general the description of the manufacturing process is acceptable. The manufacturing process is used in the commercial manufacture of the drug product. It is a standard process, which has been sufficiently validated.

Control of excipients
The excipient hydrochloric acid solution complies with the Ph. Eur. requirements. Sodium chloride solution is tested according to British pharmacopoeia since no Ph. Eur. monograph is available. The tests used to control the excipients are performed according to European or British pharmacopoeia procedures. 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, identification, assay, related substances, pH, extractable volume, particulate matter, sterility, bacterial endotoxins, uniformity of dosage units and leachable. 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 of three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three pilot batches stored at 30°C/60% RH (12 months) and 40°C/75% RH (9 months). The batches were stored in a 10 ml syringe with Tip Cap and bromobutyl plunger stopper. The conditions used in the stability studies are according to the ICH guideline. Forced degradation studies have been performed, which

confirm the stability indicating nature of the methods for assay and related impurities. On basis of the data submitted, a shelf life was granted of 18 months. The storage claim 'this medicine does not require any special storage conditions' was acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided for the sodium chloride solution and drug substance and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Velariq 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

This well-established use application contains detailed references to published literature on non-clinical aspects, as well as other evidence obtained from expert committee reports and published product monographs of licensed products. The information presented for the non-clinical pharmacology section was based on relevant scientific literature over the period of 1960 up to very recent. This is accepted. The MAH has performed a study to determine potential ecotoxicity of the active substance.

III.2 Pharmacology

The relaxant effect of oxybutynin in the urinary bladder seems to be related to more than one mechanism: an anticholinergic effect, a direct anti-spasmodic effect and a local anaesthetic effect. Radioligand binding studies in various animal tissues have shown that oxybutynin has high affinity for the muscarinic receptors M1 and M3, the affinity being 7-fold to 10-fold greater for M1 and M3 than for M2 receptors (Chapple et al., 2002). The direct anti-spasmodic effect of oxybutynin has been shown in numerous in vitro animal studies using isolated detrusor or intact bladder preparations. Growing evidence indicates that oxybutynin also modulates the afferent arc of the micturition cycle (Williams et al., 2015). Oxybutynin administered intravenously, subcutaneously or intravesically has been demonstrated to have a number of beneficial urodynamic effects, such as reducing maximum intravesical pressure during both the emptying and filling phases as well as micturition pressure and increasing

bladder threshold volume and bladder capacity (Yarker et al., 1995, Nagabukuro et al., 2011). It has to be noted that, in experimental studies, the effects of anticholinergic drugs on detrusor muscle are strongly dependent on the species, and the results cannot easily be transferred to humans (Wust et al., 2002). It is herewith recommended to consider the extensive pool of data from clinical studies with oxybutynin.

The precise mode of action of intravesical oxybutynin regarding suppression of bladder contractility is still unknown and might differ from that of oral oxybutynin. It is unclear whether the efficacy of intravesical oxybutynin results from a local or a systemic effect. Some studies have indicated that the beneficial effect of intravesical oxybutynin is due to a systemic effect following absorption of the agent across the bladder wall (Massad et al., 1992, Madersbacher and Knoll, 1995, Lehtoranta et al., 2002). Other studies consider a local effect to be responsible for the beneficial effect, since no correlation has been found between oxybutynin plasma concentration and therapeutic effects of intravesical oxybutynin (Wust et al., 1998, Massad et al., 1992).

III.3 Pharmacokinetics

Oral oxybutynin is rapidly and substantially absorbed, with maximum plasma concentrations after about an hour (Douchamps et al., 1988, Aaltonen et al., 1984). Intravesical oxybutynin also shows rapid and substantial absorption. Serum levels after intravesical instillation have been found to be as high or even higher than those after oral intake (Lehtoranta et al., 2002, Massad et al., 1992). Although oral oxybutynin is well absorbed, it undergoes extensive first-pass metabolism, with approx. 6% bioavailability in healthy subjects (Douchamps et al., 1988). Oxybutynin is metabolised primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. The primary circulating metabolite after oxybutynin oral administration is N-desethyloxybutynin (DEO) (Aprile et al., 2018, Lindeke et al., 1981). DEO has muscarinic receptor binding activity and anticholinergic and antispasmodic properties similar to those of oxybutynin (Oki et al., 2005, Uchida et al., 2004). Oxybutynin is rapidly eliminated from the body. The elimination half-life was about 2 h after oral (5 mg) and bolus intravenous (1 mg) administration (Douchamps et al., 1988). The elimination of oxybutynin as well as its metabolite was prolonged after intravesical administration compared with that reported after oral drug intake (Lehtoranta et al., 2002).

Intravesical application of oxybutynin results in a favourable ratio of oxybutynin to DEO, due to a reduced first-pass mechanism (Lehtoranta et al., 2002, Buyse et al., 1998, Amark et al., 1998), and may explain the clinically relevant reduction of side effects that characterises intravesical compared with oral oxybutynin therapy.

III.4 Toxicology

The results of sub-acute and chronic toxicity studies in mice, rats and dogs indicate that oxybutynin has a wide margin of safety and is a relatively non-toxic agent (Lish et al., 1965). LD50 values of oral toxicity in several animal species were reported between 725 mg/kg in

mice and 2030 mg/kg in rats. An oral LD50 of 560 mg/kg body weight was reported for new-born rats.
Studies in animals have shown minor reproductive toxicity. At maternal toxic doses, oxybutynin administered orally can cause foetal malformations in rats. There are no data on the intravesical use of oxybutynin in pregnant women. Data on possible effects of the use of oxybutynin on human male and female fertility are not available.
Oxubutynin should not be used during pregnancy unless the clinical condition of the woman requires treatment. Available information shows that oxybutynin is excreted in milk of rats, but it is not known whether oxybutynin is excreted in human milk. Use of oxybutynin is not recommended during breastfeeding.

There is no evidence for local toxicity of intravesically administered oxybutynin. In rats treated with intravesical oxybutynin at excessively large doses, there was no histological evidence of mucosal or bladder wall abnormality directly attributable to intravesical oxybutynin exposure (Bonney et al., 1993). Only a high concentration of oxybutynin is considered to be irritating to the bladder mucosa (Yokoyama et al., 1996). Therefore, the 0.1% oxybutynin hydrochloride solution in the medicinal product submitted for regulatory approval is unlikely to have an irritating potential.

Data from clinical studies with oxybutynin did not reveal a risk for local irritation. Further toxicological studies did not reveal any genotoxic or carcinogenic properties of oxybutynin.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The MAH has performed a study to Good Laboratory Practices to determine the n-octanol/water partition coefficient(s) (log K_{ow}) of oxybutynin. The main results of the study are summarised in Table 1.

Table 1 Summary of ERA study results of oxybutynin

Substance (INN/Invented Name): oxybutynin			
CAS-number: 5633-20-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	1.95 (pH 5) 3.54 (pH 7) 4.66 (pH 9)	No potential PBT
PBT-statement :	oxybutynin is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default	0.00894	µg/L	No >0.01 threshold
Other concerns (e.g. chemical class)	--	--	None

INN	international nonproprietary name, in pharmaceutics
CAS-number	unique numerical identifier for chemical substances
OECD123	test method (slow stirring method)
PBT	class of compounds (Persistent, Bioaccumulative and Toxic)

PEC	Predicted Environmental Concentrations
vPvB	class of compounds (very Persistent and very Bioaccumulative)

Conclusions on ERA

The submitted study is considered reliable without restrictions and can be used in the risk assessment. Considering the above data, oxybutynin is not expected to pose a risk to the environment. Oxybutynin is not considered as persistent, bioaccumulative and toxic (PBT), nor very Persistent and very Bioaccumulative (vPvB).

III.6 Discussion on the non-clinical aspects

This application refers to a medicinal product where the active substance has a well-established medicinal use in the meaning of Commission Directive 2001/83/EC, with recognised efficacy and an acceptable level of safety. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided which is based on up-to-date and adequate scientific literature, with references from 1960 up to very recent. This overview justifies why there is no need to generate additional non-clinical data on pharmacology, pharmacokinetics and toxicology. Therefore, the member states agreed that no further non-clinical studies are required.

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. encompassing the pharmacokinetics, where pharmacokinetic data of Velariq was bridged to studies using oxybutynin hydrochloride formulations. Pharmacokinetics, pharmacodynamics, clinical efficacy and safety have also been linked to clinical studies and are considered to be adequate.

IV.2 Pharmacokinetics

The medicinal product Velariq 1 mg/ml is formulated in as a prefilled, ready-to-use syringe with 10 mL solution containing 10 mg oxybutynin hydrochloride. The medicinal product contains an isotonic sodium chloride solution and 10% hydrochloric acid as excipients. The pH of the solution ranges from 3.8 to 4.2.

Based on presented composition of the formulation used in the two pharmacokinetic studies (Schröder, 2016, Krause et al., 2013) it can be concluded that those were simple solutions having the same qualitative composition (sodium chloride 0.9% and hydrochloric acid 0.1%) with similar pH range (3.8-4.2) as the product at issue.

IV.2.1 Absorption

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 application (~3 times higher for both R- and S-oxybutynin) while exposure of the metabolite was considerably lower for both enantiomers.

IV.2.2 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 5 mg oxybutynin was 193 litre.

IV.2.3 Metabolism and excretion

Oxybutynin administered orally is metabolised primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Metabolites include phenyl cyclohexyl glycolic acid, which is pharmacologically inactive, and N-desethyl oxybutynin (DEO), which is pharmacologically active.
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 DEO metabolite.

Oxybutynin is rapidly excreted from the body after oral and intravesical administration. After intravesical administration oxybutynin exhibits a prolonged elimination compared to oral administration with reported elimination half-lives of 2.56 and 1.48 h, respectively.

IV.2.4 Special populations

The MAH referred to three independent studies for evaluating the pharmacokinetics of intravesically applied oxybutynin in children (Amark et al., 1998b, Buyse et al., 1998b, Massad et al., 1992). These paediatric literature data showed high inter-individual variability of pharmacokinetic parameters, e.g. C_{max}, AUC or $T_{1/2}$ both for oxybutynin and its metabolite N-desethyl-oxybutynin after intravesical or oral administration, in line with the adult data.

Based on the provided information, it seems that the PK of oxybutynin is independent of gender or age. No information could be found on the effect of race, renal or hepatic impairment.

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 in these patients (Frankel et al., 1998, Jamil F., 2001).

It can be concluded from human as well as animal data that intravesically applied oxybutynin 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.

The pharmacodynamic interactions are well-known for an anticholinergic drug. Currently these interactions are mentioned in the SmPC of oxybutynin.

IV.4 Clinical efficacy

The submitted studies 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. As the proposed dosing regimen in the SmPC is well within the range of other registered products and those mentioned in literature, and the dosing scheme should be personalised (also stated in the SmPC) the dosing advise in the SmPC is considered acceptable.

In the pivotal, randomised, multicentre trial investigating the efficacy of intravesical oxybutynin treatment in adult patients with NDO (Schröder et al., 2016) 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. Comparison with an oral dosing regimen did not indicate differences in efficacy.

Other studies investigating the effect of intravesical oxybutynin (different formulations and preparations from dissolved crushed tablets up to pharmacy-manufactured sterile solutions in prefilled syringes) 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 (Madhuvrata et al., 2012) (threshold for increased risk of kidney damage).

Overall, the efficacy of intravesical oxybutynin treatment of NDO has been described in 42 clinical publications comprising about 550 patients. The applied doses ranged from 0.14 mg/kg to 0.9 mg/kg bodyweight. A recent meta-analysis 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 indicate a reduction in micturition and incontinence episodes. Moreover, these studies also showed that intravesical treatment using prefilled sterile syringes is more convenient resulting in an increased patient compliance (Buyse et al., 1998a, Buyse et al., 1998b, Buyse et al., 1995).

IV.5 Clinical safety

Safety and tolerability of intravesical administered oxybutynin has been investigated in various studies with different study design, with short or long-term observation, using different dosages and different preparations. The studies include about 550 patients.

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 Blood Brain Barrier (BBB) and to stimulate muscarinic receptors in the brain, adverse events affecting the Central Nervous System (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 adverse events 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 hydrochloride 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 medicinal product should be used only 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 adverse events 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 hydrochloride 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 oxybutynin.

IV.6 Scientific overview

Table 2 Pivotal publications from the dossier

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Schröder et al., Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomised, prospective, controlled multi-center trial, 2016	Design: 12-months, prospective, randomised, open-label, active-controlled, parallel group, multicentre trial Objective: Verification of efficacy, safety and tolerability of intravesical administration of 0.1% oxybutynin hydrochloride compared to oral administration for treatment of NDO	Group 1: Intravesical, 10 ml 0.1% oxybutynin, 3 times a day initially for 28 days. Group 2: Oral, 5 mg oxybutynin, 3 times a day initially for 28 days. 7 day follow-up Extended treatment period (total: 12 months)	Group 1: n=18 (14M/4 F), Group 2: n=17 (12M/5F), age 18 – 70 yrs
Enzelsberger et al., Topical administration of oxybutynin hydrochloride in women with urge incontinence. Results of a prospective randomized double-blind study. 1995	Design Prospective, parallel – no information conc. blinding or randomisation Objective: Reduction in pollacisuria and nykturia	20 mg oxybutynin (n=21) or placebo (n=18) as 40 ml sterile NaCl solution intravesically	39 women with persistent urge incontinence

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Humblet et al., Long-term outcome of intravesical oxybutynin in children with detrusor-sphincter dyssynergia: With special reference to age-dependent parameters. 2015	Design: Retrospective study 10 patients were re-evaluated 15 years after the switch from oral to intravesical oxybutynin Objective: Follow the long-term use and outcome of intravesical instillation of oxybutynin for the treatment of neuropathic bladder-sphincter dysfunction in children	Intravesical application: 5 ml of 0.1% oxybutynin two times daily (10 mg oxybutynin/day) over 15±1 yrs	n=10 (at time of re-evaluation) 4.2±3.2 yrs at start (switching from oral to intravesical oxybutynin) 18.3±2.9 yrs at re-evaluation
Lehnert et al., The effects of long-term medical treatment combined with clean intermittent catheterization in children with neurogenic detrusor overactivity. 2012	Design: Retrospective, patients with myelomeningocele and NDO Objective: Investigating the clinical and urodynamic effects of long-term intravesical oxybutynin instillation compared with a standard treatment of oral anticholinergic medication	Intravesical oxybutynin upon initial treatment with oral anticholinergics and CIC compared to oral anticholinergics and CIC; group I (responding to oral treatment): continuation of oral anticholinergics + CIC, mean follow-up time 7.1 ± 5.5 yrs; group II (poor response to oral treatment or AEs): intravesical oxybutynin + CIC, mean follow-up time 3.6 ± 1.8 yrs	n=21 (10 in group I, 11 in group II) 8.1 ± 6.6 yrs (group I) 12.5 ± 4.5 yrs (group II)
George et al., The effectiveness of intravesical oxybutynin, propantheline, and capsaicin in the management of neuropathic bladder following spinal cord injury. 2007	Design: Prospective, double-blind Objective: To compare the therapeutic response of intravesical oxybutynin, propanthelin, and capsaicin in the treatment of neurogenic detrusor overactivity.	Intravesical application: 5 mg crushed oxybutynin chloride in 10 ml sterile saline 3 times daily	n=18 (17M/1F), age range: 20-53 yrs

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Lehtoranta et al., Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. 2002	Design: Randomly allocated, placebo-controlled, double-blind, cross-over Objective: Determine the pharmacokinetics, efficacy and safety of intravesical oxybutynin in adult patients with detrusor hyperreflexia or instability	Intravesical application: two 14-day periods (I and II), third 14-day open study period (III) for PK purposes period I: 5 mg oxybutynin/30 ml 3 times daily period II: placebo (30 ml of sterile saline)	n=9 (4M/5F) mean age= 37 ± 15 yrs (range: 18 - 64 yrs)
O'Flynn et al., Intravesical instillation of oxybutynin hydrochloride for detrusor hyper-reflexia. 1993	Design: open label, single dose Objective: Efficacy of oxybutynin after intravesical application in patients with urinary incontinence due to detrusor hyper-reflexia	5 mg oxybutynin in water	15 urinary incontinence due to d
Ferrara et al., Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida. 2001	Design: Retrospective Objective: Evaluating the incidence of side-effects of oral and intravesical oxybutynin in children	Oral application (n=67): mean dose of 0.1-0.2 mg/kg bw Intravesical application (n=34): mean dose of 0.1-0.2 mg/kg bw (crushed tablets dissolved in sterile water) 3 years follow-up	n=101 mean age= 4.2 yrs (range: 0.25-10 yrs) myelomeningocele cases at high risk of upper urinary tract dysfunction

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Haferkamp et al., Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. 2000	Design: Prospective, cohort study Objective: Analysing dose dependent outcome and side effects of neurogenic bladder patients with intravesical application of oxybutynin	Start treatment: 0.3 mg/kg bodyweight (bw) per day, divided into three portions instilled every 8 h Non-responder: increase in steps of 0.2 mg/kg bw per day up to a maximum dosage of 0.9 mg/kg bw per day (n=11)	n=32 mean age: 12 yrs (range: 1 - 34 yrs) 17 with spinal cord injury, 15 with myelomeningocele
Pannek et al., Combined intravesical and oral oxybutynin chloride in adult patients with spinal cord injury. 2000	Design: Prospective, open-label Objective: Evaluating effects of intravesical oxybutynin treatment on detrusor hyperreflexia in patients in whom standard oral treatment had failed.	Intravesical application: 15 mg oxybutynin 3 times daily (15 mg oxybutynin dissolved in 15 ml sterile isotonic saline) mean follow-up: 6 months (range: 3-16 months)	n=25 (19 M/6F), mean age 36.7 yrs (range: 18-64 yrs) patients with spinal cord injury
Amark et al., Follow up of long time treatment with intravesical oxybutynin for neurogenic bladder in children. 1998a	Design: Prospective, open-label Objective: Treatment of patients suffering from myelodysplasia, neurogenic bladder and high bladder pressure with a sterile oxybutynin solution	Intravesical application: 0.1 mg/kg 2 times daily (oxybutynin dissolved in normal saline to 0.5 mg/ml, sterile, pH 5.0) mean follow-up: 2.25 yrs	n=39 (23M/16F), mean age: 7.9 yrs (range: 0.5 – 18 yrs) most patients with myelomeningocele
Amark et al., Pharmacokinetics and effects of intravesical oxybutynin on the paediatric neurogenic bladder. 1998b	Design: Prospective, open-label Objective: Evaluating the pharmacokinetics of both oxybutynin and its active metabolite upon intravesical instillation in children with NDO	Intravesical application: 0.07 to 0.17 mg/kg 2 times daily (corresponds to 0.7 up to 6.0 mg)	n=13 (8 M/5 F), mean age: 9.3 yrs

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Saito et al., Treatment of overactive bladder with modified intravesical oxybutynin chloride. 2000	Design: Open - patients who did not respond to oral anticholinergic agents and electric stimulation Objective: effects of intravesical oxybutynin chloride with hydroxypropylcellulose (modified intravesical oxybutynin)	5 mg/10 mL, twice a day	Six (two men and four women; average age, 56.5 years) overactive bladder
Saito et al., Urodynamic effects and safety of modified intravesical oxybutynin chloride in patients with neurogenic detrusor overactivity: 3 years experience. 2004	Design: Uncontrolled adults, Follow-up study, open Objective: follow-up study of patients with neurogenic overactive detrusor from their previous analysis of modified intravesical oxybutynin.	intravesical oxybutynin (5 mg/10 mL, twice a day)	Neurogenic overactive detrusor patients (3 men and 3 women, average age 53.3 years)
Buyse et al., Intravesical application of stable oxybutynin solution improves therapeutic compliance and acceptance in children with neurogenic bladder dysfunction. 1998a	Design: Prospective, open-label Objective: Evaluation of a stable oxybutynin solution for intravesical oxybutynin therapy for neurogenic bladder dysfunction.	Intravesical application: 0.2 mg/kg (max. 5 mg) 2 times daily of a 0.1% Oxybutynin solution, pH 5.85) follow-up after 4 and 24 months	n=15 (6M/9F), mean age: 6.1 yrs (range: 0.6 to 13.8 yrs)

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Vaidyananthan et al., Effect of intermittent urethral catheterization 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	Design: Prospective, open-label Objective: Comparative assessment of urinary status, quality of life and sexuality in spinal cord injury patients prior to, and during CIC with adjunctive intravesical oxybutynin therapy	Intravesical application: 5 mg oxybutynin in 30 ml 5-6 times a day, 1-3 times a day for periods ranging from 14 to 30 months	n=7 (males) mean age= 44.3 yrs patients with spinal cord injury
Holland et al., Intravesical therapy for the treatment of neurogenic bladder in children. 1997	Design: Prospective Objective: Evaluating effects of intravesical oxybutynin in patients requiring CIC for neurogenic bladder over a 1-year period.	Intravesical application: 0.1 mg/kg oxybutynin 3 times daily (catheter flushed with 2 ml sterile water afterwards) 1 year follow-up	n=7, mean age: 7.5 yrs (range: 2.5 to 15 yrs) 6 cases of spina bifida, 1 case of sacral agenesis
Guerrero et al., Intravesical oxybutynin: practicalities of clinical use. 2006	Design: Retrospective Objective: Efficacy in patients with idiopathic detrusor overactivity, whose symptoms having been unsuccessfully controlled on oral agents	Oxybutynin intravesically – no information concerning preparation or concentration of the drug	11 idiopathic detrusor overactivity (DO), symptoms having been unsuccessfully controlled on oral agents

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Szollar and Lee, Intravesical oxybutynin for spinal cord injury patients. 1996	Design: Prospective, open-label Objective: To evaluate efficacy of intravesical oxybutynin in patients with spinal cord injury	Intravesical application: 5 mg tablets (Ditropan) crushed and diluted in 30 ml saline, 3 times daily 3 months follow-up	n=13 mean age: 41 yrs (range: 20-68 yrs) patients with spinal cord injury
Painter et al., Long-term intravesical oxybutynin chloride therapy in children with myelodysplasia. 1996	Design: Retrospective study Objective: To evaluate the clinical use of long-term intravesical oxybutynin chloride in the treatment of neurogenic bladder dysfunction in children with myelodysplasia	Intravesical instillation: 5 mg tablet dissolved in 10 cc water 2 times daily long-term follow-up from 2 to 26 months	n=30 (18M/12F), mean age: 8.6 yrs (range: 1 to 17 yrs) patients with myelodysplasia
Kaplinsky et al., Expanded follow-up of intravesical oxybutynin chloride use in children with neurogenic bladder. 1996	Design: Prospective, open-label Objective: Long-term follow-up to evaluate intravesical oxybutynin chloride use in children with neurogenic bladders	Intravesical application: 5 mg crushed oxybutynin chloride in 10 ml sterile saline 2 times daily	n=28 (15M/13F), age ranging from 3 to 18 yrs 27 with myelomeningocele, 1 imperforate anus
Madersbacher et al., Intravesical application of oxybutynin: mode of action in controlling detrusor hyperreflexia. Preliminary results. 1995	Design: Prospective pilot-study Objective: Evaluation of the resorption rate of intravesically given oxybutynin in the bladder in comparison with oral intake	Comparative approach: oral: single 5 mg dose intravesical: single 5 mg dose	n=6 patients with suprasacral spinal cord lesion

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Buyse et al., Treatment of neurogenic bladder dysfunction in infants and children with neuospinal dysraphism with clean intermittent (self) catheterization and optimized intravesical oxybutynin hydrochloride therapy. 1995.	Design: Prospective, open-label Objective: Optimisation of drug preparation using purified oxybutynin and investigation of the efficacy of intravesical oxybutynin as a monotherapy	Intravesical application: 0.1% oxybutynin, 0.2 mg/kg (max 5 mg) twice daily for 6 months	n=15 (6M, 9F), mean age: 6.1 yrs. (range: 0.6 to 13.75 yrs) 12 patients with myelomeningocele, 1 with lipomeningocele, 1 with caudal dysplasia, 1 with transverse spinal cord injury
Mizunaga et al., Intravesical instillation of oxybutynin hydrochloride therapy for patients with a neuropathic bladder. 1994	Design: Prospective, open-label Objective: Investigating long-term clinical effects of intravesical instillation of oxybutynin	Intravesical application: crushed oxybutynin tablets, 5 mg oxybutynin/10 ml sterile solution, pH 5.85, twice daily for 1 month	n=17 (9M/8F), mean age: 12.3 yrs (range: 4 to 45 yrs) 15 cases with myelomeningocele, 2 cases of spinal cord tumour
Massad et al., The pharmacokinetics of intravesical and oral oxybutynin chloride. 1992	Bioavailability study Oral vs. intravesical administration of oxybutynin Objective: Pharmacokinetics of oxybutynin and its main active metabolite DEO after multiple dosing	7.5 mg/30 ml three times daily	8 children with cystometric evidence of bladder instability and marked systemic side effects to oral oxybutynin

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Kasabian et al., The use of intravesical oxybutynin chloride in patients with detrusor hypertonicity and detrusor hyperreflexia. 1994	Design: Prospective Open-label Objective: To evaluate safety and efficacy of intravesical oxybutynin treatment in patients with NDO	Intravesical application: 5 mg oxybutynin tablet dissolved in 20 to 30 cc saline twice daily some patients increased to 5 mg 4 times daily	n=18 11 children with myelomeningocele mean age: 7.7 yrs (range 4-12 yrs) 7 adults with MS (2) or spinal cord injury (5) mean age: 31.5 yrs (range 19-33 yrs)
Connor et al., Early cystometrograms can predict the response to intravesical instillation of oxybutynin chloride in myelomeningocele patients. 1994	Design: Prospective, open-label Objective: Testing efficacy of intravesical oxybutynin in a myelomeningocele population	Intravesical application: 5 mg oxybutynin tablet dissolved in 10 m sterile water twice daily for at least 3 months	n=28 only 13 completed trial (9M/4F) mean age: 8.7 yrs (range 1-19 yrs) myelomeningocele
Weese et al., Intravesical oxybutynin chloride: Experience with 42 patients. 1993	Design: Prospective, open-label Objective: To evaluate the efficacy of intravesical oxybutynin in patients with detrusor hyperreflexia (n=20), detrusor instability (n=19), bowel/bladder overactivity (n=3)	Intravesical application: 5 mg oxybutynin three times daily (5 mg oxybutynin tablet dissolved in 30 cc water) mean follow-up: 18.4 months	n=42 (15M/27F), mean age: 55 yrs (range: 16 to 79 yrs) 33 patients followed the protocol
Greenfield et al., The use of intravesical oxybutynin chloride in children with neurogenic bladder. 1991	Design: Pilot study, open-label Objective: Report on efficacy of intravesical oxybutynin children with hyperreflexic, hypertonic bladder	Intravesical application: 5 mg crushed oxybutynin tablets in 10 ml sterile saline (0.05% solution) 2 times daily	n=10 (7M/3F), 4 to 18 yrs of age 9 patients with spina bifida, 1 with imperforate anus

Author, Title, Year	Design and study objective	Study posology	Number of patients, age, gender
Madersbacher and Jilg, Control of detrusor Hyperreflexia by the Intravesical Instillation of Oxybutynine hydrochloride. 1991	Design: Prospective pilot study, open-label Objective: Evaluating efficacy and safety of oxybutynin given intravesically	Intravesical application: 5 mg crushed oxybutynin (tablets) dissolved in 30 cc water one single dose, follow-up after 6 hours	n=13 (10M/3F), mean age: 30 yrs (range: 19-60 yrs) patients with complete suprasacral spinal cord lesions
Brendler et al., Topical oxybutynin chloride for relaxation of dysfunctional bladders. 1989	Design: Prospective pilot study, open-label Objective: Testing an alternative application technique for patients with persistent urge incontinence and frequent side effects on oral anticholinergic agents	Intravesical application: 5 mg tablets dissolved in saline, instilled twice daily	n=13, mean age: 45 yrs (range: 7 - 76 yrs) patients with neurogenic bladder due to different underlying diseases

IV.7 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 Velariq 1 mg/ml.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.8 Discussion on the clinical aspects

For this well-established use application no new clinical studies were conducted.

Currently oral antimuscarinic therapy is the recommended first-line medical treatment. Current guidelines on the management of NDO. The European Association of Urology (EAU), state that anticholinergics may also be applied intravesical to reduce NDO.
Currently various intravesical oxybutynin formulations are registered within the EU.
The extent of exposure to intravesically administered oxybutynin has been documented in bibliographic studies from 1989 onwards.

Data form national registries in Germany, Sweden, and the Netherlands suggest that approximately 1.4% – 3.3% of patients with NDO resulting from spinal cord injury (SCI) are currently treated with intravesical oxybutynin in these countries. This should be considered a considerable portion of the patients especially taken into consideration that a considerable number of patients is treated with pharmacy made formulations.
The MAH demonstrated that oxybutynin is commonly used (i.e. the use by a considerable proportion of the patients) within the EU for more than 10 years.

Currently no EMA guidelines dictated 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 studies. 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.

The total of number of patients included in the various studies is about 550. Although the results within each study were highly variable, 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. The applied doses ranged from 0.14 mg/kg 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. As oxybutynin is able to cross the BBB and to stimulate muscarinic receptors in the brain, adverse events affecting the CNS may occur. It has been shown that intravesical administration of oxybutynin is accompanied by a reduced first-pass metabolism and therefore, systemic adverse events such as dry mouth, constipation or dizziness may occur less frequently.

Moreover, these studies also showed that intravesical treatment using prefilled sterile syringes is more convenient than the previous used solutions of crushed tablets resulting in an increased patient compliance.

Taken together, the use of this intravesical oxybutynin product for the proposed indication has been established as the majority of studies in subjects showed clinically relevant results. The MAH demonstrated comparability of Velariq 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. Also, the risk management is adequately addressed. Finally, it is considered that the safety issues identified are adequately addressed in the SmPC.

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 language used for the purpose of user testing the PL was English. The test consisted of: a pilot test, followed by two rounds with 10 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 package leaflet 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 Velariq 1 mg/ml intravesical solution 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 6 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.

The Board followed the advice of the assessors.

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 well-established use has been demonstrated for Velariq with the reference product and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 15 September 2021.

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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
NL/H/5240/001/IA/001	Type IAin: B.IV.1.a.1 _Addition of a step cone adapter in the packaging containing the pre-filled syringes.	Paragraph 6.5 of SmPC and PL	31 December 2021	Approval	