SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Suvexx 85 mg/457 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sumatriptan succinate corresponding to 85 mg sumatriptan and 500 mg naproxen sodium.

Excipient with known effect
Each tablet contains 60 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Capsule-shaped, medium-blue film-coated tablet with length, width, and thickness of 19 mm x 10 mm x 7 mm and debossed *"85/500"* on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Suvexx is indicated for the acute treatment of the headache phase of migraine attacks with or without aura in adults where treatment with a mono-entity product has been insufficient.

4.2 Posology and method of administration

Posology

Adults
Suvexx is indicated for the acute treatment of migraine and it should not be used prophylactically. The recommended dose of sumatriptan/naproxen should not be exceeded.

It is advisable that sumatriptan/naproxen be given as early as possible after the onset of migraine headache, but it is effective when administered at any stage of the headache phase.

The recommended dosage for adults is one tablet of sumatriptan/naproxen 85 mg/457 mg.

If the patient does not respond to the first dose of sumatriptan/naproxen, a second dose should not be taken for the same attack.
If the patient has responded to the first dose but the symptoms recur a second dose may be given provided that there is a minimum interval of two hours between the two doses.

The maximum recommended dosage in a 24-hour period is 2 tablets, taken at least 2 hours apart.
The safety of treating an average of more than 5 migraine attacks in a 30-day period has not been established.

Paediatric population

The efficacy and safety of sumatriptan/naproxen in children aged less than 18 years have not been established.

Elderly (Over 65 years of age)

Sumatriptan/naproxen has not been studied in geriatric patients and its use in this population is not recommended. Elderly patients are more likely to have age-associated decreased hepatic and renal function.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of sumatriptan/naproxen has not been studied. Sumatriptan/naproxen is contraindicated in patients with moderate and severe (Child Pugh B and C) hepatic impairment (see section 4.3). Sumatriptan/naproxen is not recommended in patients with mild hepatic impairment (Child Pugh A). If there is a need to use sumatriptan/naproxen in patients with mild hepatic impairment, only one dose should be used within a 24-hour period and patient should be monitored during treatment.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of sumatriptan/naproxen has not been studied. Sumatriptan/naproxen is contraindicated for use in patients with GFR less than 30 mL/min/1.73m^2 (see section 4.3). In patients with mild or moderate renal impairment, only one dose should be administered within a 24-hour period and renal function should be monitored during treatment.

<u>Method of administration</u>
Oral use.

Suvexx tablets should be swallowed whole with water. Tablets should not be split, crushed, or chewed as this can affect the optimised rate of drug absorption. Suvexx tablets may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

Sumatriptan/naproxen is contraindicated in patients with

- severe cardiac failure, history of myocardial infarction or ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or symptoms or signs consistent with ischaemic heart disease
- history of ischaemic stroke or transient ischemic attack (TIA), because these patients are at a higher risk of ischaemic stroke.
- previously shown hypersensitivity reactions (e.g. nasal polyps, asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory/analgesic drugs (NSAIDs). These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.
- history of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- active acute peptic ulcer or gastrointestinal bleeding or recurring previous episodes (two or more distinct episodes of proven ulceration or bleeding)
- moderate and severe hypertension and mild uncontrolled hypertension
- severe renal impairment (glomerular filtration rate, GFR <30 mL/min/1.73m^2)
- moderate and severe hepatic impairment.

Sumatriptan/naproxen must not be used

- concomitantly with ergotamine, or derivatives of ergotamine (including methysergide) or any triptan/5-hydroxytryptamine1 (5-HT$_1$) receptor agonist
- concomitantly with reversible (e.g. moclobemide) or irreversible (e.g. selegiline) monoamine oxidase inhibitors (MAOIs) (see section 4.5).
- within 2 weeks of discontinuation of therapy with MAOIs (see section 4.5).
- during the last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Sumatriptan/naproxen should only be used where there is a clear diagnosis of migraine.

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

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

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and gastrointestinal and cardiovascular risks below). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events. According to International Headache Society (IHS), regular intake of acute or symptomatic migraine medication for more than 9 days a month and more than 3 months may predispose to medication overuse headache (MOH). It usually, but not invariably, resolves after the overuse is stopped.

Cardiovascular and cerebrovascular effects

Sumatriptan
Sumatriptan, a component of Suvexx, can cause coronary artery vasospasm. Sumatriptan/naproxen is contraindicated in patients with uncontrolled hypertension, ischemic coronary artery disease, cardiac arrhythmias, and those with history of myocardial infarction (see section 4.3). Sumatriptan/naproxen is not recommended in patients with family history or risk factors predictive of coronary artery disease.

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 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 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.

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

Naproxen
Naproxen sodium, a component of Suvexx, is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Use of NSAIDs, such as naproxen sodium, which is a component of Suvexx, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure.

Information from clinical studies and epidemiological data suggest that the use of some NSAIDs (especially in high doses and with long-term use) can be associated

with a slightly increased risk of thrombosis in the arteries (for instance myocardial infarction or stroke). Epidemiological studies suggest that naproxen in low doses (1 000 mg per day) can be associated with a lower risk, some risk cannot be ruled out.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic cardiac disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. The same consideration should be made before a long-term treatment is started in patients with risk factors for cardiovascular disease (for instance hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Gastrointestinal bleeding, ulceration and perforation

Naproxen
Gastro-intestinal bleeding, ulceration and perforation, which can be fatal, have been reported with the use of all NSAIDs at any time during the treatment, with or without warning symptoms or the prior occurrence of severe gastro-intestinal side effects.

The risk of gastro-intestinal bleeding, ulceration and perforation is greater with higher doses, the prior occurrence of ulceration, in particular if complicated by bleeding and perforation (see section 4.3) and in elderly patients. These patients should start the treatment with the lowest available dosage. Combination treatment with protective products (for example misoprostol or protonpump inhibitors) should be considered in these patients as well as in patients who concomitantly need low doses of acetyl salicylic acid or other medicinal products that probably increase the gastro-intestinal risk (see section 4.5).

Patients, who previously had a problem with gastro-intestinal toxicity, in particular elderly patients, should report any unusual abdominal symptoms (especially bleeding), in particular at the beginning of the treatment. Caution is needed in patients who are concomitantly treated with medicinal products, which may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors and products that counteract the platelet aggregation, such as acetyl salicylic acid (see section 4.5).

When gastro-intestinal bleeding or ulceration occurs in patients who are receiving naproxen, the treatment should be stopped (see section 4.3). NSAIDs should be used with caution in patients with a history of gastro-intestinal diseases (ulcerative colitis, Crohn’s disease) as these conditions can worsen (see section 4.8).

Serotonin syndrome

Sumatriptan
There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following 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 a SSRI or a SNRI is clinically warranted, appropriate observation of the patient is advised (see section 4.5).

Severe cutaneous adverse reactions (SCARs)

Naproxen
Exfoliative dermatitis, Stevens-Johnson's syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal, have been reported post-marketing in association with naproxen treatment (see section 4.8). Patients appear to have the greatest risk of these reactions at the beginning of the treatment: in the majority of the cases the reaction started in the first month of the treatment. If signs and symptoms suggestive of these reactions appear, Suvexx should be withdrawn immediately. If the patient has developed SJS, or TEN or DRESS with the use of Suvexx, treatment with Suvexx must not be restarted and should be permanently discontinued.

Haematological reactions

Naproxen
Naproxen reduces the platelet aggregation and prolongs the bleeding time. Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen-containing products are administered (see section 4.5).

Seizures

Sumatriptan
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).

Hypersensitivity reactions

Sumatriptan
Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. 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.

Naproxen
Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to acetyl salicylic acid, other NSAIDs or naproxen-containing products. They may also occur in individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

Renal effects

Naproxen
Dehydration during the use of an anti-inflammatory analgesic (i.e. NSAID) increases the risk of acute renal failure, so the patient's possible dehydration should be corrected

before naproxen treatment is initiated. The naproxen treatment should be started with caution in patients with a history of considerable dehydration. Like other anti-inflammatory analgesics, long-term treatment with naproxen has caused renal papillary necrosis and other pathological renal alterations.

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and the elderly. Renal function should also be monitored in these patients (see also section 4.2).

There have been reports of impaired renal function, renal failure, acute interstitial nephritis, haematuria, proteinuria, renal papillary necrosis and occasionally nephrotic syndrome associated with naproxen.

Respiratory disorders

Naproxen
Caution is required if administered to patients suffering from or with a previous history of, bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm in such patients.

Elderly

Naproxen
The elderly and/or debilitated patients have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Prolonged use of NSAIDs in these patients is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Use in patients with impaired liver or renal function

Naproxen
As with other NSAIDs, elevations of one or more liver function tests may occur. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Severe hepatic reactions, including jaundice and hepatitis (some cases of hepatitis have been fatal) have been reported with this drug as with other NSAIDs. Cross reactivity has been reported.

In patients with renal insufficiency naproxen must be administered with extreme caution, especially if it concerns a long-term treatment. Also sufficient diuresis must be taken care of.

In case of a reduced renal perfusion, it is recommended to monitor the renal function before and during the treatment with naproxen.

Sumatriptan

Sumatriptan should be administered with caution to patients with conditions that may affect significantly the absorption, metabolism or excretion of the drugs, e.g. impaired hepatic (Child Pugh grade A or B; see sections 4.2 and 5.2) or renal function.

Combination with other NSAIDs

Naproxen
The combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 selective inhibitors, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Ocular effects

Naproxen
Studies have not shown changes in the eye attributable to naproxen administration. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilloedema, (see section 4.8) have been reported in users of NSAIDs, including naproxen, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disorders during the treatment with naproxen-containing products should have an ophthalmological examination.

Other warnings

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

Naproxen
The antipyretic and anti-inflammatory activities of naproxen may reduce fever and inflammation, thereby diminishing their utility as diagnostic signs.

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 medication.

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

In a few patients a mild peripheral oedema has been reported.

No sodium retention has been observed with metabolic studies, but it cannot be ruled out that certain patients with (presumably) abnormal cardiac functions are at a greater risk of showing this side effect symptom.

If the skin becomes delicate, if blisters or other symptoms occur indicating pseudoporphyria, the treatment must be discontinued and the patient should be carefully monitored.

In exceptional cases varicella can cause severe infectious complications of the skin and soft tissues. To this day the contributing role of NSAIDs in the potentiation of these infections cannot be ruled out. It is therefore recommended to avoid the use of naproxen in case of varicella.

Elderly patients
Caution is recommended when high doses of naproxen are administered to elderly patients, as there are indications that the quantity of non-protein bound naproxen increases in these patients.
Elderly patients more frequently experience side effects of NSAIDs, in particular gastro-intestinal bleeding and perforation, which can be fatal (see section 4.2).

Excipients
This medicinal product contains 60 mg sodium per tablet, equivalent to 3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have not been conducted with Suvexx and other drugs. Interactions with Suvexx would be expected to reflect those of the individual components.

Ergotamine and triptan/5-HT_1 receptor agonists

Sumatriptan
Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of sumatriptan/naproxen administration (see section 4.3).

The administration of sumatriptan/naproxen with other 5-HT_1 agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with coadministration of 5-HT_1 agonists, use of these drugs within 24 hours of each other is contraindicated (see section 4.3).

Monoamine oxidase inhibitors

Sumatriptan
In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan succinate clearance, significantly increasing systemic exposure. Therefore, treatment with sumatriptan/naproxen is contraindicated in patients receiving MAOIs and within 2 weeks of discontinuation of therapy with MAOIs (see section 4.3).

Selective serotonin reuptake inhibitors

Sumatriptan
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).

Naproxen

There is an increased risk of gastrointestinal bleeding (see section 4.4) when SSRIs are combined with NSAIDs.

Anticoagulants

Naproxen
It is considered unsafe to take NSAIDs in combination with anticoagulants such as warfarin or heparin unless under direct medical supervision, as NSAIDs may enhance the effects of anticoagulants (see section 4.4).

Methotrexate

Naproxen
Caution is advised where methotrexate is given concurrently because of possible enhancement of its toxicity, since naproxen, among other NSAIDs, has been reported to reduce the tubular secretion of methotrexate in an animal model.

Cardiac glycosides

Naproxen
NSAIDs may increase cardiac glycoside plasma levels when co-administered with cardiac glycosides such as digoxin. Increased monitoring and dosage adjustments of digitalis glycosides may be necessary during and following concurrent NSAID therapy.

Lithium

Sumatriptan
Concomitant use of sumatriptan and lithium can increase the risk of serotonin syndrome.

Naproxen
Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur.

Ciclosporin

Naproxen
As with all NSAIDs caution is advised when ciclosporin is coadministered because of the increased risk of nephrotoxicity.

Tacrolimus

Naproxen
There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Acetylsalicylic acid

Naproxen
Clinical pharmacodynamic data suggest that concomitant naproxen usage for more than one day consecutively may inhibit the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping naproxen therapy. The clinical relevance of this interaction is not known.

Anti-platelet agents

Naproxen
There is an increased risk of gastrointestinal bleeding (see section 4.4) when antiplatelet agents are combined with NSAIDs.
Experimental studies have found that clopidrogrel increases naproxen-induced gastrointestinal blood loss. This is likely to apply to all NSAIDs.
NSAIDs should not be combined with ticlopidine due to the additional inhibition of thrombocyte function.

Laboratory tests

The ability of sumatriptan/naproxen to interfere with commonly employed clinical laboratory tests has not been investigated.

Sumatriptan
Sumatriptan succinate is not known to interfere with commonly employed clinical laboratory tests.

Naproxen
It is suggested that naproxen therapy be temporarily discontinued 48 hours before adrenal function tests are performed, because naproxen may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxyindoleacetic acid.

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

4.6 Fertility, pregnancy and lactation

Pregnancy

Naproxen
Inhibition of the prostaglandin synthesis may negatively affect the pregnancy and/or the embryonal/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformations and gastroschisis after the use of prostaglandin synthesis inhibitors in the early stages of the pregnancy. The absolute risk of cardiovascular malformation was increased from less than 1% to approximately 1.5%. It is accepted that the risk increases with the dose and the duration of the treatment.

From the 20^{th} week of pregnancy onward, naproxen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

During the third trimester of the pregnancy all prostaglandin synthesis inhibitors can expose the foetus to:

- cardiopulmonary toxicity (premature constriction / closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may develop into renal failure with oligohydroamnios (see above and below).

At the end of the pregnancy the mother and neonate are exposed to:

- possible prolongation of the bleeding time, an anti-aggregation effect, which may occur even at very low doses
- inhibition of the contraction of the uterus resulting in a delayed or prolonged delivery.

Sumatriptan
Post-marketing data on the use of sumatriptan during the first trimester of pregnancy in over 1 000 women are available. Although the 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.

Sumatriptan/naproxen
Suvexx should not be used during the first and second trimester of the pregnancy unless this is absolutely necessary. If Suvexx is used by a woman who is trying to become pregnant, or in the first or second trimester of the pregnancy, the dose should be kept as low as possible and the treatment should be as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to naproxen for several days from gestational week 20 onward. Suvexx should be discontinued if oligohydramnios or ductus arteriosus constriction are found.
Suvexx is contra-indicated during the third trimester of the pregnancy (see section 4.3).

Breastfeeding

Both active components of Suvexx, sumatriptan and naproxen sodium have been reported to be excreted in human breast milk. Sumatriptan is excreted into breast milk with average relative infant doses of < 4% following administration of a single dose of sumatriptan. Because of the possible adverse effects of these drugs on neonates, use of Suvexx in nursing mothers should be avoided. Any breast milk expressed for at least 12 hours after treatment should be discarded.

Fertility

The use of naproxen, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of naproxen should be considered.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. Suvexx can cause drowsiness and dizziness which can influence the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

Since Suvexx contains both sumatriptan succinate and naproxen sodium, the same pattern of adverse reactions reported for these individual components may occur with the combination product.

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT_1 agonists, such as sumatriptan. These events are very rare and most have been reported in patients with risk factors predictive of coronary artery disease (CAD). Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see sections 4.3 and 4.4).

The most common adverse reactions encountered with NSAIDs, such as naproxen, are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred particularly in the elderly.

Most commonly reported adverse reactions in adults with sumatriptan/naproxen in clinical trials (incidence ≥ 2%) were: dizziness, somnolence, paresthesia, nausea, dry mouth, dyspepsia, chest discomfort. No new safety findings were identified during sumatriptan/naproxen treatment compared to the established safety profile for the individual substances.

Tabulated list of adverse reactions
Frequencies have been 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).

Sumatriptan

Organ system	Common	Rare	Very rare	Not known
Immune system disorders				Hypersensitivity reactions ranging from cutaneous hypersensitivity (such as urticaria) to anaphylaxis
Psychiatric disorders				Anxiety
Nervous system disorders	Dizziness, tingling, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia			Seizures*, tremor, dystonia, nystagmus, scotoma
Eye disorders				Flickering, diplopia, reduced vision. Loss of vision including

Organ system	Common	Rare	Very rare	Not known
				permanent defects**
Cardiac disorders				Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, angina, myocardial infarction (see sections 4.3 and 4.4)
Vascular disorders	Transient increases in blood pressure arising soon after treatment. flushing			Hypotension, Raynaud's syndrome
Respiratory, thoracic and mediastinal disorders	Dyspnoea			
Gastrointestinal disorders	Nausea and vomiting***			Ischaemic colitis, diarrhoea, dysphagia
Skin and subcutaneous tissue disorders				Hyperhidrosis
Musculoskeletal and connective tissue disorders	Myalgia			Neck stiffness, arthralgia
Reproductive system and breast disorders		Breast pain		
General disorders and administration site conditions	Pain, sensations of heat or cold, pressure or tightness (these events are usually transient and			Pain trauma activated, pain inflammation activated

Organ system	Common	Rare	Very rare	Not known
	may be intense and 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)			
Investigations			Minor disturbances in liver function tests have occasionally been observed	

*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.

**Visual disorders may also occur during a migraine attack itself.

***Occurred in some patients but it is unclear if this is related to sumatriptan or the underlying condition.

Naproxen

Organ system	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders					eosinophilia, thrombocytopenia, leucopenia, pancytopenia, haemolyti	

Organ system	Very common	Common	Uncommon	Rare	Very rare	Not known
					c anaemia, aplastic anaemia, agranulocytosis	
Immune system disorders				Hypersitivity reactions, anaphylactic reaction, angioneurotic oedema		
Metabolism and nutrition disorders			Hyperkalemia, fluid retention			
Psychiatric disorders			Mood changes, depression, impaired ability to concentrate, cognitive disorder, insomnia, sleep disorder			
Nervous system disorders		Headache, dizziness, lightheadedness	Convulsions, retrobulbar optic neuritis		Aseptic meningitis, worsening of Parkinson's disease	
Eye disorders		Visual disturbances		Corneal opacity, papillitis or papilloedema		
Ear and labyrinth disorders		Tinnitus, hearing disorders		Hearing loss		
Cardiac disorders *)		Worsening of heart failure (oedema, dyspnoea)	Palpitations			
Vascular					Vasculitis	

Organ system	Very common	Common	Uncommon	Rare	Very rare	Not known
disorders *)						
Respiratory, thoracic and mediastinal disorders				Pulmonary oedema, worsening of asthma	Eosinophilic pneumonitis	
Gastro-intestinal disorders **)	Upper abdominal pain, heartburn, nausea, constipation	Stomatitis, diarrhoea, vomiting, dyspepsia,	Gastrointestinal ulcers, haemorrhages and/or perforations, haematemesis, melaena, exacerbation of ulcerative colitis and Crohn's disease		Sialadenitis, pancreatitis	
Hepatobiliary disorders			Elevated liver enzyme levels, jaundice	Toxic hepatitis		
Skin and subcutaneous tissue disorders		Pruritus, skin rashes, urticaria, increased sweating, purpura, ecchymosis		Hair loss, photosensitivity, pseudoporphyria	Exacerbation of lichen planus, exacerbation of erythema nodosum, exacerbation of lupus erythematosus disseminatus (SLE), toxic epidermal	Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), fixed drug eruption

Organ system	Very common	Common	Uncommon	Rare	Very rare	Not known
					necrolysis, erythema multiforme, Stevens-Johnson syndrome	
Musculoskeletal and connective tissue disorders				Myalgia, muscle weakness		
Renal and urinary disorders					Haematuria, renal failure, glomerulonephritis, interstitial nephritis, nephrotic syndrome, papillary necrosis	
Reproductive system and breast disorders			Menstrual disorder			
General disorders and administration site disorders		Tiredness	Thirst			Pyrexia

Description of selected adverse reactions

*)Oedema formation, hypertension and heart failure have been reported in association with treatment with an NSAID.
Information from clinical studies as well as epidemiological data suggest that the use of naproxen, especially in high doses and with long-term use, can be associated with a slightly increased risk of thrombosis in the arteries (for instance myocardial infarction or stroke).

**)Gastrointestinal tract: Most frequently observed adverse effects are related to the gastrointestinal tract. Ulcers, perforations and gastrointestinal bleedings can appear. These can sometimes be life-threatening, especially for elderly people. Nausea, vomiting, diarrhoea, flatulence, constipation, heartburn, abdominal pain, melaena,

haematemesis, ulcerative stomatitis and exacerbation of colitis or Crohn's disease has been reported after use of naproxen. Gastritis has been observed more rarely.

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Symptoms related to naproxen overdose
Symptoms of overdose can consist of nausea, vomiting, pain in the gastric region, drowsiness, dizziness, disorientation, diarrhoea, gastric bleeding, convulsions (rarely), transient changes in hepatic functions, hypothrombinemia, renal failure, apnoea and metabolic acidosis.

Symptoms related to sumatriptan overdose
Doses in excess of 400 mg orally and 16 mg subcutaneously were not associated with side effects other than those mentioned in the SPC section 4.8.

Treatment

Treatment related to naproxen overdose
Patients should be treated symptomatically as required. Activated charcoal should be administered to the patient within one hour to inhibit absorption and to interrupt the enterohepatic circulation.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding. However, haemodialysis may still be appropriate in a patient with renal failure who has taken naproxen. Haemodialysis can accelerate elimination of the main metabolite of naproxen, 6-O-demethylnaproxen.

Administration of a H_2 blocker or proton-pump inhibitor should be considered to prevent gastrointestinal complications. Good urine output should be ensured. Renal and liver function should be closely monitored. Other measures may be indicated by the patient's clinical condition.

Treatment related to sumatriptan overdose
If overdosage 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: Antimigraine preparations, selective serotonin ($5HT_1$) agonists, ATC code: N02CC51

Mechanism of action

Suvexx is a fixed dose combination of sumatriptan succinate and naproxen sodium, each presumably contributing to the relief of migraine pain through pharmacologically different mechanisms of action.

Sumatriptan
Sumatriptan has been demonstrated to be a specific and selective 5-hydroxytryptamine 1D1 ($5HT_{1D}$) receptor agonist with no effect on other 5HT receptor ($5HT_2$-$5HT_7$) subtypes.

The vascular $5HT_{1D}$ receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation of and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man.

In addition, evidence from animal studies suggests that sumatriptan inhibits trigeminal nerve activity. Both these actions (cranial vasoconstriction and inhibition of trigeminal nerve activity) may contribute to the anti-migraine action of sumatriptan in human.

Naproxen
Naproxen is a non-steroidal anti-inflammatory agent (NSAID) with antipyretic properties as has been demonstrated in classical animal test systems. Naproxen exhibits its anti-inflammatory effect even in adrenalectomised animals, indicating that its action is not mediated through the pituitaryadrenal axis.

Clinical efficacy and safety
The efficacy of Suvexx in the acute treatment of migraine with or without aura in adults was demonstrated in 2 pivotal, single dose, randomized, double-blind, multicenter, parallel-group studies (Study 1 and Study 2) utilizing placebo and each individual active component (sumatriptan and naproxen) as comparison treatments. Subjects enrolled in these 2 studies were predominately female (87%) and white (88%), with a mean age of 40 years (range: 18 to 65 years). Subjects were instructed to treat a migraine of moderate to severe pain with 1 tablet. No rescue medication was allowed within 2 hours post-dose. The co-primary endpoints included superiority of Suvexx over placebo at 2 hours post-dose for the following endpoints: pain relief (no or mild pain); incidence of photophobia, phonophobia and nausea; and superiority of Suvexx vs. the individual components (sumatriptan and naproxen) for sustained pain-free at 24 hours. Subjects evaluated their headache pain and associated symptoms of

photophobia, phonophobia, nausea and vomiting 2 hours after taking 1 dose of study medication. Headache relief was defined as a reduction in headache severity from moderate or severe pain to mild or no pain. Sustained pain free was defined as a reduction in headache severity from moderate or severe pain to no pain at 2 hours post-dose without a return of mild, moderate, or severe pain and no use of rescue medication for 24 hours post-dose.

The results from Study 1 and 2 are summarized in Table 1. In both trials, the percentage of patients achieving headache pain relief 2 hours after treatment was significantly greater among patients receiving Suvexx (65% and 57%) compared with those who received placebo (28% and 29%). Further, the percentage of patients who remained pain free without use of other medications through 24 hours post-dose was significantly greater among patients receiving a single dose of Suvexx (25% and 23%) compared with those who received placebo (8% and 7%) or either sumatriptan (16% and 14%) or naproxen (10%) alone.

Table 1. Percentage of adult patients with 2-hour pain relief and sustained pain free following treatment[a]

	Suvexx	Sumatriptan 85 mg	Naproxen sodium 500 mg	Placebo
2-hour pain relief				
Study 1	65%[b] n = 364	55% n = 361	44% n = 356	28% n = 360
Study 2	57%[b] n = 362	50% n = 362	43% n = 364	29% n = 382
Sustained pain free (2-24 hours)				
Study 1	25%[c] n = 364	16% n = 361	10% n = 356	8% n = 360
Study 2	23%[c] n = 362	14% n = 362	10% n = 364	7% n = 382

[a] P values provided only for prespecified comparisons
[b] $P < 0.05$ vs. placebo and sumatriptan 85mg
[c] $P < 0.01$ vs. placebo and, sumatriptan 85mg, and naproxen sodium

Compared with placebo, there was a decreased incidence of migraine-associated symptoms such as photophobia, phonophobia, and nausea 2 hours after the administration of Suvexx, and a decreased likelihood of using rescue medication over the 24 hours following the first dose.

Suvexx was more effective than placebo regardless of the presence of aura; duration of headache prior to treatment; gender, age, or weight of the subject; or concomitant use of oral contraceptives or common migraine prophylactic drugs (e.g., beta-blockers, anti-epileptic drugs, tricyclic antidepressants).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Suvexx in all subsets of the paediatric population in treatment of migraine headaches. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

The comparative interaction and bioavailability clinical trials with the combination of sumatriptan and naproxen demonstrated that the combination product, Suvexx had no significant effect on the total bioavailability of sumatriptan and naproxen compared to administration of the active ingredients as single components. In a crossover trial in 16 subjects, the pharmacokinetics of both components administered as sumatriptan/naproxen were similar during a migraine attack and during a migraine-free period.

Sumatriptan
Sumatriptan succinate, when given as Suvexx, has a mean peak concentration (C_{max}) appr. 40 ng/ml when administered during migraine. The median T_{max} of sumatriptan succinate, when given as Suvexx, was 1.5 hours (range: 0.5 to 4.0 hours).

Naproxen had no signficant effect on sumatriptan pharmacokinetics following Suvexx administration. Exposure (AUC) of sumatriptan following Suvexx administration is in proportion to the dose of sumatriptan. The C_{max} is 17% higher compared to sumatriptan 85 mg given alone in healthy volunteers.

There is a 1.6 fold increase in the C_{max} of sumatriptan and dose proportional increase in AUC after two doses taken 2 hours apart compared to a single dose of Suvexx.

Bioavailability of sumatriptan succinate is approximately 14%, primarily due to presystemic (first-pass) metabolism and partly due to incomplete absorption.

Naproxen
Following administration Suvexx, the time to reach the peak concentration of naproxen is delayed and the C_{max} is 25% lower when compared to naproxen given alone in healthy volunteers. Naproxen sodium, when given as Suvexx, has a C_{max} appr. 50 µg/ml and a median T_{max} of 6 hours (range: 3 to 16 hours) during migraine , which is approximately 3 to 5.5 hours later than single dose administration of naproxen according to literature. This is most likely due to a sumatriptan-induced delay in gastric emptying.

Exposure (AUC) of naproxen following Suvexx administration is proportional to the dose of naproxen.

There is a 1.5 fold increase in the C_{max} of naproxen and a 1.6 fold increase in AUC after two doses taken 2 hours apart compared to a single dose of Suvexx.

Naproxen sodium is rapidly absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%.

Concomitant administration with food
Food had no significant effect on the bioavailability of sumatriptan succinate or naproxen sodium administered as Suvexx, but slightly delayed the T_{max} of sumatriptan succinate by about 0.6 hour. These data indicate that Suvexx may be administered without regard to food.

Distribution

Sumatriptan
Plasma protein binding of sumatriptan is low (14–21%) and the mean volume of distribution is 170 litres.

Naproxen
The protein binding of naproxen in normal doses is greater than 99%.

Biotransformation

Sumatriptan
Sumatriptan is predominantly metabolized by monoamine oxidase A. The major metabolite of sumatriptan, the indole acetic acid analogue, is mainly excreted in the urine, where it is present as a free acid and the glucuronide conjugate. It has no known $5HT_1$ or $5HT_2$ activity. Minor metabolites have not been identified.

Naproxen
30% of naproxen is converted in the liver (CYP450 isoenzymes 1A2, 2C8 and 2C9) into pharmacologically inactive 6-O-demethylnaproxen. Both naproxen and 6-O-demethylnaproxen are further metabolized to their respective glucuronide or sulphate conjugated metabolites.

Elimination

Sumatriptan
The elimination half-life of sumatriptan is approximately 2 hours. Mean total plasma clearance is approximately 1 160 mL/min and mean renal clearance is approximately 260 mL/min. Non-renal clearance accounts for about 80% of the total clearance, suggesting that sumatriptan is primarily cleared through oxidative metabolism mediated by monoamine oxidase A.

Naproxen
With increasing dosage the urinary excretion of naproxen is faster than could be expected based on linear processes. The plasma half-life is approximately 11–15 hours. Approximately 95% of the administered dose is excreted with the urine, primarily in the form of naproxen, 6-O-desmethyl naproxen or conjugated forms of the mentioned substances.

Special populations

Renal impairment

No formal clinical pharmacology studies were conducted to assess the pharmacokinetics of sumatriptan/naproxen in subjects with renal impairment.

Sumatriptan
Sumatriptan has not been studied in patients with renal impairment. However, non-renal clearance accounts for about 80% of the total clearance. Sumatriptan should be used with caution in patients with renal impairment.

Naproxen
Naproxen pharmacokinetics in subjects with renal insufficiency compared to subjects with normal renal function demonstrate no difference in half-life and no evidence of naproxen accumulation, however protein binding is decreased and unbound AUC is increased approximately 2 fold in moderately impaired patients. Naproxen metabolites are also expected to increase, therefore caution should be exercised when sumatriptan/naproxen is administered to patients with renal insufficiency. Sumatriptan/naproxen is contraindicated for use in patients with severe renal impairment (GFR < 30 mL/min/1.73m^2) (see section 4.3).

Hepatic impairment
No formal clinical pharmacology studies were conducted to assess the pharmacokinetics of sumatriptan/naproxen in subjects with hepatic impairment.

Sumatriptan
The bioavailability of sumatriptan following oral administration may be markedly increased in patients with liver disease. Patients with mild to moderate hepatic impairment had an approximately 80% increase in AUC and C_{max} compared with the healthy subjects. The pharmacokinetic profile of sumatriptan in patients with moderate hepatic impairment (Child Pugh B) showed that these patients, following an oral dose of 50 mg, have much higher plasma sumatriptan concentrations than healthy subjects. Because sumatriptan/naproxen contains 85 mg of sumatriptan, its use in patients with mild to moderate hepatic impairment is not recommended. Sumatriptan/naproxen is contraindicated in patients with moderate and severe hepatic impairment (see section 4.3).

Naproxen
Naproxen is contraindicated in patients with severe hepatic impairment or active liver disease (see section 4.3).

Elderly population
No formal clinical pharmacology study was performed to evaluate the pharmacokinetics of sumatriptan/naproxen in the elderly.

Sumatriptan
The pharmacokinetics of sumatriptan do not appear to be altered in the elderly. However, its use in elderly patients is not recommended due to the likely presence of concomitant disease, decreased hepatic function, and cardiovascular risk factors.

Naproxen
Studies with naproxen indicate that although the total plasma concentration of naproxen is unchanged, the unbound fraction is increased in the elderly. The clinical

significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

Ethnic origin
The effect of race on the pharmacokinetics of sumatriptan/naproxen has not been studied.

5.3 Preclinical safety data

Repeat-dose toxicity
Repeat-dose oral toxicology studies of up to 13 weeks in duration in mice were conducted with the sumatriptan/naproxen combination. The toxicity of the sumatriptan/naproxen after repeat oral administration to mice was characteristic of the known toxicity of naproxen (gastrointestinal tract and kidney targets); the types of toxicity that occurred were not altered by combined administration with sumatriptan. In general, females were more sensitive than males to a similar dose of naproxen; this may be related to differences in exposure (C_{max}), which was generally greater (~1.5 fold) in females compared to males at a similar dose. Deaths occurred at doses of ≥ 100 mg/kg/day naproxen in male mice and ≥ 50 mg/kg/day in female mice when administered alone and in combination with sumatriptan.

The primary toxicities occurred in the stomach and kidneys. In the stomach, changes were mainly located in the pyloric region of the glandular stomach (extending to the duodenum and jejunum in females) and were characterized by erosions and ulcers accompanied by inflammation and glandular hyperplasia in animals administered high-dose naproxen alone or in combination with sumatriptan. In the kidneys, cortical tubule dilatation was identified as primary toxicity (following administration of naproxen alone or in combination with sumatriptan). The no observable adverse effect level (NOAEL) was 100/30 mg/kg/day sumatriptan/naproxen after 13 weeks of daily repeated oral administration to male and female mice. Mean exposure ($AUC_{0\text{-}inf}$) of mice to sumatriptan at the NOAEL was 30-38 fold greater than human exposure to sumatriptan and 0.8-1.4 fold of exposure to naproxen after a single oral dose of sumatriptan/naproxen tablet.

Genotoxicity
Sumatriptan and naproxen tested alone and in combination were negative in an *in vitro* bacterial reverse mutation assay, and in an *in vivo* micronucleus assay in mice. The combination of sumatriptan and naproxen was negative in an *in vitro* mouse lymphoma tk assay in the presence and absence of metabolic activation. Naproxen alone and in combination with sumatriptan was positive in an *in vitro* clastogenicity assay in mammalian cells in the presence and absence of metabolic activation while sumatriptan alone was negative in these assays. Chromosomal aberrations were not induced in peripheral blood lymphocytes following 7 days of twice-daily dosing with combination of sumatriptan and naproxen in human volunteers.

Carcinogenicity
No carcinogenicity studies were conducted with sumatriptan/naproxen combination.

The carcinogenic potential of sumatriptan was evaluated in oral carcinogenicity studies in mice and rats. There was no evidence of an increase in tumors in either species related to sumatriptan administration. The carcinogenic potential of naproxen was evaluated in two oral carcinogenicity studies in rats. No evidence of tumorigenicity was found in either study.

Fertility

The effect of sumatriptan/naproxen combination on fertility in animals has not been studied.

In a study in which male and female rats were dosed daily with oral sumatriptan prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with 50 and 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately one-half of the human oral dose of 100 mg on a mg/m^2 basis. In a similar study of sumatriptan by the subcutaneous route there was no evidence of impaired fertility at doses up to 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately 6 times the human oral dose of 100 mg on a mg/m^2 basis. Oral administration of a maximally tolerated dose of naproxen to male and female rats prior to and throughout mating had no adverse effects on fertility or reproductive performance. The naproxen steady state AUC was estimated to be about 0.6-0.8 the human exposure to naproxen after a single sumatriptan/naproxen tablet.

Developmental toxicity

The developmental toxicity study (embryo-fetal) with sumatriptan/naproxen combination was conducted only in rabbits.

Oral treatment of pregnant rabbits with naproxen and the sumatriptan/naproxen produced maternal toxicity, reductions in fetal weight and increases in total and early resorptions and fetal deaths. Maternal toxicity presented as decreased body weight gain or body weight loss during periods of treatment and reductions in feed consumption. Fetal weights (growth) were significantly reduced at all doses administered to the mother. Increases in the mean number of total resorptions per litter and early resorptions per litter, and resorbed conceptuses per litter occurred in all dosage groups. Slightly higher incidences of three types of malformations occurred in the treated groups - fused caudal vertebrae, isolated interventricular septal defect, and persistent truncus arteriosis with secondary interventricular septal defect. The NOAEL was not identified in this study, and the lowest combination dose evaluated was associated with naproxen exposure (AUC) of dams less than or equal to exposure in humans after a single sumatriptan/naproxen tablet.

In previous studies, oral treatment of pregnant rats with sumatriptan during the period of organogenesis was associated with an increased incidence of cervicothoracic and umbilical blood vessel abnormalities, embryo/fetal toxicity, an increased incidence of a syndrome of malformations and decreased pup survival. The highest no-effect dose was approximately 60 mg/kg/day, which is approximately 6 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. Oral treatment of pregnant rats with naproxen (25 mg/kg/day) during the period of organogenesis was associated with decreased numbers of live fetuses, increased pre- and post-implantation loss and an increased incidence of cervical rib secondary to significant maternal toxicity. Exposure of the pregnant dams to naproxen at steady state was 0.6-0.8 of human exposure to naproxen after a single sumatriptan/naproxen tablet. Fetal naproxen plasma concentrations were approximately 0.6 of the maternal concentrations.

Peri- and postnatal reproductive toxicity
There was no prenatal and postnatal developmental study conducted with sumatriptan/naproxen combination.

Oral treatment of rats with sumatriptan during late gestation and throughout lactation was associated with a decrease in pup survival. The highest no-effect dose for this finding was 100 mg/kg/day, approximately 10 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. Oral treatment of rats with naproxen throughout gestation and lactation was associated with decreased F_1 viability and body weights, delayed maturation and a slightly lower F_2 live litter size. The naproxen steady state AUC for F_0 dams in this study was estimated to be about 0.6-0.8 the human exposure to naproxen after a single sumatriptan/naproxen tablet.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate
Cellulose, microcrystalline
Croscarmellose sodium
Sodium hydrogen carbonate
Povidone K30
Magnesium stearate
Talc

Coating
Hypromellose
Titanium dioxide (E171)
Triacetin
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Container: 3 years.
Blister: 3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE container with child-resistant polypropylene (PP) screw closure: 9 tablets
Each container contains a silica gel canister desiccant and a PET coil.

PVC/Al/OPA/Al blisters: 3 or 9 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 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER(S)

PL 27925/0131

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10 DATE OF REVISION OF THE TEXT

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