SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AQUIETTE 2.5 mg TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The tablets contain 2.5 mg of oxybutynin hydrochloride.

Excipient with known effect: Lactose Monohydrate 59.45 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

Tablets are light blue marked $\frac{\text{OXB}}{2.5}$ with a scoreline on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AQUIETTE is indicated for the treatment of longstanding (>1 month) overactive bladder symptoms, i.e. urinary urgency and frequency without dysuria, which may occasionally lead to incontinence, which is not adequately controlled by bladder training alone.

4.2 Posology and method of administration

Posology

AQUIETTE is for use in women ≥ 18 years and ≤ 65 years of age

The dose is one 2.5 mg tablet two or three times daily, depending on symptom response. Doses should be separated by at least 6 hours. The lowest effective daily dose should be used.

Before initiating treatment with AQUIETTE women should always be advised to undertake bladder training for at least 6 weeks and to adopt lifestyle advice. If symptoms are not adequately controlled following bladder training alone, the patient should be reassessed and, if appropriate, AQUIETTE can be recommended in addition to bladder training and lifestyle measures.

If symptoms remain inadequately controlled after 6 weeks treatment with AQUIETTE, women should be advised to stop AQUIETTE and see their doctor.

If after 6 weeks treatment with AQUIETTE symptoms are adequately controlled, women should be advised to continue taking AQUIETTE together with bladder training and lifestyle measures, for a further 6 weeks. After 12 weeks of treatment, women should stop AQUIETTE. If symptoms of urgency and frequency return, women should be advised to see their doctor since they may need longer-term treatment.

Paediatric Population

AQUIETTE is not indicated for use in children

Method of administration

The tablets are for oral administration. The tablets should be swallowed whole with an appropriate amount of water or other fluid.

4.3 Contraindications

AQUIETTE is contraindicated in:

Men and in children ≤ 18 years.
Women > 65 years.
Pregnant women, women who are suspected of being pregnant and breast-feeding women.

Women with

- A previous diagnosis of other causes of frequent urination (diabetes, cardiac disease, renal disease)
- A known neurogenic cause for detrusor overactivity

Women with a history of any of the following

- Hypersensitivity to oxybutynin or any of the excipients listed in section 6.1
- Patients with bladder outflow obstruction where urinary retention may be precipitated
- Gastro-intestinal obstructive disorders, including pyloric stenosis, intestinal atony or paralytic ileus
- Patients with ileostomy, colostomy, toxic megacolon, ulcerative colitis
- Myasthenia gravis
- Narrow-angle glaucoma or shallow anterior chamber

4.4 Special warnings and precautions for use

Women with recent (within 1 month) onset of symptoms, or prone to recurrent or frequent urinary tract infection should be assessed by a doctor before treatment.

Women with symptoms suggesting the following conditions, should be referred to a doctor for diagnosis before treatment:

- Diabetes mellitus (increased thirst, frequent urination, fatigue, frequent infections, unexplained weight loss)
- Atrophic vaginitis (vaginal pain and dryness, with pain or burning on urination or frequent urination)
- Prolapse (feeling a bulge / lump from or in the vagina, heaviness in the pelvic region, sometimes with constipation and frequent urinary tract infections)
- Symptoms suggestive of urinary obstruction or urinary tract malignancy such as dysuria and poor urinary flow or haematuria (visible blood in the urine).
- Symptoms suggestive of a urinary tract infection (dysuria, haematuria. pyrexia, loin pain or cloudy urine)
- Symptoms suggestive of an ovarian mass (consistent bloating, swollen abdomen or discomfort in the pelvic region)
- Uterine disease such as fibroids or malignancy (abnormal menstrual bleeding such as heavy periods, inter-menstrual bleeding or any postmenopausal bleeding).

Oxybutynin should be used only under medical supervision in women:

- over 65 years as they may be more sensitive to the adverse effects of oxybutynin, see section 4.3

- who experience incontinence only during exertion (e.g. during coughing, sneezing, or exercise); these women may have stress incontinence and should consult a doctor before treatment.
- with autonomic neuropathy (such as those with Parkinson's Disease), hepatic or renal impairment and severe gastro-intestinal motility disorders
- taking cholinesterase inhibitors used in Alzheimer's, as oxybutynin may reduce their effectiveness, see section 4.5
- with a history of anxiety, depression or other psychiatric illness requiring treatment
- taking anticholinergic medicinal products (see section 4.5)
- who have hiatus hernia/gastro-oesophageal reflux
- taking CYP3A4 inhibitors as oxybutynin exposure may be increased, see section 4.5
- who have hyperthyroidism, congestive heart failure, cardiac arrhythmia, coronary heart disease or hypertension as oxybutynin may aggravate tachycardia
- who have cognitive disorders.

Women taking AQUIETTE should be advised to consult their doctor:

- if their symptoms fail to respond to treatment
- if their symptoms are not adequately controlled after 6 weeks treatment

Women should contact their doctor immediately if they develop a sudden loss of visual acuity or ocular pain, haloes around lights, headaches, dilated pupils, red eye or nausea and vomiting since oxybutynin can cause narrow-angle glaucoma.

Anticholinergic CNS effects (e.g. hallucinations, agitation, confusion, somnolence) have been reported; consider discontinuing therapy or reducing the dose if anticholinergic CNS effects develop.

Oxybutynin may reduce salivary secretions which could result in dental caries, peridontitis or oral candidiasis.

When oxybutynin is used in high environmental temperatures, this can cause heat prostration due to decreased sweating.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Patients taking other anticholinergic agents should not take AQUIETTE as potentiation of anticholinergic effects may occur.

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. procyclidine, levodopa), antihistamines, antipsychotics (e.g. phenothiazines (eg. chlorpromazine), butyrophenones (e.g. haloperidol), clozapine), tricyclic antidepressants (e.g. amitriptyline, nortriptyline, clomipramine), atropine and related compounds like atropinic antispasmodics.

By reducing gastric motility, oxybutynin may affect the absorption of other drugs.

Oxybutynin is metabolised by cytochrome P 450 isoenzyme CYP 3A4. Concomitant administration with a CYP3A4 inhibitor (e.g. erythromycin, itraconazole) can inhibit oxybutynin metabolism and increase oxybutynin exposure, see section 4.4. Caution is recommended when using mifepristone and oxybutynin. The lowest dose of oxybutynin possible should be used if concomitant use is required.

Oxybutynin may antagonize prokinetic therapies (e.g. metoclopramide, domperidone).

Concomitant use with cholinesterase inhibitors (e.g. donepezil, galantamine, rivastigmine) may result in reduced cholinesterase inhibitor efficacy.

During concomitant use of rufinamide patients should be monitored for a reduction in the efficacy of oxybutynin for 2 weeks after starting, stopping or changing the dose of rufinamide.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin (see section 4.7).

4.6 Fertility, pregnancy and lactation

Pregnancy: there are no adequate data from the use of oxybutynin in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential risk for humans is unknown. AQUIETTE should not be used during pregnancy.

Breast-feeding: when oxybutynin is used during lactation, a small amount is excreted in mother's milk. Women who are breastfeeding should not use AQUIETTE.

4.7 Effects on ability to drive and use machines

Oxybutynin may cause drowsiness or blurred vision which could seriously hamper the patient’s ability to perform activities requiring mental alertness, which may be enhanced with alcohol, see section 4.5. If physical or mental ability is affected while taking oxybutynin, patients should not drive, operate machinery or perform hazardous work while taking AQUIETTE.

4.8 Undesirable effects

Classification of expected frequencies:

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).

Infections and infestations

Not known: urinary tract infection

Gastro-intestinal disorders

Very common: constipation, nausea, dry mouth

Common: diarrhoea, vomiting

Uncommon: abdominal discomfort, anorexia, decreased appetite, dysphagia

Not known: gastroesophageal reflux disease, pseudo-obstruction in patients at risk (elderly or patients with constipation and treated with other medicinal products that decrease intestinal motility)

Psychiatric disorders

Common: confusional state

Not known: agitation, anxiety, hallucinations, nightmares, paranoia, cognitive disorders in elderly, symptoms of depression, dependence (in patients with history of drug or substance abuse)

Nervous system disorders

Very common: dizziness, headache, somnolence

Not known: cognitive disorders, convulsions

Cardiac disorders

Not known: tachycardia, arrhythmia

Injury, poisoning and procedural complications

Not known: heat stroke

Eye disorders

Common: dry eyes

Not known: Angle closure glaucoma, mydriasis, ocular hypertension, vision blurred

Renal and urinary disorders

Common: urinary retention

Vascular disorders

Common: flushing

Skin and subcutaneous tissue disorders

Very common: dry skin

Not known: angioedema, rash, urticaria, hypohidrosis, photosensitivity

Immune system disorders

Not known: 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow card Scheme at: www.mhra.gov.uk./yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The symptoms of overdosage with oxybutynin progress from an intensification of the usual adverse 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.

Management

Measures to be taken are:

1. immediate gastric lavage

2. physostigmine by slow intravenous injection:

Adults: 0.5 to 2.0 mg i.v. slowly, repeated if necessary, up to a maximum of 5 mg.
Children: 30 μg/kg i.v. slowly, repeated if necessary, up to a maximum of 2 mg.

Fever should be treated symptomatically.

In pronounced restlessness or excitation, diazepam 10 mg may be given by intravenous injection. Tachycardia may be treated with intravenous propranolol and urinary retention managed by bladder catheterisation.

In the event of progression of curare-like effects to paralysis of the respiratory muscles, mechanical ventilation will be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other urologicals, including antispasmodics, urinary antispasmodics

ATC code: G04BD04

Oxybutynin hydrochloride has direct antispasmodic action on the smooth muscle of the bladder detrusor as well as anticholinergic action in blocking the muscarinic effects of acetylcholine on smooth muscle.

These properties cause relaxation of the detrusor muscle of the bladder and in patients with an unstable bladder, oxybutynin hydrochloride increases bladder capacity and reduces the incidence of spontaneous contraction of the detrusor muscle.

5.2 Pharmacokinetic properties

Absorption: Oxybutynin hydrochloride is rapidly and well absorbed from the gastro-intestinal tract. In a bioequivalence study peak plasma concentrations for oxybutynin were reached in 0.5 to 1.25 hours with a mean of 0.7 hours. Peak plasma concentrations for desethyloxybutynin (the pharmacologically active major metabolite were reached in 0.5 to 1.5 hours with a mean of 0.9 hours. Mean elimination half-life for oxybutynin and desethyloxybutynin were 1.4 hours and 2.1 hours respectively.

Distribution: In man oxybutynin hydrochloride is 83-85% bound to plasma albumin. It is distributed throughout most of the body, with high concentrations in the stomach, intestines and liver, but only very small amounts are found in the central nervous system. It is estimated that only 0.01% of the dose will enter the cerebrospinal fluid. In rats the concentrations achieved in breast milk and in the foetus are approximately 50-60% of those found in the maternal blood. Distribution of the drug in the foetus is similar to that in the mother.

Biotransformation: Following oral administration, oxybutynin hydrochloride undergoes extensive first-pass metabolism in the liver. This shows considerable inter-subject variability, with maximum plasma concentrations differing by as much as four-or five-fold amongst individuals. However, this does not significantly affect the pharmacological actions of oxybutynin hydrochloride as much of the oral dose (approximately 90%) is metabolised to desethyloxybutynin. This is the major metabolite which is pharmacologically active with similar potency and efficacy to the parent compound.

Elimination: The elimination of oxybutynin hydrochloride is rapid with a short plasma elimination half life so that repeated administration of oxybutynin hydrochloride results in little accumulation. Very little oxybutynin hydrochloride is excreted unchanged in the urine – more is excreted in the faeces (approximately 23% compared with 8%).

5.3 Preclinical safety data

There was no evidence of genotoxic or carcinogenic potential. High doses of oxybutynin increased the incidence of extra thoracolumbar ribs in rat foetuses as well as mortality of neonates. However, these effects on the reproductive processes occurred only at doses associated with maternal toxicity (100mg/kg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone
Microcrystalline cellulose,
Lactose monohydrate,
Magnesium stearate,
Indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Three years

Do not use after the 'Use Before' date given on the pack.

6.4 Special precautions for storage

Store below 25°C in a dry place

6.5 Nature and contents of container

The tablets are available in Aluminium / uPVC/PVdC strips in boxes of 28 and 30.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Maxwellia Ltd, Alderley Park, Alderley Edge, England, SK10 4TG

8 MARKETING AUTHORISATION NUMBER(S)

PL 42807/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 November 2017

10 DATE OF REVISION OF THE TEXT

TBC