

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Migrastat 100 mg film-coated tablets.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Film coated tablet.

Each film-coated tablet contains Sumatriptan 100 mg base (as succinate salt).

Excipients: Each tablet contains 93.0mg lactose monohydrate

For a full list of excipients, see Section 6.1.

## 3 PHARMACEUTICAL FORM

Film coated tablet for oral use.

White, round, film coated tablet marked 'SU100' on one side and 'G' on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the acute treatment of migraine attacks (with or without aura) including the acute treatment of menstrually associated migraine.

### 4.2 Posology and method of administration

The tablets should be swallowed whole with water.

Migrastat is indicated for the acute intermittent treatment of migraine. It should not be used prophylactically.

Migrastat is recommended as monotherapy for the acute treatment of migraine and **should not** be given concomitantly with other acute migraine therapies. If a patient fails to respond to a single dose of Migrastat there are no reasons, either on theoretical grounds or from limited clinical experience, to withhold products containing aspirin or non-steroidal anti-inflammatory drugs for further treatment of the attack.

It is advisable that Migrastat be given as early as possible after the onset of an attack of migraine but it is equally effective at whatever stage of the attack it is administered.

#### Adults only

The recommended adult dose of oral sumatriptan is a single 50 mg tablet. Some patients may require 100 mg.

If a patient does not respond to the first dose of Migrastat, a second should not be taken for the same attack. Migrastat 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 not more than 300 mg is taken in any 24 hour period. An interval of two hours should generally be allowed to elapse between doses.

#### Patients with Hepatic Impairment:

Impairment of hepatic function gives rise to an 80% increase in plasma sumatriptan levels after an oral dose of 100 mg. The drug should therefore be used with extreme caution and at reduced dosage in these patients.

Patients with Renal Impairment:

There is no information on the effect of renal impairment.

Paediatric population:

The efficacy and safety of Migrastat film-coated 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 Migrastat film-coated 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 Migrastat film-coated tablets in children 10 to 17 years of age is not recommended (see section 5.1).

Use in patients aged more than 65 years:

Experience of the use of sumatriptan 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 Migrastat in patients aged over 65 years is not recommended.

**4.3 Contraindications**

Use in patients with severe hepatic impairment  
 Hypersensitivity to any component of the preparation  
 Ischaemic heart disease or symptoms or signs consistent with this  
 Previous Myocardial infarction  
 Prinzmetals angina/coronary vasospasm  
 Peripheral vascular disease  
 Diabetic patients  
 Uncontrolled hypertension  
 Use in patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).  
 Concomitant use of ergotamine or derivatives of ergotamine  
 Concurrent administration of monoamine oxidase inhibitors or use within two weeks of discontinuation of MAOI therapy

Until further data are available the use of Migrastat is contraindicated in patients receiving concurrent treatment with certain antidepressants e.g. selective 5-HT reuptake inhibitors and lithium.

**4.4 Special warnings and precautions for use**

Migrastat should only be used where there is a clear diagnosis of migraine.

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

As with other migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions.

There have been a number of reports of cerebrovascular accident (stroke, paresis), where a temporal association with sumatriptan intake was seen. It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. CVA, TIA).

Migrastat should not be used in patients with underlying cardiac disorders and in patients who, although asymptomatic, have significant risk factors predisposing to coronary artery disease. Therefore a careful history to exclude pre-existing cardiac disease should be taken before sumatriptan is prescribed. 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 and in the absence of known risk factors.

Patients in whom undiagnosed coronary artery disease is a possibility on the basis of age or the presence of other risk factors, such as family history of coronary artery disease, tobacco smoking, diabetes, hypercholesterolaemia, should receive the product only with great caution and if the benefit of treatment is judged to outweigh the possible risk. Use of sumatriptan should be carefully considered in patients who may be at risk of thrombotic episodes.

There have been rare reports of patients on hormone replacement therapy who have had cardiac ischaemic events.

Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat and arms. These symptoms may mimic angina pectoris but, in patients in whom cardiac investigations have been performed, they have only rarely been found to have been the result of coronary vasospasm. Although rare, the vasospasm may result in arrhythmia including ventricular fibrillation/ischaemia or myocardial infarction. If the patient experiences symptoms which are severe or persistent or are consistent with angina, further doses should not be taken until appropriate investigations have been carried out to check for the possibility of ischaemic changes.

There have been a number of fatalities from ventricular fibrillation and myocardial infarction.

Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

Migrastat should be administered with caution to patients with conditions which may affect significantly the absorption, metabolism or excretion of the drug e.g. impaired hepatic or renal function.

Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. Reactions may range from cutaneous hypersensitivity to anaphylaxis.

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

The recommended dose of Migrastat should not be exceeded.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency glucose-galactose malabsorption should not take this medicine.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Studies in healthy subjects show that Migrastat does not interact with propranolol, flunarizine, pizotifen or alcohol.

There are limited data on an interaction with ergotamine containing preparations. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contra-indicated. The period of time that would elapse between the use of sumatriptan and ergotamine containing preparations is not known. This will also depend on the doses and type of ergotamine containing products used. The effects may be additive. It is advisable to wait for at least 24 hours following the use of ergotamine containing preparations before administering sumatriptan. Conversely, it is advised to wait at least 6 hours following use of sumatriptan before administering an ergotamine containing product.

An interaction may occur between sumatriptan and MAOIs and concomitant administration is contra-indicated.

## 4.6 Fertility, pregnancy and lactation

Although no teratogenic effects have been seen in rats or rabbits, reproduction studies in rabbits, using high and maternally toxic doses, associated with blood levels more than fifty times those seen in humans after therapy, have shown an increased incidence of minor variation in the position of certain foetal blood vessels. Reproduction studies performed in rats have revealed no evidence of impaired fertility or postnatal development due to sumatriptan. The drug should not be used during pregnancy.

Sumatriptan is excreted in breast milk in animals. No data exist in humans therefore administration of Migrastat to a nursing woman is not recommended.

## 4.7 Effects on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with Migrastat. Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

## 4.8 Undesirable effects

Adverse events are listed by system organ class and frequency. Frequencies are defined as; very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000) including isolated reports.

### Immune System Disorders

Very rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to rare cases of anaphylaxis.

### Nervous System Disorders

Common: Tingling, dizziness, drowsiness

Very rare: 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.

### Eye disorders

Very rare: Flickering, diplopia, reduced vision.

Loss of vision (usually transient).

However, visual disorders may also occur during a migraine attack itself.

Visual disorders may also occur during a migraine attack itself. Patients treated with Migrastat rarely exhibit visual disorders like flickering and diplopia. Additionally cases of nystagmus, scotoma, reduced vision and retinal vascular occlusions have been observed. Very rarely loss of vision has occurred, which although usually transient, has included isolated irreversible cases.

### Cardiac Disorders

Very rare: Bradycardia, tachycardia, palpitations, Cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction (see Contraindication, Warnings and Precautions).

### Vascular disorders

Common: Transient increases in blood pressure arising soon after treatment. Flushing.

Very rare: Hypotension, Raynaud's phenomenon.

### Gastrointestinal

Common: Nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear.

Vary rare: Ischaemic colitis.

### Musculoskeletal and Connective Tissue Disorders

The following symptom is usually transient and may be intense and can affect any part of the body including the chest and throat:

Common: Sensations of heaviness.

### General Disorders and Administration Site Conditions

The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat.

Common: Pain, sensations of heat, pressure or tightness.

The following symptoms are mostly mild to moderate in intensity and transient:

Common: Feelings of weakness, fatigue

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

## 4.9 Overdose

There have been some reports of overdose with sumatriptan.

Patients have received single injections of up to 12mg subcutaneously without significant adverse effects. Doses up to 16mg subcutaneously and up to 400mg orally were not associated with side effects other than those mentioned. There is no experience of doses greater than these.

If overdose with Migrastat occurs, the patient should be monitored for at least ten hours and standard supportive treatment applied as required.

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective 5HT receptor agonist. ATC code: NO2CCO1.

Sumatriptan has been demonstrated to be a specific and selective 5-hydroxytryptamine-1 (5-HT<sub>1</sub>) receptor agonist with no effect on other 5-HT receptor (5HT<sub>2</sub> – 5HT<sub>7</sub>) subtypes. The vascular 5HT<sub>1d</sub> receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals sumatriptan selectively constricts the carotid arterial circulation. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues, such as the meninges. Dilation and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man. Clinical response begins 30 minutes following oral administration.

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

Although the recommended dose of oral Migrastat is 50 mg, migraine attacks vary in severity both within and between patients. Doses of 25-100 mg have shown greater efficacy than placebo in clinical trials, but 25mg is statistically significantly less effective than 50 and 100 mg.

### 5.2 Pharmacokinetic properties

#### Absorption:

Rapid. However bioavailability is low (approximately 14% of a dose), primarily because of presystemic hepatic metabolism and, to a lesser extent, because of incomplete absorption. The rate and extent of absorption are not affected to a clinically significant extent by administration with food or by the gastric stasis that may accompany migraine headaches.

Bioavailability is increased by 80% in patients with hepatic impairment.

**Distribution:**

Sumatriptan is rapidly and extensively distributed to tissues, but passage across the blood-brain barrier is limited.

**Protein binding:**

In plasma - low (14 to 21%).

**Biotransformation:**

Hepatic and extensive; approximately 80% of a dose is metabolised.  
The major metabolite is an inactive indole acetic acid derivative.

**Half-life:**

Elimination: Approximately 2 hours. One study reported a terminal half-life of approximately 7 hours that became apparent about 12 hours after administration of multiple oral doses, but did not contribute substantially to the overall disposition of the medication.

**Onset of action:**

Within 30 minutes.

**Time to peak concentration:**

In serum (single 100 mg dose): Approximately 1.5 hours (range, 0.5 to 5 hours). The wide interindividual variability found in pharmacokinetic studies may be related to the appearance of multiple peaks in the concentration over time. Approximately 80% of the maximum value is achieved within 45 minutes.

**Peak concentration:**

In serum (single 100 mg dose): Approximately 54 nanograms per ml; (0.13 micromoles/L) (range 26.7 to 137 nanograms per ml; 0.06 to 0.33 micromoles/L).

**Time to peak effect:**

Relief of headache (i.e. moderate or severe pain being reduced to mild or no pain)-(single 100 mg dose): Within 2 hours in 50 to 75%, and within 4 hours in an additional 15 to 25% of patients.

Relief of associated symptoms (nausea, vomiting, photophobia, phonophobia)-(single 100 mg dose): Within 2 hours.

**Duration of action:**

Return of migraine headache occurs within 24 to 48 hours in approximately 40% of patients who initially obtain a beneficial response to sumatriptan, i.e. after moderate or severe headache pain has been reduced to mild or no pain. Whether this represents development of a new migraine or breakthrough of a prolonged migraine after the effects of sumatriptan have worn off has not been established.

**Elimination:**

Renal, via active renal secretion, following hepatic metabolism. Approximately 80% of a dose is eliminated as metabolites. After oral administration, approximately 57% of a dose is eliminated in the urine (3% of the dose as unchanged sumatriptan, 35% as the indole acetic acid metabolite) and another 38% of the dose is eliminated in the faeces (9% as unchanged sumatriptan and 11% as the indole acetic acid metabolite).

The effects of renal function impairment on clearance of sumatriptan have not been studied. Hepatic impairment produces an increase of 80% in plasma levels after oral dosing.

### **5.3 Preclinical safety data**

No additional data of relevance.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Tablet:

Lactose monohydrate  
Microcrystalline cellulose  
Croscarmellose  
Magnesium stearate

Film coat:

Titanium dioxide (E171)  
Polydextrose (E1200)  
Hypromellose (E464)  
Glycerol triacetate (E1518)  
Macrogol

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

No special storage conditions.

### **6.5 Nature and contents of container**

Aluminium/aluminium foil blister packs within a cardboard carton. Each pack contains either 2, 4 or 6 tablets. Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

McDermott Laboratories Ltd  
(t/a Gerard Laboratories)  
35-36 Baldoyle Industrial Estate  
Grange Road  
Dublin 13  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA 0577/078/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 January 2006

Date of last renewal : 30th November 2008

**10 DATE OF REVISION OF THE TEXT**

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