Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Renamel 5mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Renamel 5mg contains 5mg of oxybutynin hydrochloride.

3 PHARMACEUTICAL FORM

Tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oxybutynin hydrochloride has antispasmodic/anticholinergic actions.

Its uses are:

Adults:
Urinary incontinence, frequency and urgency in patients with an unstable bladder (urge syndrome).
Neurogenic bladder disorders causing detrusor hyperreflexia in conditions such as multiple sclerosis and spina bifida.

Children over 5 years of age:
Neurogenic bladder disorders and voiding symptoms due to detrusor instability. The latter include secondary nocturnal enuresis or diurnal enuresis where there is a significant component of detrusor instability.

Oxybutynin hydrochloride may also be useful in the management of continent or incontinent children with vesicoureteric reflux.

4.2 Posology and method of adminstration

Renamel tablets are for oral administration. The tablet should be swallowed with plenty of water or other fluid, to ensure passage through the oesophagus.

Adults:
The dose is usually one tablet of 2.5 mg or 5 mg given two or three times daily, although this may be increased up to a maximum of 5 mg four times daily if required to obtain a clinical response, providing that the side effects are tolerated. It is usually wise to institute treatment slowly to minimise the anticholinergic side effects especially that of a dry mouth.

Frail elderly:
A dose of 2.5 mg or 5 mg twice daily is likely to be adequate for the elderly (over 80 years) since the elimination time is doubled as compared to healthy young volunteers. In the frail elderly peak plasma concentrations have also been shown to be greater than in healthy young volunteers.

Children 5 years of age and over:
A dose of 2.5mg to 5mg twice daily should be given initially and this can be increased up to 5 mg three times daily to obtain a clinical response. In cases of nocturnal enuresis alone, the usual dose is 5 mg two or three times daily with the

last dose given before bedtime.

Children under 5 years of age:
The safety and efficacy of oxybutynin hydrochloride have been demonstrated for children 5 years of age and older. There is insufficient clinical data for children under the age of 5 years so that it is not recommended for this age group.

Following initial control, a reduced maintenance dose may be introduced.

4.3 Contraindications

Oxybutynin hydrochloride is contra-indicated in patients:
- who have demonstrated hypersensitivity to the product;
- with untreated angle closure glaucoma or with untreated narrow anterior chamber angles since anticholinergic drugs may aggravate these conditions;
- with partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, toxic megacolon complicating ulcerative colitis, severe colitis;
- with myasthenia gravis;
- with obstructive uropathy as urinary retention may be precipitated;
- with unstable cardiovascular status in acute haemorrhage;
- who are breast-feeding.

Oxybutynin hydrochloride should not be used in children under 5 years of age.

4.4 Special warnings and precautions for use

Oxybutynin hydrochloride, when administered in the presence of high environmental temperature, can cause heat prostration (fever and heat stroke due to decreased sweating).

Diarrhoea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with oxybutynin hydrochloride would be inappropriate and possibly harmful.

Precautions:
Oxybutynin hydrochloride should be used with caution in the frail elderly and in patients with autonomic neuropathy, hepatic or renal disease.

The symptoms of hyperthyroidism, coronary artery disease, congestive cardiac failure, cardiac arrhythmias, tachycardias and prostatic hypertrophy may be aggravated following the administration of oxybutynin hydrochloride.

Special care should be taken in patients with hiatus hernia associated with reflux oesophagitis, as anticholinergic drugs may aggravate this condition. If oxybutynin is administered in such patients then this should be accompanied by some clinical monitoring.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken if other anticholinergic agents are administered together with oxybutynin hydrochloride, as potentiation of anticholinergic effects could occur.

Occasional cases of interaction between anticholinergics and phenothiazines, amantadine, haloperidol, levodopa, digitalis and tricyclic antidepressants have been reported and care should be taken if oxybutynin hydrochloride is administered concurrently with such drugs.

Oxybutynin hydrochloride may cause drowsiness. Alcohol or other sedative drugs may enhance this effect.

4.6 Pregnancy and lactation

Pregnancy:
There are no data relating to the safety of oxybutynin hydrochloride in human pregnancy but in pregnant rats it has been noted that oxybutynin crosses the placenta unchanged. The foetal blood levels reach 50% maternal levels after six hours and decline more slowly than maternal levels. Oxybutynin should therefore not be given to pregnant women unless, in the judgement of the physician, the probable clinical benefits outweigh the potential hazards.

Lactation:
Oxybutynin hydrochloride has been detected in breast milk in animal studies (approximately 60% of that found in the maternal blood). These concentrations decline more slowly than in maternal blood so that oxybutynin should not be taken by breast-feeding mothers.

4.7 Effects on ability to drive and use machines

As oxybutynin hydrochloride may cause drowsiness or blurred vision, the patient should be cautioned regarding activities requiring mental alertness such as driving a motor vehicle, operating machinery or performing hazardous work whilst taking this drug.

4.8 Undesirable effects

Oxybutynin hydrochloride may produce all the side effects that may be associated with anticholinergic drugs:

Cardiovascular: palpitations, tachycardia, vasodilatation and facial flushing.

Dermatologic: decreased sweating, rash.

Gastrointestinal/Genitourinary: constipation, decreased gastrointestinal motility, dry mouth, nausea, urinary hesitance and retention.

Nervous system: Asthenia, dizziness, drowsiness, hallucinations, insomnia, restlessness.

Ophthalmic: blurred vision, dry eyes.

Other: impotence, suppression of lactation.

4.9 Overdose

The symptoms of overdose with oxybutynin hydrochloride 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.

Measure to be taken are:
1. Immediate gastric lavage and
2. slow intravenous injection of 1.0 to 2.0 mg of physostigmine, repeated as necessary up to a total of 5 mg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

The optimal dose required to bring about the desired effect is in the range 3-15 mg daily.

5.2 Pharmacokinetic properties

Following oral administration, oxybutynin 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, 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.

Oxybutynin hydrochloride is rapidly and well absorbed from the gastro-intestinal tract. In the 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 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.

In man oxybutynin 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.

The elimination of oxybutynin is rapid with a short plasma elimination half life so that repeated administration of oxybutynin and desethyloxybutynin results in little accumulation. Metabolites are excreted in the urine. Very little oxybutynin is excreted unchanged in the urine - more is excreted in the faeces (approximately 23% compared with 8%).

5.3 Preclinical safety data

Two year carcinogenicity and teratogenicity studies in rats given up to 160 mg/kg daily were negative. Dependency studies performed in rats at doses between 2.5 and 40 mg/kg daily over a 40 day period demonstrated no physical dependence on oxybutynin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone Ph.Eur.
Microcrystalline cellulose Ph.Eur.
Lactose monohydrate Ph.Eur.
Magnesium stearate Ph.Eur.
Indigo Carmine Aluminium Lake (E132)

6.2 Incompatibilities

None stated.

6.3 Shelf Life

Two years.

6.4 Special precautions for storage

Store below 25°C in a dry place.

6.5 Nature and contents of container

Nature: Aluminium/µPVC/PVdC strips.
Contents: Renamel tablets are available in packs of 20, 28, 30, 60, 84 and 120.

6.6 Instructions for use and handling

None.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited
1 The Cam Centre
Wilbury Way
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Hertfordshire
SG4 0TW
United Kingdom

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