

GLAXOSMITHKLINE SOUTH AFRICA (PTY) LIMITED	Submission Date	25 Aug 2015	Type	Clinical
NARAMIG	Implementation Date	immediate	Category	Reg 9 Notification
Tablets (2,5 mg naratriptan (as HCl)/tablet)			Reference	GDS-6 - v0001

CONFIDENTIAL

1.3 South African labelling and packaging

1.3.1 South African Package Insert

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NARAMIG

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

NARAMIG® tablet

COMPOSITION:

Each tablet contains 2,5 mg naratriptan as naratriptan hydrochloride.

Excipients:

Tablet core: Microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, magnesium stearate.

Film coat: Methylhydroxypropylcellulose, titanium dioxide (E171), triacetin, Iron oxide yellow (E172), indigo carmine aluminium lake (E132).

PHARMACOLOGICAL CLASSIFICATION:

A 7.3 Vascular medicines, Migraine preparations

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Naratriptan is a selective agonist for the vascular 5-hydroxytryptamine₁ (5-HT₁) receptor. This receptor is found predominantly in intracranial (cerebral and dural) blood vessels. Naratriptan has high affinity for human cloned 5-HT_{1B} and 5-HT_{1D} receptors; the human 5-HT_{1B} receptor is thought to correspond to the vascular 5-HT₁ receptor mediating contraction of intracranial blood

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26 vessels. Naratriptan has little effect at other 5-HT receptor (5-HT₂, 5-HT₃, 5-HT₄ and 5-HT₇)
27 subtypes. In animals, naratriptan selectively constricts the carotid arterial circulation which
28 supplies blood to the extracranial and intracranial tissues such as the meninges. In addition,
29 experimental evidence suggests that naratriptan inhibits trigeminal nerve activity. Both these
30 actions may contribute to the anti-migraine action of naratriptan in humans.

31

32 **Pharmacokinetic Properties:**

33 Following oral administration, naratriptan is absorbed with maximum plasma concentrations
34 observed at 2-3 hours. After administration of a 2,5 mg naratriptan tablet, C_{max} is approximately
35 8,3 ng/ml in women and 5,4 ng/ml in men. The mean elimination half-life is 6 hours.

36 Naratriptan is predominantly excreted in the urine with 50 % of an oral dose recovered as
37 unchanged naratriptan and 30 % recovered as inactive metabolites. *In vitro*, naratriptan is
38 metabolised by a wide range of cytochrome P450 isoenzymes and does not interact with
39 monoamine oxidase.

40

41 **INDICATIONS:**

42 NARAMIG tablets are indicated for the acute treatment of migraine attacks with or without aura.

43

44 **CONTRA-INDICATIONS:**

45 Hypersensitivity to any component of the preparation.

46 NARAMIG should not be used in patients who have had a myocardial infarction or have
47 ischaemic heart disease, or Prinzmetal's angina/coronary vasospasm, or peripheral vascular
48 disease or patients who have symptoms or signs consistent with ischaemic heart disease.

49 NARAMIG should not be administered to patients with a history of cerebrovascular accident
50 (CVA) or transient ischaemic attack (TIA).

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51 The use of NARAMIG in patients with uncontrolled hypertension is contra-indicated.
52 NARAMIG is contra-indicated in patients with severely impaired renal or hepatic function.
53 The concomitant administration of ergotamine, derivatives of ergotamine (including
54 methysergide) and other triptans with NARAMIG is not recommended.

55

56 WARNINGS AND SPECIAL PRECAUTIONS:

57 NARAMIG should only be used where there is a clear diagnosis of migraine.
58 Before treating headaches in patients not previously diagnosed as migraineurs, and in
59 migraineurs who present with atypical symptoms, care should be taken to exclude other
60 potentially serious neurological conditions. It should be noted that migraineurs may be at risk
61 of certain cerebrovascular events (e.g. CVA or TIA).
62 NARAMIG is not indicated for use in the management of hemiplegic, basilar or
63 ophthalmoplegic migraine.
64 NARAMIG should not be given to patients in whom unrecognised cardiac disease is likely
65 without a prior evaluation for underlying cardiovascular disease. Such patients include
66 postmenopausal women, males over 40 years and patients with risk factors for coronary
67 artery disease. If symptoms consistent with ischaemic heart disease occur appropriate
68 evaluation should be carried out.
69 The recommended dose of NARAMIG should not be exceeded.
70 NARAMIG contains a sulphonamide component therefore there is a theoretical risk of a
71 hypersensitivity reaction in patients with known hypersensitivity to sulphonamides.
72 Caution is recommended in patients performing skilled tasks (e.g. driving or operating
73 machinery) as drowsiness may occur as a result of migraine.
74 The safety and effectiveness of NARAMIG in the elderly (over 65 years of age) have not
75 been evaluated. There is a moderate decrease (26 %) in clearance with increasing age.

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76 NARAMIG is not recommended for use in children (under 12 years of age) or adolescents
77 (12-17 years of age).

78

79 **INTERACTIONS:**

80 There is no evidence of interactions with β -blockers, tricyclic antidepressants, selective
81 serotonin reuptake inhibitors, alcohol or food.

82 NARAMIG does not inhibit monoamine oxidase enzymes; therefore interactions with
83 monoamine oxidase inhibitors are not anticipated. In addition, the limited metabolism of
84 naratriptan and the wide range of cytochrome P450 isoenzymes involved suggest that
85 significant drug interactions with NARAMIG are unlikely.

86

87 **PREGNANCY AND LACTATION:**

88 The safe use of NARAMIG in pregnant women has not been established.

89 NARAMIG and/or drug related metabolites are secreted into the milk of lactating rats.

90 Caution should be exercised when considering administration of NARAMIG to nursing
91 women.

92

93 **DOSAGE AND DIRECTIONS FOR USE:**

It should not be used prophylactically.

94 NARAMIG tablets should be taken as early as possible after the onset of a migraine
95 headache but may be effective if taken at a later stage.

96 The tablets should be swallowed whole with water.

97 The recommended dose of NARAMIG Tablets is a single 2,5 mg tablet.

98 A minimum interval of four hours should be left between doses.

99 No more than two 2,5 mg tablets in any 24 hour period.

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100 Maximum total daily dose in renal/hepatic impairment: one 2,5 mg tablet.

101 If a patient does not respond to the first dose of NARAMIG tablets it is unlikely that a second
102 dose will be of benefit in the same attack.

103

104 **SIDE EFFECTS:**

105 Adverse events are listed below by system organ class and frequency. Frequencies are
106 defined as: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1 000,
107 < 1/100), rare (> 1/10 000, < 1/1 000) and very rare (< 1/10 000). Common and uncommon
108 frequencies were determined from clinical trial data. Very rare frequencies were generally
109 derived from spontaneous data.

110

111 **Clinical trial data:**

112 At therapeutic doses of naratriptan, the incidence of side effects reported in clinical trials
113 was similar to placebo.

114 ***Nervous system disorders:***

115 Common: tingling

116 This is usually of short duration, may be severe and may affect any part of the body
117 including the chest or throat.

118 ***Gastrointestinal:***

119 Common: nausea and vomiting

120 ***Musculoskeletal and connective tissue disorders:***

121 Common: sensations of heaviness

122 This is usually of short duration, may be severe and may affect any part of the body
123 including the chest or throat.

124 ***General disorders and administration site conditions:***

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125 The following symptoms are usually of short duration, may be severe and may affect any
126 part of the body including the chest or throat:

127 Common: pain, sensations of tingling and heat

128 Uncommon: sensations of pressure or tightness.

129

130 **Post-marketing data:**

131 ***Immune system disorders:*** hypersensitivity reactions ranging from cutaneous

132 hypersensitivity to anaphylaxis

133 ***Cardiovascular:*** coronary artery vasospasm transient ischaemic ECG changes, angina and

134 myocardial infarction (see CONTRA-INDICATIONS, WARNINGS AND SPECIAL

135 PRECAUTIONS and SIDE EFFECTS)

136 ***Vascular disorders:*** peripheral vascular ischaemia

137 ***Gastrointestinal disorders:*** ischaemic colitis.

138

139 **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

140 Administration of a high dose of 25 mg naratriptan in one healthy male subject increased
141 blood pressure by up to 71 mmHg and resulted in adverse events including light-
142 headedness, tension in the neck, tiredness and a loss of co-ordination. Blood pressure
143 returned to baseline by 8 hours after dosing without other pharmacological intervention.

144 It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma
145 concentrations of naratriptan.

146

147 **Treatment:** If overdosage with naratriptan occurs, the patient should be monitored for at
148 least 24 hours and standard supportive treatment applied as required.

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150 **IDENTIFICATION:**

151 NARAMIG tablets are green film-coated, D shaped, biconvex, with 'GX CE5' engraved on
152 the one face.

153

154 **PRESENTATION:**

155 NARAMIG tablets are packed in double foil blister packs of 2, 4, 6 and 12 tablets.

156

157 **STORAGE INSTRUCTIONS:**

158 Store below 30 °C.

159 Protect from light.

160 Keep out of reach of children.

161

162 **REGISTRATION NUMBER:**

163 32/7.3/0463

164

165 **NAME AND BUSINESS ADDRESS OF THE OF THE HOLDER OF THE CERTIFICATE OF**

166 **REGISTRATION:**

167 GlaxoSmithKline South Africa (Pty) Ltd

168 39 Hawkins Avenue

169 Epping Industria 1, 7460

170

171 **DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

172 5 October 2007

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Namibia: Reg No 04/7.3/0903 **NS2**

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GDS-06

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HISTORY:

- 180 Amended: 02 April 2002 (Applicant name change)
- 181 Amended: 03/05/2004 (In line with GCT-006)
- 182 Amended: 06 September 2006 (In response to CC Recommendations dated 10 March 2006)
- 183 Amended: 15 May 2007 (Compliant pi as per CC Recommendations dated 24/04/07) Approved 05 October 2007
- 184 Amended: 31 August 2011 (Applicant address change Bryanston to CT)
- 185 **Amended: 25 August 2015. Notification to bring pi in line with Reg 9. Implemented**
- 186