1. NAME OF THE MEDICINAL PRODUCT

Oxybutynin Unimedic 0.5 mg/ml intravesical solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 0.5 mg oxybutynin hydrochloride corresponding to 0.454 mg oxybutynin.

Excipient with known effect
The solution contains 3.5 mg (0.15 mmol) sodium per ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intravesical solution.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of frequency, urgency or urge incontinence as may occur in bladder overactivity due to neurogenic bladder disorder (e.g. myelomeningocele or spinal injury), in situations where the anticholinergic side effects with orally administered oxybutynin are not tolerated. The intravesical solution should only be used when clean intermittent catheterisation (CIC) has already been established.

Oxybutynin Unimedic is intended for adults and children over 5 years of age.

4.2 Posology and method of administration

This medicinal product is administered by health care personnel but can also be administered at home by the patient or relative/caregiver. It is a requirement that the patient and relative/caregiver receive adequate training by competent health care personnel, e.g. urologist or urotherapist prior to the first administration.

Posology
Adults:
The dosing is individual with a starting dose of 5 mg (10 ml) intravesically in the morning and evening. The dose can be adjusted after one week of treatment. Lowest effective dosing should be chosen. The daily dose may be increased to between 5 mg (10 ml) x 3 and 10 mg (20 ml) x 2 to achieve adequate effect, provided that side effects are tolerated.

Paediatric population
Children above 5 years:
The dosing is individual with a starting dose of 0.1 mg/kg intravesically in the morning and evening. The dose can be adjusted after one week of treatment. Lowest effective dosing should be chosen. The daily dose may be increased up to 0.15 mg/kg twice daily to achieve adequate effect, provided that side effects are tolerated. Not more than 5 mg should be administered per single dose.

The safety and efficacy of oxybutynin hydrochloride in children below 5 years of age have not yet been established.

Special populations
There is no data on intravesical use in the elderly or patients with hepatic and renal insufficiency. A lower starting dose than recommended above should be considered to reduce the risk of adverse events. Close monitoring of adverse events occurrence is advised when administering the product in these populations (see sections 4.4 and 5.2).

Method of administration
For intravesical use. To ensure the complete dose reaches the bladder the volume of the catheter is determined using a syringe to fill the catheter with saline solution. Register the volume required until the solution reaches the end of the catheter. This volume of saline solution is added to the volume oxybutynin solution prescribed for the treatment. After emptying of the bladder via clean intermittent catheterisation (CIC), first the oxybutynin solution, and thereafter the saline solution, is injected into the bladder via the catheter while it is still in place. Thereafter the catheter is removed. Emptying of the bladder should occur every 4 hours, via CIC.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Myasthenia gravis
- Narrow-angle glaucoma or shallow posterior eye chamber
- Gastrointestinal obstruction, paralytic ileus or intestinal atonia
- Patients with ileostomy, colostomy, toxic megacolon, severe ulcerative colitis
- Patients with urinary obstruction where urinary retention may occur
- Frequent urination at night caused by heart or kidney disease

4.4 Special warnings and precautions for use

Oxybutynin should be used with caution in elderly patients and children, who may be more sensitive to the effects of the medicinal product.

The product shall be used with caution in patients with autonomic neuropathy (e.g. Parkinson's disease) and in patients with liver or kidney diseases.

Anticholinergic medicinal products may decrease gastrointestinal motility and should be used with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention, and in conditions such as ulcerative colitis and intestinal atony. Anticholinergic medicinal products should be used with caution in patients with hiatus hernia/gastroesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate esophagitis.

The use of oxybutynin may aggravate the symptoms of hyperthyroidism, cardiac insufficiency, cardiac arrhythmias, coronary artery disease, tachycardia, hypertension, and prostatic hypertrophy.

Oxybutynin decreases perspiration, which can lead to heat exhaustion in patients, if the medicinal product is used in high temperature environments.

Since oxybutynin may trigger narrow-angle glaucoma the patient should be instructed to immediately contact a doctor if the visual acuity suddenly disappears. Visual acuity and intraocular pressure should be followed during treatment.

Proper dental care is important since treatment with oxybutynin increases the risk of caries due to dryness of the mouth.

Anticholinergic medicinal products such as oxybutynin may decrease the cognitive ability and cause CNS effects such as agitation and sleep disorders. Serious atropine symptoms may occur, particularly in children, that may require dose adjustment or termination of treatment.

The risk for anticholinergic adverse events is clearly lower with intravesical use compared to oral administration. This is probably due to oxybutynin being absorbed over a longer period with a delayed peak serum level and a lower degree of metabolism to the active metabolite N-desethyloxybutynin which is the main cause of these side effects.

During long term treatment with intravesical oxybutynin an increased frequency of asymptomatic bacteriuria and lower urinary tract infections have been observed. At urinary tract infections during oxybutynin treatment appropriate antibacterial treatment should be initiated.

Paediatric population
In children on long term treatment with intravesical oxybutynin an increased frequency of asymptomatic bacteriuria and lower urinary tract infections have been observed. At urinary tract infections during oxybutynin treatment appropriate antibacterial treatment shall be initiated.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions:
The anticholinergic activity of oxybutynin is increased by concomitant use of other anticholinergics or medicinal products with anticholinergic activity such as amantadine and other anticholinergic antiparkinsonian medicinal products (e.g. biperiden, levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones, clozapine), quinine, tricyclic antidepressants, atropine and related compounds like atropinic antispasmodics, dipyridamole.

Alcohol may increase the drowsiness caused by anticholinergic drugs such as oxybutynin (see section 4.7).

Oxybutynin may antagonize prokinetic therapies.

Oxybutynin can potentially modify the absorption of certain concomitantly administered medicinal products because of the anticholinergic effect on gastrointestinal motility.

Sublingual nitrates may dissolve to a lesser extent under the tongue due to mouth dryness, which can lead to decreased therapeutic effect of the nitrates. Patients should be instructed to moisten the mouth before taking a tablet.

The concomitant use of cholinesterase inhibitors can decrease the cholinesterase inhibiting effect.

Pharmacokinetic interactions:
Oxybutynin is metabolised via cytochrome P450 isoenzyme CYP 3A4.
Concomitant administration of inhibitors of CYP3A4 (e.g. itraconazole, erythromycine, grapefruit juice) could inhibit the metabolism of oxybutynin resulting in an increased systemic exposure.

4.6 Fertility, pregnancy and lactation

Pregnancy: Clinical experience from pregnant women is limited. Studies in animals have shown reproductive toxicity (see section 5.3). Until further experience is gained it is not recommended that Oxybutinin Unimedic is used during pregnancy.

Breastfeeding: Small amounts are excreted in the mother’s milk and there may be a risk that the child will be affected even at therapeutic doses. Use of oxybutynin while breast-feeding is therefore not recommended.

Fertility: There are no data available on the effect on human fertility. Animal studies have shown decreased fertility in female animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Treatment with oxybutynin may cause dizziness, drowsiness and blurred vision, which affects the ability to drive or use machines.

4.8 Undesirable effects

The systematic undesirable effects are less pronounced at intravesical compared to oral administration. Exact frequency of undesirable events at intravesical administration is not known.

Dose dependent anticholinergic undesirable events may occur at oxybutynin treatment. The following adverse events might occur with the frequency not known (cannot be estimated from the available data):

System organ class	**Frequency not known (cannot be estimated from the available data)**
Infections and infestations	Urinary tract infections
Psychiatric disorders	Anxiety, confusion, restlessness, disorientation, agitation
Nervous system disorders	Headache, dizziness, somnolence, drowsiness
Eye disorders	Dry eyes, blurred vision, narrow-angle glaucoma, light hypersensitivity
Cardiac disorders	Tachycardia
Vascular disorders	Facial flushing
Gastrointestinal disorders	Mouth dryness, constipation, abdominal discomfort, diarrhoea
Skin and subcutaneous tissue disorders	Dry skin
Renal and urinary disorders	Urinary retention
Injury, poisoning and procedural complications	Heat exhaustion

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Experience from overdose of oxybutynin is limited, but has been associated with anticholinergic effects.

Symtoms:

Anxiety, agitation, confusion, hallucinations, CNS depression, CNS exitation.
Tachycardia, ventricular extra systoles. Gastrointenstinal problems including vomiting.
Seizures, mydriasis, urinary retention, fever, dehydration.

Treatment:
Empty the urinary bladder. At anxiety, agitation or seizures diazepam is administered. At central anticholinergic symptoms and no other cardic effect than tachycardia, possible treatment with physostigmine. Symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for urinary frequency and incontinence. ATC code: G04B D04

Mechanism of action: Oxybutynin is an antimuscarinic anticholinergic i.e. a competitive antagonist of acetylcholine at the muscarinic receptors. Intravesicular administration also provides a direct spasmolytic effect on bladder smooth muscle (calcium antagonistic and local anesthetic effect).

Pharmacodynamic effects:
In therapeutic doses oxybutynin decreases the detrusor muscle contraction capacity, resulting in an increased volume of the urinary bladder to first detrusor contraction and a prolonged time interval between micturitions. Oxybutynin thus decreases the frequency of urinary urgency and consequently also the incontinence episodes and voluntary urination.
Intravesically administered oxybutynin has less pronounced central effects and also less effect on the coronary heart system compared to oral exposure.

Oxybutynin is a racemic (50:50) mixture of R- and S-isomers. Antimuscarinic activity resides predominantly in the R-isomer, showing greater selectivity for the M1 and M3 muscarinic subtypes (predominant in cerebral cortex and parotid gland, and in the bladder detrusor muscle and ileum respectively) compared to the M2 subtype (predominant in cardiac tissue). The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin *in vitro* studies, but has a greater binding affinity for parotid tissue than oxybutynin. The free base form of oxybutynin is pharmacologically equivalent to oxybutynin hydrochloride.

5.2 Pharmacokinetic properties

Absorption

Intravesical oxybutynin is well absorbed through the bladder wall into systemic circulation. Measurements of oxybutynin plasma concentrations after intravesical administration revealed extensive inter-individual variability, but there was a substantial absorption of the drug also after intravesical application with maximum concentrations in plasma achieved after about one hour.

The pharmacokinetics of intravesical oxybutynin hydrochloride has been investigated in healthy volunteers. Systemic exposure (AUC) to racemic oxybutynin was significantly greater after instillation (294 %) compared to oral administration. In contrast, systemic exposure of the metabolite N-desethyl-oxybutynin was significantly lower after instillation (21 % of exposure after oral administration). As a consequence, the metabolite-to-parent ratio was 14-fold lower in case of intravesical application. These observations clearly indicate that the mode of administration strongly influences absorption and, in particular, first-pass metabolism of oxybutynin.

Obviously, the first-pass effect is significantly reduced in case of intravesical application. Considering the reported oxybutynin bioavailability of about 6 % after oral administration, an absolute

bioavailability of about 20 % might be estimated for the parent compound after intravesical instillation.

Distribution
Oxybutynin is to a large extent distributed to body tissue after systemic absorption.
The distribution volume is estimated to 193 liters after intravenous administration of 5 mg oxybutynin hydrochloride. Approximately 85% of oxybutynin in blood is bound to serum albumin.

Metabolism:
Oxybutynin administered orally is metabolised primarily by the cytochrome P450 system, mainly CYP3A4, found mostly in the liver and gut wall. Metabolites include mainly N-desethyloxybutynin, which is pharmacologically active, and phenylcyclohexylglycolic acid, which is pharmacologically inactive. Intravesical administration of oxybutynin bypasses the first-pass gastrointestinal and hepatic metabolism, clearly reducing the formation of the N-desethyl metabolite, which can increase the tolerability for the substance. N-desethyl oxybutynin is believed to be the cause of many anticholinergic adverse events. C_{max} for oxybutynin is lower and AUC flatter at intravesical compared to oral administration, which is also considered to contribute to the lower frequency of anticholinergic adverse events.

The influence of age, weight, race and tobacco use on the pharmacokinetics of oxybutynin is unknown.

Elimination
The half life of oxybutynin is approximately 2 hours regardless of whether the substance is administered orally or intravenously. The half life after intravesical administration is longer. Oxybutynin is largely metabolised by the liver (see above) and less than 0.1% of the administered dose is excreted unchanged in the urine. Less than 0.1% of the administered dose is excreted as the metabolite N-desethyloxybutynin.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on studies for acute toxicology, repeat dose toxicity, genotoxicity, carcinogenic potential, and local toxicity. At a concentration of 0.4 mg/kg/day oxybutynin administered subcutaneously, the occurrence of organ anomalies is significantly increased, but is observed only in the presence of maternal toxicity. However, in the absence of understanding the association between maternal toxicity and developmental effect, the relevance to human safety cannot be addressed. In the subcutaneous fertility study in rats, while no effects were reported in males, in females, fertility was impaired. A NOAEL (no observed adverse effect level) of 5 mg/kg was identified.

Environmental Risk Assessment (ERA)
The active substance oxybutynin is persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.
Opened package: From a microbiological point of view the medicinal product should be used immediately. If not used immediately the storage time and storage conditions before administration are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25ºC.
For storage conditions after opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass vial with a bromobutyl stopper and an aluminum cap: 10x20 ml.

6.6 Special precautions for disposal and other handling

For instillation in the urinary bladder via catheter.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2020-12-20

Detailed information on this medicinal product is available on the website of {name of MS/Agency}