SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sumatriptan 50 mg, tabletten
Sumatriptan 100 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg sumatriptan (as succinate).

Excipients with known effect
Each tablet contains 176.20 mg lactose (as monohydrate) and up to 0.15 micrograms of sulphites per tablet.

Each tablet contains 100 mg sumatriptan (as succinate).

Excipients with known effect
Each tablet contains 110.39 mg lactose (as monohydrate) and up to 0.3 micrograms of sulphites per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

50 mg tablets:
Pink, oblong tablet with a break notch on both sides.
The tablet can be divided into equal doses.

100 mg tablets:
White to slightly yellow, oblong tablet with a break notch on both sides.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{Nationally completed name} is indicated for the acute treatment of migraine attacks with or without aura.

4.2 Posology and method of administration

General recommendations with regard to use and administration:

Sumatriptan should not be used prophylactically.

Sumatriptan is recommended as monotherapy for the acute treatment of a migraine attack and should not be given concomitantly with ergotamine or derivatives of ergotamine (including methysergide) (see section 4.3).

It is advisable that sumatriptan be given as early as possible after the onset of a migraine headache. It is equally effective at whatever stage of the attack it is administered.

Posology
The following recommended doses of sumatriptan should not be exceeded.

Adults
The recommended dose for adults is 50 mg sumatriptan. Some patients may require 100 mg sumatriptan.

Although the recommended oral dose of sumatriptan is 50 mg, it must be taken into account that the severity of migraine attacks varies both within and between patients. Doses of 25 mg - 100 mg have shown to be more effective than placebo in clinical trials but 25 mg is statistically significantly less effective than 50 mg and 100 mg.

If a patient does not respond to the first dose of sumatriptan, a second dose should not be taken for the same attack. In these cases the attack can be treated with paracetamol, acetylsalicylic acid, or non-steroidal anti-inflammatory drugs. Sumatriptan tablets may be taken for subsequent attacks.
If the patient has responded to the first dose, but the symptoms recur a second dose may be given in the next 24 hours, provided that there is a minimum interval of 2 hours between the two doses. No more than 300 mg should be taken in any 24- hour period.

Paediatric population
The efficacy and safety of sumatriptan tablets in children aged less than 10 years have not been established. No clinical data are available in this age group.
The efficacy and safety of sumatriptan tablets in children 10 to 17 years of age have not been demonstrated in the clinical trials performed in this age group. Therefore, the use of sumatriptan tablets in children 10 to 17 years of age is not recommended (see section 5.1).

Elderly (over 65 years of age)
Experience of the use of sumatriptan tablets in patients aged over 65 years is limited. The pharmacokinetics do not differ significantly from a younger population, but until further clinical data are available, the use of sumatriptan in patients aged over 65 years is not recommended.

Hepatic impairment
In patients with mild to moderate hepatic insufficiency low doses of 25-50 mg sumatriptan should be considered.

Method of administration
The tablets must be taken with water. The sumatriptan substance has a bitter taste. The bitter taste is masked with the aid of a grapefruit flavour.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- A history of myocardial infarction
- Ischaemic heart disease, coronary vasospasm (Prinzmetal’s angina)
- Peripheral vascular disease
- Symptoms or signs consistent with ischaemic heart disease

- A history of stroke (cerebrovascular accident (CVA)) or transient ischaemic attack (TIA)
- Severe hepatic impairment
- Moderate to severe hypertension, mild uncontrolled hypertension
- Concomitant administration of preparations containing ergotamine or ergotamine derivatives (including methysergide) or any triptan/5-hydroxytryptamine 1 (5-HT_1) receptor agonist (see section 4.5)
- Concomitant use of monoamine oxidase inhibitors (MAOIs) and the use of sumatriptan within 2 weeks after discontinuation of therapy with monoamine oxidase inhibitors

4.4 Special warnings and precautions for use

Sumatriptan should only be used where there is a clear diagnosis of “migraine”.

Sumatriptan is not indicated for use in the management of basilar, hemiplegic or ophthalmoplegic migraine.

Before treating with sumatriptan, care should be taken to exclude potentially serious neurological conditions (e.g. CVA, TIA) if the patient presents with atypical symptoms or if they have not received an appropriate diagnosis for sumatriptan use.

Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat (see section 4.8). Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan should be given and an appropriate evaluation should be carried out.

Sumatriptan should be given with caution in patients with mild controlled hypertension, since transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients (see section 4.3).

Sumatriptan should not be given to patients with risk factors for ischaemic heart disease, including those patients who are heavy smokers or users of nicotine substitution therapies, without prior cardiovascular evaluation (see section 4.3). Special consideration should be given to postmenopausal women and males over 40 years of age with these risk factors. These evaluations however, 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 (see section 4.8).

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs). If concomitant treatment with sumatriptan and an SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised (see section 4.5).

Sumatriptan should be administered with caution to patients with conditions which may affect significantly the absorption, metabolism or excretion of the active substance, e.g. impaired hepatic (Child-Pugh grade A or B; see section 5.2) or renal function (see section 5.2).

Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold, as seizures have been reported in association with sumatriptan (see section 4.8).

Patients with known hypersensitivity to sulfonamides may exhibit an allergic reaction after use of sumatriptan. The reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of

cross sensitivity is limited, however, caution should be exercised before using sumatriptan in these patients.

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's Wort (*Hypericum perforatum*).

Prolonged use of any type of 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 medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

[Nationally completed name] contains lactose, sulphites and sodium
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains sulphites which may rarely cause severe hypersensitivity reactions and bronchospasm.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence of interactions with propranolol, flunarizine, pizotifen or alcohol.

There are limited data on an interaction with preparations containing ergotamine or another triptan/5-HT_1 receptor agonist. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contraindicated (see section 4.3).

The period of time that should elapse between the use of sumatriptan and ergotamine containing preparations or another triptan/5-HT1 receptor agonist is not known. This will also depend on the doses and types of products used. The effects may be additive. It is advised to wait at least 24 hours following the use of ergotamine containing preparations or another triptan/5-HT1 receptor agonist before administering sumatriptan. Conversely it is advised to wait at least 6 hours following use of sumatriptan before administering an ergotamine-containing product and at least 24 hours before administering another triptan/5-HT1 receptor agonist.

An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see section 4.3).

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of SSRIs and sumatriptan. Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (see section 4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy
Post-marketing data on the use of sumatriptan during the first trimester of pregnancy in over 1,000 women are available. Although these data contain insufficient information to draw definitive conclusions, they do not point to an increased risk of congenital defects. Experience with the use of sumatriptan in the second and third trimester is limited.

Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on peri- and postnatal development. However, embryo-foetal viability might be affected in the

rabbit (see section 5.3). Administration of sumatriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Breast-feeding
It has been demonstrated that following subcutaneous administration, sumatriptan is secreted into breast milk. Infant exposure can be minimised by avoiding breast-feeding for 12 hours after treatment, during which time any breast milk expressed should be discarded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Drowsiness, dizziness and weakness may occur as a result of migraine or its treatment with sumatriptan. This may influence the ability to drive and to operate machinery.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency.
Frequencies are defined as:
Very common (≥ 1/10)
Common (≥1/100 to <1/10),
Uncommon (≥1/1,000 to <1/100),
Rare (≥1/10,000 to <1/1,000),
Very rare (<1/10,000), not known (cannot be estimated from the available data).

Some of the symptoms reported as undesirable effects may be associated symptoms of migraine.

Immune system disorders
Not known: Hypersensitivity reactions ranging from cutaneous hypersensitivity (such as urticaria) to anaphylaxis

Psychiatric disorders
Not known: Anxiety

Nervous system disorders
Common: Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia
Not known: Seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent.
Nystagmus, scotoma, tremor, dystonia

Eye disorders
Not known: Flickering, diplopia, reduced vision, loss of vision including reports of permanent defects. However, visual disorders may also occur during a migraine attack itself.

Cardiac disorders
Not known: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, angina, myocardial infarction (see sections 4.3 and 4.4)

Vascular disorders
Common: Transient increases in blood pressure arising soon after treatment, flushing
Not known: Hypotension, Raynaud’s phenomenon

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea

Gastrointestinal disorders
Common: Nausea and vomiting occurred in some patients but it is unclear if this is related to sumatriptan or the underlying condition
Not known: Ischaemic colitis, diarrhoea, dysphagia

Skin and subcutaneous tissue disorders
Not known: Hyperhidrosis

Musculoskeletal and connective tissue disorders
Common: Sensations of heaviness (usually transient and may be intense and can affect any part of the body including the chest and throat), myalgia
Not known: Neck stiffness, arthralgia

General disorders and administration site conditions
Common: Pain, sensations of heat or cold, pressure or tightness (these events are usually transient and may be intense and can affect any part of the body including the chest and throat); feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient)
Not known: Pain trauma activated, pain inflammation activated

Investigations
Very rare: Minor disturbances in liver function tests have occasionally been observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs
Doses in excess of 400 mg orally and 16 mg subcutaneously were not associated with adverse reactions other than those mentioned. Patients have received single injections of up to 12 mg subcutaneously without significant adverse reactions.

Treatment
If overdose occurs, the patient should be monitored for at least 10 hours and standard supportive treatment applied as required. It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analagesics, selective serotonin ($5HT_1$) agonists
ATC code: N02CC01

Mechanism of action

Sumatriptan is a specific and selective 5-hydroxytryptamine-1d receptor agonist, and has not demonstrated activity on the other 5HT ($5HT_2$-$5HT_7$) receptors.

Pharmacodynamic effects
The vascular $5HT_{1d}$ receptor is found predominantly in the cranial blood vessels and has a vasoconstrictor effect. In experimental animals, it has been shown that sumatriptan causes vasoconstriction of the arterioles and the arteriovenous anastomata of the carotid vascular bed. This vascular bed provides the blood supply to the extracranial and intracranial tissues, such as the meninges. It has been proposed that dilatation of these arterial vessels, and the formation of oedema here, is the underlying cause of a migraine attack in humans. There is also evidence from animal experiments to suggest that sumatriptan inhibits the activity of the trigeminal nerve. Both effects (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) might contribute to the anti-migraine effect of sumatriptan in humans.

Clinical efficacy and safety
A clinical response occurs approximately 30 minutes after oral administration of a dose of 100 mg.

The recommended oral dose for sumatriptan tablets is 50 mg.
In clinical trials, doses of 25-100 mg have appeared to be more effective than placebo; however, 25 mg is less effective than 50 and 100 mg (statistically significant).

Sumatriptan is effective for the acute treatment of migraine attacks that occur during menstruation in women, i.e. in the period from 3 days before to 5 days after the beginning of menstruation.

The efficacy of sumatriptan tablets 50 mg and 100 mg have been demonstrated in two clinical trials in 2,696 people with moderate to severe migraine. The patients reported the time to pain reduction (defined as no pain or mild pain).

The percentage with pain reduction within 2 hours was 42% for placebo, 67% for the 50 mg tablet and 72% for the 100 mg tablet. Half of these respondents had pain reduction within 56 minutes.

The percentage of patients pain-free within 2 hours was 15% for placebo, 40% for the 50 mg tablet and 46% for the 100 mg tablet. Half of these patients were pain-free within 75 minutes.

Paediatric population
A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in approximately 800 children and adolescent migraineurs aged 10-17 years. These studies failed to demonstrate relevant differences in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in adolescents aged 10-17 years was similar to that reported from studies in the adult population.

5.2 Pharmacokinetic properties

Absorption
Following oral administration sumatriptan is rapidly absorbed, the maximum concentration being reached after approx. 45 minutes. After oral administration of 100 mg the peak plasma concentration is on average 54 ng/ml. Absolute bioavailability after oral administration is on average 14%. This is partly due to presystemic metabolism and partly to incomplete absorption. In patients with hepatic insufficiency, presystemic clearance after oral administration is reduced, resulting in an increase in the plasma levels of sumatriptan.

Distribution
Protein binding is low (14-21%) and the mean volume of distribution is 170 litres.

Biotransformation and elimination
The elimination half-life is approximately 2 hours. Mean total clearance is 1160 ml/minute and mean renal clearance is approximately 260 ml/minute. Non-renal clearance is approximately 80% of total clearance, suggesting that sumatriptan is primarily cleared through oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of sumatriptan, is excreted in the urine as the acid or as the glucuronide conjugate. This metabolite has no known 5HT1 or 5HT2 activity. Minor metabolites have not been identified.

The pharmacokinetics of the oral administration of sumatriptan does not appear to be influenced by a migraine attack.

Special populations
Elderly
The kinetics in the elderly has not been sufficiently studied to permit a statement on possible differences in the kinetics between older and young volunteers.

Hepatic impairment
Sumatriptan pharmacokinetics after an oral dose (50 mg) and a subcutaneous dose (6 mg) were studied in 8 patients with mild to moderate hepatic impairment matched for sex, age, and weight with 8 healthy subjects. Following an oral dose, sumatriptan plasma exposure (AUC and C_{max}) almost doubled (increased approximately 80%) in patients with mild to moderate hepatic impairment compared to the control subjects with normal hepatic function. There was no difference between the patients with hepatic impairment and control subjects after the s.c. dose. This indicates that mild to moderate hepatic impairment reduces presystemic clearance and increases the bioavailability and exposure to sumatriptan compared to healthy subjects.

Following oral administration, pre-systemic clearance is reduced in patients with mild to moderate hepatic impairment and systemic exposure is almost doubled.

The pharmacokinetics in patients with severe hepatic impairment have not been studied (see sections 4.3 and 4.4).

5.3 Preclinical safety data

Experimental studies on acute and chronic toxicity have not shown any evidence of toxic effects within the human therapeutic dosing range. In a fertility study in the rat, a reduction in the success of insemination was seen on exposure to concentrations higher than the maximum exposure in humans. In rabbits embryolethality was observed, without marked teratogenic effects.

Sumatriptan was devoid of genotoxic and carcinogenic activity in *in-vitro* systems and animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

50 mg tablets:
Ammonium methacrylate copolymer type A
Carboxymethylcellulose sodium (E 466)
Microcrystalline cellulose (E 450)
Croscarmellose sodium (E 468)
Lactose monohydrate
Magnesium stearate (E 470b)
Flavouring (grapefruit) (contains sulphites)

Red iron oxide (E 172)
Yellow iron oxide (E 172)

100 mg tablets:
Ammonium methacrylate copolymer type A
Carboxymethylcellulose sodium (E 466)
Microcrystalline cellulose (E 450)
Croscarmellose sodium (E 468)
Lactose monohydrate
Magnesium stearate (E 470b)
Flavouring (grapefruit) (contains sulphites)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are packed in aluminium/aluminium blister strips and inserted in a cardboard carton.

50 mg tablets:
2, 3, 4, 6, 8, 12, 18, 20, 24, 30, 50, 100 tablets

100 mg tablets:
2, 3, 4, 6, 12, 18, 19, 20, 24, 30 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 29126
RVG 29127

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 1 december 2004
Datum van laatste verlenging: 1 december 2009

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 7: 8 februari 2024