Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Easofen Max Strength 400 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg ibuprofen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Round, white, biconvex film-coated tablets, 12 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the short term management of muscular pain, backache, dental pain and dysmenorrhoea.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Posology

Adults and adolescents (over the age of 12 years)
The usual dose is 400 mg and subsequently if necessary 400 mg every four to six 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 12 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).

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

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

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 or other gastrointestinal disorder).

(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 12 years of age.

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

(vi) During the last trimester of pregnancy.

4.4 Special warnings and precautions for use

- The use of Ibuprofen 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 possible duration to control symptoms (see section 4.2, and GI and cardiovascular risks below). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

- 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.

- *Cardiovascular and cerebrovascular effects:* Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (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 suggest 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 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.

- *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). Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.
- *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 NSAID doses, 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 section 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 Ibuprofen, the treatment should be withdrawn.

- 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).

- Ibuprofen should be used with caution in patients with asthma or a history of bronchospasm.

- The use of ibuprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other signs of hypersensitivity.

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 Max Strength 400 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.

4.5 Interaction with other medicinal products and other forms of interactions

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:

Anti-hypertensivessuch 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.
Ciclosporin 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).
Anticoagulants:	Enhanced anticoagulant effect.

Quinolone antibiotics:	Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have increased risk of developing convulsions.
Aminoglycosides:	Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.
Probenecid:	Reduction in metabolism and elimination of NSAIDs and metabolites.
Oral hypoglycaemic agents:	Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.
Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):	Increased risk of gastrointestinal bleeding (see 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/foetal 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.

During the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen 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. During the third trimester of pregnancy all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

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. Increased formation of oedema in the mother could occur.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

Fertility
See Section 4.4 regarding female fertility.

Breast-feeding
In the limited studies so far available, ibuprofen appears in the breast milk in very low concentrations and is unlikely to adversely affect the breast-fed infant.

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 forms of skin reactions such as erythema, erythema multiforme, toxic epidermal necrolysis, bullous reactions, Stevens-Johnson Syndrome, maculopapular rash and exfoliative dermatitis can occur.
	not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

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.
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 the 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) (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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Toxicity:
Signs and Symptoms of toxicity have generally not been observed at doses below 100mg/kg in children or in 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 rarely 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 also 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 involved.

Treatment of overdosage:
There is no specific antidote to ibuprofen.

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

Pharmacotherapeutic Group: Anti-inflammatory and Anti-rheumatic Products. Non Steroids.

ATC code: M01AE01

Ibuprofen, a derivative of propionic acid, has useful anti-inflammatory, analgesic and antipyretic activity.Similar to other propionic acid derivatives such as naproxen and fenoprofen it can cause gastrointestinal erosions (gastric, duodenal and intestinal) in experimental animals.

All produce gastrointestinal side effects in man but they are usually less severe than with acetylsalicylic acid.The propionic acid derivatives are all effective inhibitors of the cyclooxygenease responsible for the biosynthesis of prostaglandins.All of these agents alter platelet function and prolong 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 when single 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 rapidly absorbed following oral administration to man, and peak concentrations in plasma are observed after 1 to 2 hours. The half-life in plasma is about 2 hours. Ibuprofen is extensively (99%) and firmly bound to plasma proteins, but the drug occupies only a fraction of the total drug binding sites at usual concentrations.

Ibuprofen passes slowly into the synovial spaces and may remain there in higher concentrations as the concentrations in plasma decline.In experimental animals, ibuprofen and its metabolites pass easily across the placenta. The excretion of ibuprofen is rapid and complete. Greater than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates, and no ibuprofen *per se* is found in the urine. The major metabolites are a hydroxylated and a carboxylated compound.

5.3 Preclinical safety data

No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Maize starch
Sodium starch glycolate (Type A)
Magnesium stearate

Film-coating
Hypromellose
Macrogol 400
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 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 9 µm aluminium foil with 50 g/m^2 sulphate paper and 250 µm white opaque PVC.

Pack size:
10, 12, 18, 20 and 24 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/060/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 9th September 2016

10 DATE OF REVISION OF THE TEXT

January 2019