VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Indication: Migraine Headache

In the United States, more than 30 million people have 1 or more migraine headaches per year. This corresponds to approximately 18% of females and 6% of males. Approximately 75% of all persons who experience migraines are women. The female-to-male ratio increases from 2.5:1 at puberty to 3.5:1 at age 40 years. Attacks usually decrease in severity and frequency after age 40 years, except for women in perimenopause.

Race-related differences in prevelance

The prevalence of migraine appears to be lower among African Americans and Asian Americans than among whites.

International statistics

The World Health Organization (WHO) estimates the worldwide prevalence of current migraine to be 10% and the lifetime prevalence to be 14%. The adjusted prevalence of migraine is highest in North America, followed by South and Central America, Europe, Asia, and Africa.

Approximately 3000 migraine attacks per million persons worldwide occur every day. According to the WHO, migraine is 19th among all causes of years lived with disability.

VI.2.2 Summary of treatment benefits

The efficacy, safety and tolerability of eletriptan (40 mg and 80 mg) in acute treatment of migraine was evaluated in a multinational, randomized, double-blind, parallel-group, placebo-controlled study treating 1153 patients. In the initial attack, significantly more eletriptan patients reported headache relief and complete pain relief at 2 h vs. placebo (40 mg 62% and 32%, 80 mg 65% and 34%, placebo 19% and 3%;). Headache relief occurred faster after eletriptan, with more patients at both doses reporting relief 30 min and 1 h after treatment than after placebo. There was a significantly lower recurrence rate with eletriptan 80 mg compared with placebo. Adverse events for all treatments were generally mild or moderate and self-limiting. Eletriptan 40 mg and eletriptan 80 mg both appear to be effective and well-tolerated acute migraine treatments.

Reference: *Efficacy, safety and tolerability of oral eletriptan in the acute treatment of migraine: results of a phase III, multicentre, placebo-controlled study across three attacks., Stark R1, Dahlöf C, Haughie S, Hettiarachchi J; Eletriptan Steering Committee., Cephalalgia. 2002 Feb;22(1):23-32.*

VI.2.3 Unknowns relating to treatment benefits

Not Applicable

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions, including angioedema	Allergic reactions may arise to patients with hypersensitivity to the active substance or any of the excipients. Patients with	Patients with known hypersensitivity to the active substance or any of the excipients and patients with

Risk	What is known	Preventability
	hereditary problems of galactose intolerance or glucose-galactose malabsorption should not take this medicine. Immune system disorders including angioedema may also occur.	galactose intolerance should not take this medicine. Allergic reactions should be referred to the doctor at their onset.
Hypertension	Slight and transient increases in blood pressure have been seen with eletriptan doses of 60 mg or greater. The effect was much more pronounced in renally impaired and elderly subjects. In renally impaired subjects, the range of mean maximum increases in systolic blood pressure was 14 -17mmHg (normal 3mmHg) and for diastolic blood pressure was 14 - 21mmHg (normal 4mmHg). In elderly subjects, the mean maximum increase in systolic blood pressure was 23mmHg compared with 13mmHg in young adults (placebo 8mmHg). Post-marketing reports of increases in blood pressure have also been received for patients taking 20 and 40 mg doses of eletriptan, and in non-renally impaired and non-elderly patients.	[PRODUCT NAME] is contraindicated in patients with moderately severe or severe hypertension, or untreated mild hypertension. Patients with renal impairment are of higher risk and monitoring of their blood pressure is recommended.
Serotonin syndrome following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs)	Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs). These reactions can be severe.	If concomitant treatment with eletriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication.

Risk	What is known	Preventability
Asthenia, somnolence, nausea and dizziness	Migraine or treatment with [PRODUCT NAME] may cause drowsiness or dizziness in some patients. Eletriptan has been administered in clinical trials to over 5000 subjects, taking one or two doses of Eletriptan 20 or 40 or 80 mg. The most common adverse reactions noted were asthenia, somnolence, nausea and dizziness. In clinical studies using doses of 20, 40 and 80 mg, a trend for a dose-dependency of the incidence of adverse events has been shown.	Patients should be advised to evaluate their ability to perform complex tasks such as driving during migraine attacks and following administration of [PRODUCT NAME].
Drug-drug interactions	Patients with cardiac failure Eletriptan should not be given without prior evaluation, to patients in whom unrecognised cardiac disease is likely, or to patients at risk of coronary artery disease (CAD) [e.g., patients with hypertension, diabetes, smokers or users of nicotine substitution therapy, men over 40 years of age, post-menopausal women and those with a strong family history of CAD]. Cardiac evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred, in patients without underlying cardiovascular disease when 5-HT1 agonists have been administered. 5-HT1 receptor agonists have been associated with coronary vasospasm. In rare cases, myocardial ischaemia or infarction, have been reported with 5-HT1 receptor agonists. Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St. John's wort (Hypericum perforatum). Serotonin syndrome Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin	Eletriptan is contraindicated in patients with concomitant administration of other 5-HT1 receptor agonists. Patients in whom CAD is established, should not be given Eletriptan. If concomitant treatment with eletriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication. Eletriptan should not be used together with potent CYP3A4 inhibitors e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, josamycin and protease inhibitors (ritonavir, indinavir and nelfinavir). It is recommended that either ergotamine-containing or ergot-type medications (e.g., dihydroergotamine) should not be taken within 24 hours of eletriptan dosing. Conversely, at least 24 hours should elapse after the administration of an ergotamine-containing preparation before eletriptan is given.

Risk	What is known	Preventability
	reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs). These reactions can be severe. Potent CYP3A4 inhibitors and protease inhibitors In clinical studies with erythromycin (1000 mg) and ketoconazole (400 mg), specific and potent inhibitors of CYP3A4, significant increases in eletriptan Cmax (2 and 2.7- fold) and AUC (3.6 and 5.9- fold) respectively, were observed. This increased exposure was associated with an increase in eletriptan t1/2 from 4.6 to 7.1 hours for erythromycin and from 4.8 to 8.3 hours for ketoconazole. Caffeine/ergotamine In clinical studies with oral (caffeine/ergotamine) administered 1 and 2 hours after eletriptan, minor though additive increases in blood pressure were observed which are predictable based on the pharmacology of the two drugs.	
Medication overuse headache	Prolonged use of any painkiller for headaches can make them worse.	If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Myocardial ischaemia or infarction	Eletriptan can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat. Where such symptoms are thought to indicate ischaemic heart disease, no further dose should be taken and appropriate evaluation should be carried out. [PRODUCT NAME] should not be given without prior evaluation, to patients in whom unrecognised cardiac disease is likely, or to patients at risk of coronary artery disease (CAD) [e.g. patients with hypertension, diabetes, smokers or users of nicotine substitution therapy, men over 40 years of age, post-menopausal women and

Risk	What is known (Including reason why it is considered a potential risk)
	those with a strong family history of CAD]. 5-HT1 receptor agonists have been associated with coronary vasospasm. In rare cases, myocardial ischaemia or infarction, have been reported with 5-HT1 receptor agonists.
Ischaemic colitis	Rare reports of ischaemic colitis related to the administration of Eletriptan have been received

Missing information

Risk	What is known
Use in patients over 65 years	The safety and effectiveness of eletriptan in patients over 65 years of age have not been systematically evaluated due to the small number of such patients in clinical trials. Use of [PRODUCT NAME] in the elderly is therefore not recommended.
Use in paediatric population	The efficacy of Eletriptan in adolescents aged 12 to 17 years has not been established The safety and efficacy of Eletriptan in children aged 6 to 11 years has not been established. Recommendation on a posology can be made for the above groups.

VI.2.5 Summary of risk minimisation measures by safety concern

[PRODUCT NAME] has a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for [PRODUCT NAME] can be found in Annex 2.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not Applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	July 2014	Identified Risks • Hypersensitivity reactions including Lactose intolerance • Slight and transient increase in blood	-

Version	Date	Safety Concerns	Comment
		pressure (especially in patients with renal impairment) • Serotonin syndrome following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRI´s) or serotonin noradrenaline reuptake inhibitors (SNRI´s) • Excretion of eletriptan in human breast milk • Asthenia, somnolence, nausea and dizziness • Serious symptoms occurring from overdose <u>Potential Risks</u> • Danger of serious cardiac events <u>Missing information</u> • The safety and effectiveness of eletriptan in patients over 65 years • The safety and effectiveness of eletriptan in paediatric population • Use in patients with severe hepatic impairment • Use during pregnancy	
2.0	March 2015	The following safety concerns were added as important identified risks: • Drug-drug interactions • Medication overuse headache The identified risk "Hypersensitivity reactions including Lactose intolerance" was rephrased to the following: • Allergic reactions, including angioedema The identified risk "Slight and transient increase in blood pressure (especially in patients with renal impairment)" was rephrased to the following: • Hypertension The following identified risks were deleted: • Excretion of eletriptan in human breast milk • Serious symptoms occurring from overdose The following safety concern was added as an important potential risk: • Ischaemic coloitis The important potential risk "Danger of serious cardiac events" was rephrased to the following: • Myocardial ischaemia or infarction The following safety concerns were rephrased: • The safety and effectiveness of eletriptan in patients over 65 years • The safety and effectiveness of eletriptan in paediatric population To the following: • Use in patients overs 65 years of age • Use in the paediatric population Parts VI.1 and VI.2 were completed in their entirety.	Requirements arisen from RMS Day 70 Preliminary Assessment report within DCP DK/H/2453/001-002/DC