SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vesoxx

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 1 mg oxybutynin hydrochloride.

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

Excipient with known effect: sodium 3.56 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intravesical solution.

Clear, colourless solution with a pH of 3.6 to 4.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vesoxx is indicated for the suppression of neurogenic detrusor overactivity (NDO) in children from 6 years of age and adults, who are managing bladder emptying by clean intermittent catheterisation (CIC), if they cannot be adequately managed by oral anticholinergic treatment due tolack of efficacy and/or intolerable side effects.

4.2 Posology and method of administration

Posology
Initial dose adjustment shall be done by a neuro-urologist under close urodynamic control.

There are no fixed rules for the dose regimen as high interindividual differences in bladder pressure and doses required to improve neurogenic detrusor overactivity exist. The dose regimen (doses and timings) must therefore be determined individually according to the patient´s need.

Individual dosages will be applied to control uro-dynamic parameters sufficiently (maximum detrusor pressure < 40 cm H_2O) aiming at complete inhibition of neurogenic detrusor overactivity.

In the course of intravesical oxybutynin therapy, urodynamic parameters shall be controlled in regular intervals as defined by the attending urologist.

Paediatric population
The safety and efficacy of oxybutynin hydrochloride in children aged 0 to 5 years of age have not yet been established.

Dose recommendations in adolescents from 12 years and above, adults and elderly
The dose recommendations have been calculated according to the body weight percentiles of the different age groups (table 1).

Table 1: Dose recommendations in adolescents from 12 years and above, adults and elderly

Age group	Age [years]	Recommended daily starting dose [mg]	Recommended total daily dose [mg]
Adolescents	12 - 18	10	10 - 40
Adults	19 - 65	10	10 - 40
Elderly	over 65	10	10 - 30

If higher doses than the starting dose are considered necessary, the dose should be increased using a step-wise approach until neurogenic detrusor overactivity is sufficiently controlled to allow close monitoring of both efficacy and safety. The required daily maintenance doses may be divided into several applications (table 2). Given a number of six clean intermittent catheterisations (CICs) per day, the following dose scheme is recommended:

Table 2: Recommended dose scheme for 10 mg starting doses (adolescents from 12 years and above, adults and elderly)

Daily dose [mg]	Administered dose per application [mg]					
	CIC 1	**CIC 2**	**CIC 3**	**CIC 4**	**CIC 5**	**CIC 6**
10	5	-	5	-	-	-
20	10	-	10	-	-	-
30	10	-	10	-	10	-
40	10	10	10	-	10	-

Children (from 6 - 12 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 6 years of age have not yet been established.

Elderly (over 65 years)
As with other anticholinergic drugs caution should be observed in frail and elderly patients, especially if doses higher than 30 mg per day are considered as required (see section 4.4).

Hepatic or renal impairment
Vesoxx should be used with caution in patients with hepatic or renal impairment. The use of Vesoxx in those patients should be carefully monitored and dose reductions may be needed(see section 4.4).

Method of administration
Intravesical use.

To ensure safe and effective treatment, patients must be familiar with the procedure of clean intermittent catheterisation (CIC). The patients and/or relative, carer shall be trained on CIC and the administration procedure by specialised health care professionals.

As soon as the environmental conditions are aseptic, a sterile disposable urethral catheter is inserted into the bladder. The bladder has to be drained completely before the instillation.

The scaled prefilled syringe is taken from the blister and the cap is removed from the syringe.

Polypropylene prefilled syringe (for direct connection with standard catheter systems)

The tapered cone of the syringe is connected directly to the catheter. The required amount of the oxybutynin solution is instilled into the bladder by constant pressing on the plunger of the syringe.

If the application of less than 10 ml (one syringe content) is required, the solution that is not used remains in the syringe which has to be brought to a pharmacy for disposal later.

After the instillation the catheter is removed.

The instilled solution remains in the bladder until the next catheterisation.

Any unused medicinal product and the urethral catheter have to be discarded (see section 6.3).

The duration of treatment depends on the symptoms, the underlying disease and / or the treatment goal and is determined by the treating physician.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe gastro-intestinal condition (e. g. severe ulcerative colitis and toxic megacolon)
- Myasthenia gravis
- Narrow angle glaucoma and in patients who are at risk for these conditions.
- Patients with urinary obstruction where urinary retention may occur.
- Frequent urination at night caused by heart or kidney disease.
- Concomitant oxygen therapy

4.4 Special warnings and precautions for use

If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Vesoxx should be used with caution in elderly (over 65 years) patients, who may be moresensitive to the effects of centrally acting anticholinergics.

Psychiatric and central nervous system (CNS) anticholinergic events like sleep disorders (e.g. insomnia) and cognitive disorders have been associated with oxybutynin use, especially in elderly patients. Caution should be exercised when oxybutynin is administrated concomitantly with other anticholinergic medicines (see also section 4.5). If a patient experiences such events, drug discontinuation should be considered.

Sublingual nitrates may fail to dissolve under the tongue owing to dry mouth, resulting in reduced therapeutic effect (see section 4.5).

The use/administration of oxybutynin products may warrant the following cautionary statements:

Gastrointestinal disorders
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. They should also be used with caution in patients who have hiatus hernia/gastro-oesophageal reflux.

Anticholinergic medicinal products should be used with caution in patients who have autonomic neuropathy or cognitive impairment and in patients with liver or kidney diseases (see section 4.2).

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin are used in a hot environment.

Oxybutynin may exacerbate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension and prostatic hypertrophy.

Since oxybutynin may trigger narrow-angle glaucoma the patient should be instructed to immediately contact a physician if they are aware of a sudden loss of visual acuity or ocular pain. Visual acuity and intraocular pressure should be followed during treatment occasionally.

Oxybutynin may lead to suppressed salivary secretions which could result in dental caries, parodontosis or oral candidiasis.

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.

Paediatric population
In children Vesoxx should be used with caution as they may be more sensitive to the effectsof the product, particularly the CNS and psychiatric adverse reactions.

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.

This medicinal product contains 3.56 mg sodium per ml, equivalent to 0.18% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Anticholinergic agents may potentially alter the absorption of some concomitantly administered medicinal products due to anticholinergic effects on gastrointestinal motility.

Anticholinergic medicinal products should be used with caution in patients who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.

Due to dry mouth, sublingually administered nitrates may dissolve to a lesser extent, which can lead to decreased therapeutic effect of the nitrates. Patients treated with sublingual nitrates should therefore be instructed to moisten the oral mucosa before use (see section 4.4).

Oxybutynin is metabolised by cytochrome P 450 isoenzyme CYP 3A4. By applying oxybutynin intravesically, this first-pass metabolism is mainly circumvented. However, interactions with medicinal products that inhibit cytochrome P 450 isoenzyme CYP 3A4 cannot be ruled out. This should be borne in mind when using azole antifungals (e.g. ketoconazole) or macrolide antibiotics (e.g. erythromycin) concurrently with oxybutynin.

The anticholinergic activity of oxybutynin is increased by concurrent 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), quinidine, tricyclic antidepressants, atropine and related compounds like atropinic antispasmodics, dipyridamole.

Oxybutynin may antagonise prokinetic therapy.

Concomitant use with cholinesterase inhibitors may result in reduced cholinesterase inhibitor efficacy.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the intravesical use of oxybutynin in pregnant women. Studies in animals have shown minor reproductive toxicity (see section 5.3). Vesoxx should not be used during pregnancy

unless the clinical condition of the woman requires treatment.

Breast-feeding
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 breast-feeding.

Fertility
Data on possible effects of the use of oxybutynin on human male and female fertility are not available.

4.7 Effects on ability to drive and use machines

Because Vesoxx may produce somnolence, or accommodation disorders, patients should beadvised to exercise caution when driving or using machinery.

4.8 Undesirable effects

Undesirable effects observed with oxybutynin hydrochloride such as dry mouth, somnolence, and constipation mainly reflect the typical anticholinergic properties of the active ingredient.

Table 4 includes adverse reactions from clinical trials with intravesical use of oxybutynin hydrochloride. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥1/10), Common (≥1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Table 4: Adverse reactions from clinical trials with intravesical use of oxybutynin hydrochloride

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Urinary tract infection, asymptomatic bacteriuria	unknown
Endocrine disorders	Hyperprolactinaemia, prolactin increase	unknown

System Organ Class	Adverse reaction	Frequency
Psychiatric disorders	Listless, hallucinations, cognitive disorders, hyperactivity, insomnia, agoraphobia, disorientation	unknown
Nervous system disorders	Disturbance in attention, dizziness, headache, somnolence, fatigue, dysgeusia, depressed level of consciousness, loss of consciousness, anticholinergic syndrome, seizure	unknown
Ear and labyrinth disorders	Vertigo	unknown
Eye disorders	Dry eye, abnormal sensation in eye, accommodation disorder	unknown
Cardiac disorders	Supraventricular tachycardia	unknown
Vascular disorders	Hypotension, facial flushing	unknown
Gastrointestinal Disorders	Constipation, dry mouth, abdominal discomfort, abdominal pain lower, abdominal pain upper, nausea, dyspepsia, diarrhoea	unknown

Skin and subcutaneous tissue disorders	Hypohidrosis, rash, nocturnal sweating	unknown
Renal and urinary disorders	Micturition urgency, proteinuria, haematuria, micturition disorder	unknown
General disorders and administration site conditions	Instillation site pain, thirst, chest discomfort, feeling cold	unknown

One patient experienced decreased oxygen saturation during home oxygen therapy (see section 4.3).

Paediatric population
Children may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

Adverse reactions known to be associated with anticholinergic therapy, but not observed with intravesical use of oxybutynin during clinical studies are vomiting, anorexia, decreased appetite, dysphagia, gastroesophageal reflux disease, pseudo-obstruction in patients at risk (elderly or patients with constipation and treated with other drugs that decrease intestinal motility), confusional state, agitation, anxiety, nightmares, paranoia, symptoms of depression, dependence to oxybutynin (in patients with history of drug or substance abuse), arrhythmia, heat stroke, angle closure glaucoma, ocular hypertension, dry skin, angioedema, urticaria, photosensitivity, hypersensitivity.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

No cases of overdose have been reported with intravesical use of oxybutynin.

Symptoms
The symptoms of overdosage with oxybutynin progress from an intensification of the usual side effects of CNS disturbances (from restlessness and excitement to psychotic behaviour), circulatory changes (flushing, fall in blood pressure, circulatory failure etc.), respiratory failure, paralysis and coma.

Treatment
The bladder should be emptied immediately via the catheter.

In case of overdose, patients should be closely monitored and treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals – drugs for urinary frequency and incontinence, ATC code: G04B D04.

Mechanism of action
Oxybutynin acts as a competitive antagonist of acetylcholine at post-ganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle.

Oxybutynin hydrochloride is an anticholinergic agent, which also exerts a direct antispasmodic effect on smooth muscle. It inhibits bladder contraction and relieves spasm induced by various stimuli; it increases bladder volume, diminishes the frequency of contractions and delays the desire to void in the disturbance of neurogenic bladder. The relaxation of smooth muscle results from the papaverin like effect of the antagonism of the processes distal to the neuromuscular junction in addition to the anticholinergic blocking action of the muscarinic type receptors. In addition, oxybutynin hydrochloride has local anaesthetic properties.

Pharmacodynamic effects
Pharmacodynamic properties of oxybutynin were studied after intravesical application to children with neurogenic detrusor overactivity. The effects on incontinence and urodynamic variables were pronounced, improving both in the majority of cases. Number of hyperactive contractions decreased significantly. Increase of mean cystometric bladder capacity and mean cystometric-to-expected bladder capacity was shown while end filling bladder pressure decreased.

Clinical efficacy and safety
The efficacy of intravesical oxybutynin treatment of neurogenic bladder dysfunction has been investigated in clinical studies in both short-term and long-term use.

In almost all studies, intravesical treatment with oxybutynin hydrochloride was efficacious and was shown to be well tolerated in patients (adults and children) suffering from neurogenic detrusor overactivity. The NDO was mainly the result of a spinal cord injury or meningomyelocele although also patients with tetraplegia, paraplegia, multiple sclerosis and Parkinson's disease were included in the studies.

In a prospective clinical trial in 15 children, mean cystometric bladder capacity increased from 114.2 mL at baseline to 127.4 mL ($p>0.05$) and 161.1 mL ($p=0.0091$) after 1.5 hours and 4 months of intravesical treatment, respectively (Buyse et al., 1995). Mean bladder compliance was significantly increased from 2.5 mL/cm H_2O at baseline to 11.495 mL/cm H_2O ($p=0.0114$) after 4 months of therapy. In a further prospective trial in 13 children, 12 showed markedly improved continence after intravesical treatment (Åmark et al., 1998). In a retrospective long-term evaluation in 13 children, the mean end filling bladder pressure decreased from 52.5 ± 24 to 24.5 ± 14.4 cm H_2O (Humblet et al., 2014).
The efficacy of intravesical vs. oral application of oxybutynin was examined in a further prospective multi-center clinical trial conducted on 35 patients (age between 18 and 70 years) suffering from NDO confirmed by previous urodynamic studies and minimum experience of 6 weeks with CIC (Schröder et al., 2016). The study confirmed that the maximum bladder capacity significantly increased upon the intravesical treatment from 18.1 mL (upon oral application) to 116.6 mL (upon intravesical application).

Additional study in a duration of 6 months subjected 25 adult patients (age between 18 and 64 years) with spinal cord injury under intravesical treatment of oxybutynin with whom standard oral oxybutynin treatment had failed (Pannek et al., 2000). Intravesical treatment led to an increase in bladder storage volume from 349 to 420 mL. The mean maximum storage pressure was significantly reduced from 54 to 26.5 cm H_2O. Detrusor storage pressures returned to values less than 40 cm H_2O in

21 out of 25 patients in the duration of the study.

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 widely distributed in body tissues following systemic absorption. The volume of distribution was estimated to be 193 l after intravenous administration of 5 mg oxybutynin hydrochloride.

Biotransformation
Oxybutynin administered orally is metabolised primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Metabolites include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and N-desethyloxybutynin (DEOB), which is pharmacologically active.

Intravesical administration of oxybutynin mainly circumvents the first-pass gastrointestinal and hepatic metabolism, reducing the formation of the N-desethyl metabolite.

The N-desethyl metabolite appears to produce greater anticholinergic side effects, particularly on the salivary glands, than the parent compound.

Elimination
Oxybutynin is rapidly excreted from the body after oral and intravesical administration. It was concluded from PK studies that intravesical oxybutynin exhibits a prolonged elimination compared to oral administration with reported elimination half-lives of 2.56 and 1.48 h, respectively. Concentrations of both, oxybutynin and its main metabolity N-desethyloxybutynin were still detectable in serum 24 h after intravesical administration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of acute toxicology, repeat-dose toxicity, genotoxicity, carcinogenic potential and local toxicity.

At maternal toxic doses, oxybutynin administered orally can cause foetal malformations in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid
Water for injections

6.2 Incompatibilities

Not known.

6.3 Shelf life

The expiry date is indicated on the packaging materials.

The prefilled syringes are single dose containers - 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 30^{O}C.

6.5 Nature and contents of container

Polypropylene prefilled syringe (for direct connection with standard catheter systems)

10 ml solution in a prefilled syringe (polypropylene) with a plunger stopper (synthetic bromobutyl rubber) and a tip cap (synthetic bromobutyl rubber).

Carton with 100 prefilled syringes. Carton with 12 prefilled syringes.

Not all of the pack sizes listed may be marketed

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Propharm Ltd., P.O.Box 4046, Ben-Gurion 23, Zichron Yaacov 30900

8. MANUFACTURER

Klosterfrau Berlin GmbH
Motzener Strasse 41, D-12277 Berlin, Germany

9. MARKETING AUTHORISATION NUMBER

174-61-37610-99

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