

Amendment date: 12 April 2019
Approved: 26 June 2019

1 **1.3.1.1 Package Insert (clean)**
2

3 **SCHEDULING STATUS**

4 S2
5

6 **PROPRIETARY NAME AND DOSAGE FORM**

7 **Uricon**[®] granules
8

9 **COMPOSITION**

10 Each tablet contains trospium chloride 20 mg

11 Contains sugar
12

13 **PHARMACOLOGICAL CLASSIFICATION**

14 A 18 Medicines acting on the genito-urinary system
15

16 **PHARMACOLOGICAL ACTION**

17 **Pharmacodynamic properties**

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

22 Trospium chloride binds with high affinity to muscarinic receptors of the so-called M₁-,
23 M₂- and M₃ – subtypes and demonstrates negligible affinity to nicotinic receptors.

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

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26 tone of smooth muscle in the gastro-intestinal and genito-urinary tract is diminished
27 by trospium chloride. It can reduce the secretion of bronchial mucous, saliva and
28 sweat and it can affect ocular accommodation.
29 No effects in the central nervous system have so far been observed.

30

31 **Pharmacokinetic properties**

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

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

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

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

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50 No pharmacokinetic data is available in patients with liver disease.

51

52 **INDICATIONS**

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

55

56 **CONTRA-INDICATIONS**

57 Urinary retention, including urinary retention due to prostatic disease (e.g. benign
58 prostatic hyperplasia) and bladder neck and / or urethral stenosis, narrow-angle
59 glaucoma, tachyarrhythmia, myasthenia gravis, severe ulcerative colitis, toxic
60 megacolon, dialysed renal insufficiency, (creatinine clearance < 10 ml/min/1,73 m²).
61 Mechanical stenosis or obstructive lesions of the gastro-intestinal tract. Severe
62 impairment of hepatic function.

63

64 **WARNINGS:**

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

- 66 • Autonomic neuropathy
- 67 • Hiatus hernia associated with reflux oesophagitis

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

70

71 **INTERACTIONS:**

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

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

76

77 **PREGNANCY AND LACTATION**

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

79

80 **DOSAGE AND DIRECTIONS FOR USE**

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

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

83

84 **In patients with moderate renal impairment the recommended dosage is:**

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

86

87 **SIDE EFFECTS AND SPECIAL PRECAUTIONS**

88 **SIDE EFFECTS:**

89 Very common (10 %); common (1 % - < 10 %); uncommon (0,1 % - < 1 %); rare (0,01
90 % - < .1 %); very rare (< 0,01 %) including isolated cases.

91

92 Anticholinergic effects may occur during the treatment with trospium chloride.

93

94 **Cardiovascular disorders**

95 *Uncommon:* Tachycardia

96 *Rare:* Tachyarrhythmia

97

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98 **Gastro-intestinal disorders**

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

100 *Uncommon:* Diarrhoea, flatulence, vomiting

101

102 **Hepatobiliary disorders**

103 *Rare:* Mild to moderate increase in serum transaminase levels

104

105 **Nervous system disorders:**

106 *Uncommon:* Vision disorders, such as disorders of accommodation

107

108 **Renal and urinary system disorders**

109 *Uncommon:* Micturition disorders, e.g. residual urine

110 *Rare:* Urinary retention

111

112 **Reproductive disorders**

113 *Common:* Decrease bronchial mucous production

114 *Uncommon:* Dyspnoea

115

116 **Skin and subcutaneous tissue disorders**

117 *Common:* Decreased sweating

118 *Uncommon:* Rash

119 *Rare:* Angio-oedema

120

121 **Whole body disorders**

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

124

125 **SPECIAL PRECAUTIONS:**

126 **Uricon**[®] should be used with caution in patients with:

127 - detrusor – sphincter – dyssynergia, with risk of residual urine and urinary
128 retention

129 - hiatus hernia

130 - impaired renal function

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

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

137

138 **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS**

139 **TREATMENT**

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

143 No manifestations of severe overdose or toxicity in humans have been reported to
144 date. Increased anticholinergic symptoms are to be expected as signs of toxicity.

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

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- 146 - gastric lavage and reduction of absorption, e.g. activated charcoal
- 147 - local administration of pilocarpine to glaucoma patients
- 148 - catheterisation in patients with urinary retention
- 149 - treatment with a parasympathomimetic agent, e.g. neostigmine, in the case of
- 150 severe symptoms
- 151 administration of beta-blockers in the case of insufficient response, pronounced
- 152 tachycardia and/or circulatory instability, e.g. initially 1 mg propranolol intravenous
- 153 along with monitoring of ECG and blood pressure.

154

155 **IDENTIFICATION**

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

157

158 **PRESENTATION**

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

160 tablets.

161

162 **STORAGE INSTRUCTIONS**

163 Store below 25 °C.

164 KEEP OUT OF REACH OF CHILDREN

165

166 **REFERENCE NUMBER**

167 35/18/0406

168

Applicant: TAKEDA (PTY) LTD to XIXIA PHARMACEUTICALS (PTY) LTD
(Transfer of Applicancy)
Product Name: URICON
Dosage form and strength: Each tablet contains 20,0 g trospium chloride

MODULE 1
1.3.1.1

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169 **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION**

170 **CERTIFICATE**

171 XIXIA PHARMACEUTICALS (PTY) LTD

172 Building 6

173 Greenstone Hill Office Park

174 Emerald Boulevard

175 Modderfontein

176 1645

177

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

179 19 October 2007