1.3.1.1 Package Insert (clean)

SCHEDULING STATUS

S2

PROPRIETARY NAME AND DOSAGE FORM

Uricon® granules

COMPOSITION

Each tablet contains trospium chloride 20 mg

Contains sugar

PHARMACOLOGICAL CLASSIFICATION

A 18 Medicines acting on the genito-urinary system

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Trospium chloride is a quarternary derivative of nortropan and therefore belongs to the class of parasympatholytic or anticholinergc drugs, as it competes with acetylcholine which is the body's endogenous neuro-transmitter at parasympathic post-synaptic binding sites.

Trospium chloride binds with high affinity to muscarinic receptors of the so-called M_1-, M_2- and M_3 – subtypes and demonstrates negligible affinity to nicotinic receptors.

The anticholinergic effect of trospium chloride exerts a relaxing action on smooth muscle tissue and organ functions mediated by muscarinic receptors. The contractile

tone of smooth muscle in the gastro-intestinal and genito-urinary tract is diminished by trospium chloride. It can reduce the secretion of bronchial mucous, saliva and sweat and it can affect ocular accommodation.

No effects in the central nervous system have so far been observed.

Pharmacokinetic properties

After oral administration of trospium chloride maximum plasma level is reached between 4 to 6 hours. Following a single dose of 20 mg, the maximum plasma level is about 4 ng/ml. Within the tested interval, 20 to 60 mg as a single dose, the plasma levels are proportional to the administered dose. The absolute bio-availability of a single oral dose of 20 mg of trospium chloride is 9,6 ± 4,5 % (mean value ± standard deviation).

At steady state the intra-individual variability is 16 %, and the inter-variability is 36 %. The terminal elimination half-life is approximately 12 hours.

Simultaneous intake of food, especially a high fat diet, reduces the bioavailability of trospium chloride. After a high fat meal C_{max} and AUC are reduced to 15 – 20 % of values in the fasted state.

Most of the systemically available trospium chloride is excreted unchanged by the kidneys, though a small portion (10 % of the renal excretion) appears as the spiro-alcohol, a metabolite formed by ester hydrolysis. The terminal elimination half-life is in the range of 10 – 20 hours. No accumulation occurs. The plasma protein binding is 50 – 80 %. In a study in patients with severe renal impairment, (creatinine clearance 8- 32 mg/min) mean AUC was 4-fold higher, C_{max} twofold higher and mean half-life prolonged two-fold.

No pharmacokinetic data is available in patients with liver disease.

INDICATIONS

Uricon® is indicated for the treatment of adults with detrusor instability / over activity and associated symptoms of urinary frequency, urgency or urge incontinence.

CONTRA-INDICATIONS

Urinary retention, including urinary retention due to prostatic disease (e.g. benign prostatic hyperplasia) and bladder neck and / or urethral stenosis, narrow-angle glaucoma, tachyarrhythmia, myasthenia gravis, severe ulcerative colitis, toxic megacolon, dialysed renal insufficiency, (creatinine clearance < 10 ml/min/1,73 m^2). Mechanical stenosis or obstructive lesions of the gastro-intestinal tract. Severe impairment of hepatic function.

WARNINGS:

Trospium chloride should be used with caution by patients who suffer from:

- Autonomic neuropathy
- Hiatus hernia associated with reflux oesophagitis

Not recommended for use in patients under 18 years of age as insufficient data is available.

INTERACTIONS:

Possible potentiation of effects of drugs with anticholinergic action such as amantadine, tricyclic antidepressants, quinidine, antihistamines and disopyramide.

Enhancement of tachycardiac action of β-sympathomimetics. Decrease in efficacy of pro-kinetic agents, e.g. metoclopramide and cisapride.

PREGNANCY AND LACTATION

Safety of use in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

The tablets should be swallowed whole with a glass of water before meals.

One tablet twice daily (equivalent to 40 mg of trospium chloride per day).

In patients with moderate renal impairment the recommended dosage is:

One tablet per day (equivalent to 20 mg of trospium chloride per day)

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS:

Very common (10 %); common (1 % - < 10 %); uncommon (0,1 % - < 1 %); rare (0,01 % - < -.1 %); very rare (< 0,01 %) including isolated cases.

Anticholinergic effects may occur during the treatment with trospium chloride.

Cardiovascular disorders

Uncommon: Tachycardia

Rare: Tachyarrhythmia

Gastro-intestinal disorders

Common: Dryness of the mouth, dyspepsia, abdominal pain, nausea, constipation

Uncommon: Diarrhoea, flatulence, vomiting

Hepatobiliary disorders

Rare: Mild to moderate increase in serum transaminase levels

Nervous system disorders:

Uncommon: Vision disorders, such as disorders of accommodation

Renal and urinary system disorders

Uncommon: Micturition disorders, e.g. residual urine

Rare: Urinary retention

Reproductive disorders

Common: Decrease bronchial mucous production

Uncommon: Dyspnoea

Skin and subcutaneous tissue disorders

Common: Decreased sweating

Uncommon: Rash

Rare: Angio-oedema

Whole body disorders

Uncommon: Asthenia, chest pain, tiredness, headache, somnolence or sleep disorder

SPECIAL PRECAUTIONS:

Uricon® should be used with caution in patients with:

- detrusor – sphincter – dyssynergia, with risk of residual urine and urinary retention
- hiatus hernia
- impaired renal function

The organic causes of detrusor instability / overactivity and associated symptoms of urinary frequency, urgency or urge incontinence (such as heart disease, diseases of the kidneys, infections or tumours of urinary organs) should be excluded before commencing therapy.

Disorders of accommodation can lower the ability to operate machinery and drive motor vehicles.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

After administration of a maximum single dose of 360 mg trospium chloride to healthy volunteers, dryness of the mouth, tachycardia and disorders of micturition were observed to an increased extent.

No manifestations of severe overdosage or toxicity in humans have been reported to date. Increased anticholnergic symptoms are to be expected as signs of toxicity.

In the case of toxicity, the following measures should be taken:

- gastric lavage and reduction of absorption, e.g activated charcoal
- local administration of pilocarpine to glaucoma patients
- catheterisation in patents with urinary retention
- treatment with a parasympathomimetic agent, e.g. neostigmine, in the case of severe symptoms

administration of beta-blockers in the case of insufficient response, pronounced tachycardia and/or circulatory instability, e.g. initially 1 mg propranolol intravenous along with monitoring of ECG and blood pressure.

IDENTIFICATION

Brownish-yellow, glossy sugar-coated tablet with a diameter of 7 mm.

PRESENTATION

PVC/Aluminium blister strips containing 10 tablets, packed into an outer carton of 60 tablets.

STORAGE INSTRUCTIONS

Store below 25 ºC.

KEEP OUT OF REACH OF CHILDREN

REFERENCE NUMBER

35/18/0406

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170 **CERTIFICATE**

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178 **DATE OF PUBLICATION OF THE PACKAGE INSERT**

179 19 October 2007