Public Assessment Report
Scientific discussion

Oxybutynin Unimedic
(oxybutynin hydrochloride)

Asp no: 2016-1468

This module reflects the scientific discussion for the approval of Oxybutynin Unimedic.
The procedure was finalised on 2017-12-19. For information on changes after this date
please refer to the module ‘Update’.
I. INTRODUCTION

Unimed AB has applied for a marketing authorisation for Oxybutynin Unimedic, 0.5mg/ml, intravesical solution. The active substance is oxybutynin hydrochloride which has an antimuscarinic action.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.
III. NON-CLINICAL ASPECTS

III.1 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. No safety pharmacology data has been presented. However, adverse cardiovascular, CNS or respiratory effects are not expected based on the clinical experience of the product.

III.2 Pharmacokinetics
Oxybutynin will be administered intravesically. Metabolism of absorbed oxybutynin will likely primarily occur in the hepatic circulation and is mediated by the cytochrome P450 3A4 and 3A5 isozymes. Excretion of oxybutynin occurred primarily by the fecal route in rats, and in equal amounts in feces and urine in dogs. Pharmacokinetic interactions may occur with drugs that are CYP3A4 substrates/inhibitors/inducers.

III.3 Toxicology
The Applicant has provided genotoxicity information from CDER and from the EPAR for Kentera. As there is no data protection for these data, and there is no concern regarding genotoxicity for oxybutynin, it can be concluded that no additional evaluation of genotoxicity is considered necessary. Carcinogenicity studies are sparse, but a study by CDER which evaluated carcinogenic potential of oxybutynin showed a negative result. Reproductive and developmental toxicity studies with oxybutynin referenced by the Applicant have shown an increased incidence of fetal malformations, extended gestation period and impaired postnatal performance of offspring in rat. In an embryotoxicity study in the rabbit, the occurrence of organ anomalies is significantly increased at a concentration of 0.4 mg/kg/day oxybutynin administered subcutaneously. Thus, based on the data provided it can be concluded that oxybutynin should not be used during pregnancy. Local tolerance studies in rat and rabbit bladders with instilled intravesical oxybutynin collectively support that no major local toxicities are to be expected with intravesical oxybutynin instillation in the clinic.

III.4 Ecotoxicity/environmental risk assessment
The Applicant had not performed an adequate ERA which is in accordance with relevant guidelines. Thus, the Applicant was asked to provide with a revised and updated ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, 01 December 2006). In the response, the Applicant submitted an ERA, and a justification for not performing an ERA initially. While the submitted ERA has its limitations, it is agreed that oxybutynin is intended for generic substitution, and that this will not lead to an increased exposure to the environment.
IV. CLINICAL ASPECTS

IV.1 Introduction

Oxybutynin was approved in 1975 to treat bladder overactivity due to neurogenic detrusor overactivity, or idiopathic detrusor overactivity (urge incontinence). However, oxybutynin for intravesical application has previously not been approved in Sweden.

The earliest reports on intravesical treatment were published during the 1990ies (Singh 1995, Szollar 1996, von Zweibergk 1996, Vaidyananthan 1998). There are recommendations and guidelines for multiple sclerosis with neurogenic bladder disorder (Lycke et al 2015), in the treatment of NDO, MPA (Läkemedelsverket 2011) and the Swedish Neuropaediatric Association (2011) for medical follow-up of spina bifida (MMC). The Swedish Association of Urology (2015) states that intravesical treatment is more efficacious than oral treatment but the administration, with two to three self-instillations each day, is clearly more demanding. “In adults: the patient instills 10 - 20 ml of a 0.5 mg/ml solution two to three times daily. The most common drug in children is oxybutynin hydrochloride in the dose 0.1-0.15 mg/kg x 2. “

Local treatment guides are available at the University Hospital of Skåne as well as in Queen Silvias Hospital for children and youth (Holmdahl 2016) and from a Swedish paediatric surgeon at University Hospital of Skåne (Börjesson 2017). “The patient is prescribed Oxybutynin HCl sterile solution 0.5 mg/ml. The posology is 0.1 mg/kg morning and evening.”

IV.2 Pharmacokinetics

Absorption

Following intravesicle administration of 5 mg oxybutynin 0.17 mg/ml (30 ml) tid for two weeks, the total exposure (over 24h) of N-desethyloxybutynin was about 2-fold higher than the exposure of parent compound. Cmax of the metabolite was ca 1.5-fold higher than Cmax of oxybutynin.

The total exposure of oxybutynin was about 3-fold higher and N-desethyloxybutynin only about 20% after an intravesicle instillation of 10 mg oxybutynin compared to after an oral dose of 5 mg (dose-normalized to 10 mg) in adults, using a ready to use solution Oxybutynin 0.1% and a Oxybutynin tablet 5 mg Dridase.

The literature shows a Cmax of about 10 ng/ml oxybutynin following intravesicle administration of oxybutynin 5 mg in adults, irrespective of concentration of the formulation used. No clear data on the total exposure are available.

Distribution

The protein binding of oxybutynin is reported to be 85% in human serum and the volume of distribution has been calculated to 193 L.

Elimination

Sparse data/information on excretion of oxybutynin have been provided. After oral administration about 10-25% of the dose was excreted as metabolites in the urine. Eight metabolites have been identified in human urine.

In vitro, using human liver microsomes, CYP3A mediated formation of N-desethyloxybutynin seems as the main metabolic pathway.
**Special population**
No data has been provided in patients with renal or hepatic impairment. Neither are any data on potential influence on the PK of gender, race and weight presented or PK of oxybutynin in the elderly.

The systemic exposure of oxybutynin and N-desethyloxybutynin following intravesicle instillation have been determined in children 1-18 years. Doses of 0.04-0.25 mg/kg have been given using *ex tempore* solutions 0.25 and 1 mg/ml but no discussions are provided considering doses, systemic exposure and age distribution in the children population.

Following administration of oxybutynin 5 mg in children resulted in higher exposure compared to in adults.

**Interactions**
Sparse data/information on potential PK drug interactions are provided. Co-treatment with CYP3A inhibitors may lead increased systemic exposure resulting in potentiated anticholinergic effect.

**Discussion on Clinical Pharmacology**
This is a full application for Oxybutynin Unimedic® 0.5 mg/ml via the National Procedure according to Article 10a well-established use. A full application should cover all aspects based on relevant literature, however, the submitted file lacks data on basic PK of oxybutynin in many aspects.

The systemic exposure following intravesicle instillation of oxybutynin 5 mg has been determined in adults using formulations with varying concentrations, a $C_{max}$ of *ca* 10 ng/ml oxybutynin was achieved irrespective of concentration of the formulation. No consistency is seen in the reported exposure of N-desethyloxybutynin.

The Applicant refers to Kennelly (2010) who compares exposure of parent compound and the metabolite following oral and topical administration. About a 4- to 5-fold higher exposure of the metabolite compared to oxybutynin was seen after an oral dose and up to about 1.3-fold higher after an administration with no first pass metabolism which is the case following intravesicle dosing.

The exposure of both oxybutynin and N-desethylbutynin was higher in children compared to adults (Buyse *et al*1998).

Oxybutynin is a racemate but details on the bioanalytical assays used are lacking except in one publication (Krause *et al* 2013) were an enantioselective assay was used.

The steady state total exposure of the N-desethyloxybutynin was about 2 fold higher than the exposure of parent compound following intravesicle instillation tid with 5 mg oxybutynin 0.17 mg/ml (Lehtoranta *et al* 2002). But after a single instillation of 10 mg oxybutynin 1 mg/ml the total exposure of R-forms (active) of oxybutynin and N-desethyloxybutynin are comparable (Krause *et al* 2013). The levels of the S-forms seemed to be slightly higher than the levels of the R-forms. The potential inter-conversion has not been considered.

*In vitro* data shows comparable skin flux of R- and S-oxybutynin. Stereoselective metabolism was seen after both transdermal and oral administration of oxybutynin but more pronounced following the oral route. After intravesicle administration, a higher exposure of S-oxybutynin compared to the R-form was seen and slightly higher levels R-desethyloxybutynin compared the S-desethyl-oxybutynin.

To understand / predict potential DDIs, the elimination *ie* both excretion and metabolism will
have to be known. Eight metabolites have been identified in human urine following oral administration. About 10-25% of the dose was excreted as metabolites in the urine. How the remaining 75% is eliminated is unclear.

*In vitro*, CYP3A mediated formation of N-desethoxybutynin seems as the main metabolic pathway.

The PK of active metabolites and others with high exposure are lacking.

The effect oxybutynin is local following instillation in the bladder but the systemic exposure will influence the safety. The Applicant has provided PK following oral administration of 5 mg and instillation of 5 and 10 mg in adults as well as instillation of 0.04-0.2 mg/kg in children. Different concentrations of the solutions used for the instillations have been used. The interindividual variability in the systemic exposure is large. The Applicant has not defined the clinical consequences *ie* safety of the higher exposure seen in children compared to adults following intravesicle administration of oxybutynin 5 mg. As a consequence individual dose titration based on effect and safety should be clearly stated in the SmPC.

The elimination pathways of oxybutynin are unclear and hence potential risks in treatment of elderly patients and patients diagnosed with renal or hepatic impairment are unknown. The SmPC should clearly state that careful monitoring for adverse events should be undertaken in these patients.

**Conclusions on Clinical Pharmacology**

Basic clinical pharmacology data are missing and as a consequence individual dose titration based on effect and safety will have to be applied. Careful monitoring in special population is also a prerequisite.

**IV.3 Pharmacodynamics**

The intravesical oxybutynin exerts a direct effect on the bladder muscle, a topical anaesthetic effect, or an indirect effect of absorbed oxybutynin and its metabolites. The secondary pharmacodynamic effects observed with oxybutynin result from a lack of selectivity for the bladder, resulting in actions at other organ systems, such as the iris, intestine, and salivary gland. The reported pharmacodynamics studies on overactive bladder and neurogenic detrusor overactivity indicates an increased bladder capacity and decreased risk of ADRs with intravesical administration. The provided studies are limited and used different intravesical compositions and administration of oxybutynin. The included patients were instilled two or three times per day.

**IV.4 Clinical efficacy**

Neurogenic bladder dysfunction leads to three main problems: high intravesicular filling pressure, micturition disturbances and urine leakage. Fighting high pressure is the primary goal of the treatment of the neurogenic bladder. High pressure causes a risk of kidney damage. The pressure should not exceed 40 cm of water and probably the pressure in the bladder should only exceed 20-30 cm of water as assessed by cystometry (Swedish Association of Urology 2015). Oral oxybutynin has been available for more than 30 years to treat OAB. Oxybutynin is now available in SE as oral formulation and as a transdermal patch. One of the major big disadvantages using the oral route is the occurrence of dry mouth in patients.
The medical product Oxibutynin Unimedic 0.5mg/ml intravesical solution contains oxybutynin hydrochloride as active ingredient. The applied product is intended for patients with neurogenic bladder disorder. The patients have usually had severe detrusor hyperreflexia (DH) plus a disorder of bladder emptying, and because of residual urine have been performing intermittent clean self-catheterization (CIC).

Main studies
From 1989 up to 2015 numerous small studies have been published investigating the efficacy of intravesical oxybutynine in NDO patients. The 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.

NDO is a rare condition and no clear prevalence and/or incidence is known. NDO due to myelomeningocele is reported at an incidence of 0.3/1000 neonates in Sweden (Swedish Association of Urology 2015).

Overall, the efficacy of intravesical oxybutynin treatment of NDO has been investigated in more than 30 clinical studies comprising about 550 adult patients and 170 children. Although the results within each study were highly variable some 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. The applied doses ranged from about 0.1 mg/kg to 1.0 mg/kg bw. 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. 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 H2O (threshold for increased risk of kidney damage).

Paediatric population
The Applicant presents uncontrolled studies in children and some review articles in support for the current application. One study reported bladder instillation with oxybutynin in twelve children with myelomeningocele. Totally six boys and six girls in the ages of 2-15 years (mean 8.2 years) were included. The dose was normally 0.1 mg/kg body weight and day divided in 1-3 doses daily. One patient discontinued due to adverse reactions. The authors reported few adverse reactions, mainly of anticholinergic nature.

A review article concludes that intravesical oxybutynin represents a useful alternative to the standard medical treatment of pediatric neurogenic bladder although there is a lack of formal randomized controlled trial.

In another review article that include totally 297 children, that adjunctive intravesical oxybutynin therapy increased maximum bladder capacity and decreased bladder pressure in children with neurogenic bladder. It is an alternative for children refractory to oral oxybutynin or those who experience severe side effects. However, the level of evidence of the studies was low and there was insufficient evidence to recommend this treatment for children with neurogenic bladder.
In a further review article 9 studies in children were evaluated. From the reported studies, the intravesical administration of oxybutynin indicates an increased cystometric bladder capacity, reductions in detrusor pressure and a lower CIC frequency. The author concludes that intravesical oxybutynin chloride is relatively safe and has excellent efficacy for neurogenic bladder due to spinal cord disease. Only limited numbers of patients have been studied and drawbacks in the CNS and frequent occurrence of UTIs were reported in some cases in the literature.

In conclusion
The applicant has confirmed well-established use based on literature data and information from treatment guidelines, including data on off-label use for treatment in patients with neurogenic bladder disorders and established CIC who cannot use oral oxybutynin due to adverse events or when oral oxybutynin is not effective. The bibliographic data provided on intravesical administration of oxybutynin indicates a decreased filling pressure, an increased bladder capacity verified in cystometric measurements or micturition protocols and a lower CIC frequency in some studies although the trials are limited, many are old and non-comparative studies are in majority.

IV.5 Clinical safety

This application is based solely on bibliographical data. 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 I-IV). The studies published from 1989 till 2015 include about 550 adult patients and 170 children.

The profile of 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. 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 0.5mg/ml 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 is not recommended during pregnancy. 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 oxybutynine. Non-serious local reactions such as administration site pain may occur. Intravesical oxybutynine showed an acceptable safety profile in both, short-term as well as long-term clinical use. All systemic adverse events, 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 adverse events, particularly when high doses are indicated.

One author evaluated the incidence of side-effects of oral and intravesical oxybutynin chloride in children with meningomyelocele (MMC) and a neurogenic bladder with urodynamic testing and voiding cysto-urethrography, to identify those at high risk of upper tract damage. The patients received oxybutynin either orally or intravesically at a mean dose of 0.1–0.2 mg/kg. In all, 101 children (mean age 4.2 years, range 0.25 – 10 years) had uncoordinated detrusor sphincter function and low compliance and they were treated with either oral or intravesical oxybutynin or clean intermittent catheterization. Of the 101 patients, 67 were treated with oral oxybutynin; in 11 the treatment was discontinued because of the side-effects. The other 34 patients used both clean intermittent catheterization and intravesical oxybutynin. The reported incidence rates of 16.4% (11/67) and 17.6% (6/34), respectively was comparable. Six patients (18%) stopped using intravesical oxybutynin because of systemic AEs. The authors concluded that oral and intravesical oxybutynin is effective for managing neurogenic bladder dysfunction, but intravesical administration is safer and better tolerated than oral oxybutynin in the treatment of children with MMC. Adverse effects such as cognitive impairment can occur in children treated with intravesical oxybutynin and these patients must be closely monitored because these effects may differ from those with oral administration.

Other problems have been reported where the inconvenience of the preparation is often cited as a reason for drug withdrawal, accounting for 25% of study dropouts.

From the reported studies, the intravesical administration of oxybutynin indicates an increased cystometric bladder capacity, reductions in detrusor pressure and a lower CIC frequency. Inoue et al concludes that intravesical oxybutynin chloride is relatively safe and has excellent efficacy for neurogenic bladder due to spinal cord disease. As only limited numbers of patients have been studied and drawbacks in the CNS and the frequent occurrence of UTIs were reported in some cases in the literature, the oxybutynin for intravesical application is not a first line therapy. It replaces the use of oral oxybutynin in patients with neurogenic bladder disorders when oral oxybutynin does not work or in patients who suffer from adverse events of the drug when taken orally.

In conclusion: The applicant provided sufficient documentation to support all safety aspects of the product.
IV.6 Risk Management Plans

The MAH has submitted an updated risk management plan, (version 3.0, dated 11 September 2017) 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 Oxybutynin Unimedic 0,5 mg/ml intravesical solution.

Safety specification
Summary table of safety concerns as proposed in RMP

| Important identified risks                  | • Urine retention  
|                                           | • Urinary tract infections |
| Important potential risks                  | • Gastro-intestinal motility disorders  
|                                           | • Cardiovascular disease aggravation |
| Missing information                        | • None |

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP is approved.

V. USER CONSULTATION

The package leaflet 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 PIL was Swedish. The results show that the package leaflet 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 benefit/risk ratio is considered positive and Oxybutynin Unimedic, 0,5mg/ml, intravesical solution is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

Oxybutynin Unimedic, 0,5mg/ml, intravesical solution was approved in the national procedure on 2017-12-19.
## Public Assessment Report – Update

<table>
<thead>
<tr>
<th>Procedure number*</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Summary/Justification for refuse</th>
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*Only procedure qualifier, chronological number and grouping qualifier (when applicable)*