SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Melfen 400 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg ibuprofen.

Excipients:

For a 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

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) Use in patients with a known hypersensitivity to ibuprofen.
(ii) Use in patients with asthma, bronchospasm, rhinitis or urticaria associated with hypersensitivity to aspirin 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 heart failure.

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 trial and epidemiological data suggest that use of ibuprofen, particularly at a high dose (2400 mg daily) and in long term treatment 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 daily) is associated with an increased risk of myocardial infarction.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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 aspirin, 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.

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 aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Melfen, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

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.

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.

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.

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.
Aspirin:	Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and 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.
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:	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).

4.6 Fertility, pregnancy and lactation

Pregnancy
While no teratogenic effects have been demonstrated in animal toxicity studies, the use of ibuprofen during pregnancy should, if possible, be avoided. Congenital abnormalities have been reported in association with ibuprofen administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (closure of ductus arteriosus), use in late pregnancy should be avoided.

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, 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, nephritic 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).

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (2400 mg daily), and in long term treatment may be associated with a small increased risk of arterial thrombosis (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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Symptoms include nausea, vomiting, dizziness and rarely loss of consciousness. Large overdoses are generally well tolerated when no other drugs are involved.

Treatment of overdosage: Gastric lavage and if necessary, correction of serum electrolytes. There is no specific antidote to ibuprofen.

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 aspirin. 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 inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and 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
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 25ºC.

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

6.5 Nature and contents of container

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

Pack size: 10, 20, 50 100 and 250 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 Limited,
Waterford Road,
Clonmel,
Co. Tipperary.

8 MARKETING AUTHORISATION NUMBER(S)

PA 126/12/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th July 1980.
Date of last renewal: 11th July 2010.

10 DATE OF REVISION OF THE TEXT

June 2014