Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Easofen 200mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg ibuprofen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Round, white, biconvex film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short term management of mild to moderate pain such as is associated with headache, dental pain, period pain, muscle strain and for the management of head cold and influenza.

4.2 Posology and method of administration

Posology

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

Adults and adolescents (over the age of 12 years)

The usual initial dose is 400 mg and subsequently if necessary 200 to 400 mg every four hours with a maximum of 1200 mg in a twenty-four hour period.

If in adolescents this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Not recommended in children under the age of twelve years.

Elderly

NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. *See also Section 4.4.*

Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Method of administration

Oral.

4.3 Contraindications

(i) History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

(ii) Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

(iii) Use in patients with asthma, bronchospasm, rhinitis or urticaria associated with hypersensitivity to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.

(iv) Use in children under the age of twelve years.

(v) During the last trimester of pregnancy.

(vi) Patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV).

4.4 Special warnings and precautions for use

- The use of Easofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.
- Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (*see GI and cardiovascular risks below*).
- *Cardiovascular and cerebrovascular effects:* Clinical studies suggest that use of ibuprofen, particularly at high doses (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not show that low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400mg/day) are required.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Cases of Kounis syndrome have been reported in patients treated with Easofen Tablets. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

- *Elderly:* The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (*see section 4.2*).
- *Gastrointestinal bleeding, ulceration and perforation:* GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAIDs dosage, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (*see section 4.3*), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (*see below and 4.5*). Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. NSAIDs should be given with care to patients with a history of inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).
- Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake

inhibitors or anti-platelet agents such as acetylsalicylic acid (*see section 4.5*). When GI bleeding or ulceration occurs in patients receiving Easofen, the treatment should be withdrawn.

- In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

- There is a risk of renal impairment in dehydrated adolescents.
- Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.
- As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage, bleeding diathesis, or idiopathic thrombocytopenia purpura (ITP).
- At the outset of treatment, monitoring of the urine volume and renal function is necessary in cardiac insufficiency, cirrhotic and nephritic patients, in patients taking a diuretic and in those with chronic renal in sufficiency. The use of NSAIDs should preferably be avoided in patients with pre-existing renal disease or volume depletion.
- Patients who are pregnant or suffering from asthma or renal, cardiac or hepatic insufficiency should consult their doctor.

- **Severe cutaneous adverse reactions (SCARs)** Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use ibuprofen (see section 4.8)

Most of these reactions occurred within the first month.

If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Easofen 200 mg Film-coated Tablets in case of varicella.

- **SLE and mixed connective tissue disease:** Caution is advised in patients with systemic lupus erythematosus as well as those with connective tissue disease, due to increased risk of aseptic meningitis (see section 4.8).
- 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' should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

- Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs long-term should undergo regular supervision to monitor for adverse events.
- There is some evidence that drugs which inhibit cyclo-oxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

- *Masking of symptoms of underlying infections:*Easofen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in

bacterial community acquired pneumonia and bacterial complications to varicella. When Easofen is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen. ExcipientsThis 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

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Care should be taken in patients treated with any of the following drugs as interactions have been reported:

Antihypertensives such as diuretics, ACE inhibitors and Angiotensin II Antagonists:	NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions considered in patients taking ibuprofen concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter. The concomitant administration of ibuprofen and potassium-sparing diuretics or ACE-inhibitors can result in hyperkalaemia. Careful monitoring of potassium levels is necessary.
Acetylsalicylic acid:	Concomitant administration of ibuprofen and acetylsalicylic acid is generally not recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (*see section 5.1*).
Cardiac glycosides:	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.
Lithium:	Decreased elimination of lithium.
Methotrexate:	Decreased elimination of methotrexate.
Cyclosporin or tacrolimus:	Increased risk of nephrotoxicity with NSAIDs.
Other NSAIDs:	Avoid concomitant use of two or more NSAIDs.
Corticosteroids:	Increased risk of gastrointestinal ulceration or bleeding (*see section 4.4*).
Aminoglycosides:	Reduction in renal function in susceptible individuals,

	decreased elimination of aminoglycoside and increased plasma concentrations.
Probenecid:	Reduction in metabolism and elimination of NSAID and metabolites.
Oral hypoglycaemic agents:	Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.
Anti-coagulants:	NSAIDs may enhance the effects of anti-coagulants, such as warfarin (*see section 4.4*).
Anti-platelet agents, Selective Serotonin Reuptake Inhibitors (SSRIs):	Increased risk of gastrointestinal bleeding (*see Reuptake Inhibitors (SSRIs), section 4.4*).
Zidovudine:	Increased risk of haematological toxicity when NSAISs are given with Zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (positive) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Mifepristone:	NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, Easofen 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. Therefore, during the first and second trimester of pregnancy, Easofen should not be given unless clearly necessary. If Easofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Easofen for several days from gestational week 20 onward. Easofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Easofen is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely..

Fertility

There is some evidence that active substances which inhibit cyclooxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see section 4.4).

4.7 Effects on ability to drive and use machines

Ibuprofen may cause dizziness or tiredness. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Gastrointestinal Disorders	**Uncommon:**	Abdominal pain, dyspepsia and nausea.
	Rare:	Diarrhoea, flatulence, constipation and vomiting.
	Very rare:	Peptic ulcer, perforation or gastrointestinal haemorrhage, sometimes fatal, particularly in the elderly (see section 4.4). Melaena, haematemesis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see section 4.4). Less frequently, gastritis has been observed.
Nervous System	**Uncommon:**	Headache, dizziness, hearing disturbance.
Renal	**Very rare:**	Decrease of urea excretion and oedema can occur. Also, acute renal failure. Papillary necrosis, especially in long-term use, and increased serum urea concentrations have been reported.
Hepatobiliary Disorders	**Very rare:**	Liver disorders, especially in long-term treatment.
Blood and Lymphatic system Disorders	**Very rare:**	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding.
Skin and Subcutaneous tissue Disorders	**Very rare:**	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, erythema, bullous reactions and maculopapular rash)
	Not known:	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) Acute generalised exanthematous pustulosis (AGEP) Photosensitivity reactions
Immune System	**Very rare:**	In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4).
Hypersensitivity Reactions	**Uncommon:**	Hypersensitivity reactions with urticaria and pruritus.
	Very rare:	Severe hypersensitivity reactions. Symptoms could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). Exacerbation of

		asthma and bronchospasm.
Cardiac Disorders	**Very rare:**	Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment at high doses.
	Not known:	Kounis syndrome
Infections and infestations	**Very rare:**	Exacerbation of infection related inflammation (e.g. development of necrotizing fasciitis), in exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection.

Post-marketing surveillance:
Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

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:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Toxicity:
Signs and symptoms of toxicity have generally not been observed at doses below 100mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400mg/kg or greater. In serious poisoning metabolic acidosis may occur.

Symptoms:
Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4-6 hours.

The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnea and depression of the CNS and respiratory system have also been reported. Hyperkalaemia may develop. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia, has been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken.

Treatment:
There is no specific antidote for ibuprofen overdose. Gastric emptying followed by supportive measures is recommended if the quantity ingested exceeds 400mg/kg within the previous hour. Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively in adults, gastric lavage should be considered within one hour of a potentially life threatening overdose.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

For the most current information, contact the local poison control centre.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic group: Propionic acid derivatives.

ATC code: MO1AE01

Ibuprofen has analgesic, anti-inflammatory and antipyretic properties; it is an inhibitor of prostaglandin synthetase. Ibuprofen, a propionic acid derivative, alters platelet function and prolongs bleeding time.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that whensingle doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred.

Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1-2 hours after ingestion. Ibuprofen is extensively bound to plasma proteins and has a half-life of about 2 hours.

It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in urine as unchanged ibuprofen and about 14% as conjugated ibuprofen.

5.3 Preclinical safety data

No information submitted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Sodium starch glycolate Type A
Magnesium stearate

Film-coating
Hypromellose
Marcogol 400
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister strips consisting of aluminium foil, 9µm with 50 g/m^2 sulphate paper and PVC foil 250µm white opaque.

Pack size
10, 12, 20, 24, 28, 30, 48, 50 and 60 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

Clonmel Healthcare Ltd
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8 MARKETING AUTHORISATION NUMBER

PA0126/060/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 July 1986

Date of last renewal: 02 July 2006

10 DATE OF REVISION OF THE TEXT

May 2024