Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Melfen 200mg Film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated 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, 10mm in diameter

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an adjunct in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute articular and periarticular disorders, fibrositis, cervical spondylitis, low back pain, painful musculo-skeletal conditions.

4.2 Posology and method of administration

Adults only
The usual daily dosage is 600 - 1200 mg in divided doses. The maximum daily dosage is 2,400 mg in divided doses.

Older people
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) Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
(ii) Use in patients with asthma, bronchospasm, rhinitis or urticaria associated with hypersensitivity to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
(iii) 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 chronic dyspepsia.
(iv) Severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV).

4.4 Special warnings and precautions for use

The use of Melfen 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.

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 (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.

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 Melfen, 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).

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

The use of Melfen 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 Melfen 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. Melfen 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.

Paediatric population
There is a risk of renal impairment in dehydrated children and adolescents.

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:

Anti-hypertensives:	Reduced anti-hypertensive effect.
Acetylsalicylic acid:	Concomitant administration of ibuprofen and acetylsalicylic acid is not generally 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 effects 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).
Diuretics:	Reduced diuretic effects. Diuretics can increase the risk of

	nephrotoxicity of NSAIDs. The concomitant administration of ibuprofen and potassium sparing diuretics or ACE-inhibitors can result in hyperkalaemia. Careful monitoring of potassium levels is necessary.
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

Gastrointestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, gastrointestinal perforation or bleeding, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, malaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) anaphylaxis, (b) asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) skin disorders, including rash , pruritus, urticaria, purpura, angioedema and, very rarely, bullous disorders(including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

Cardiovascular: Oedema, hypertension and cardiac failure has been reported in association with NSAID treatment.

Other adverse events reported less commonly and for which causality has not necessarily been established include:

Renal: Nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatic: Abnormal liver function, hepatitis and jaundice.

Neurological & special senses: Visual disturbances, optic neuritis, headaches, paraesthesia, depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological: Photosensitivity (see 'Hypersensitivity' for other skin reactions).

Infections and infestations: Very rarely reported is 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.

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) (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.

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. 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

ATC Code: M01AE01

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

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 if 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.

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

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, 20, 50, 100 and 250 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 Limited
Waterford Road
Clonmel
Co Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 0126/012/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 July 1980

Date of last renewal: 11 July 2010

10 DATE OF REVISION OF THE TEXT

July 2017