Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Advil Maximum Strength 400mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 400 mg ibuprofen.

Excipients:

Each effervescent tablet contains:

- 4.3 mmol (170 mg) potassium, as potassium carbonate.
- 17.7 mmol (407 mg) sodium, as sodium hydrogen carbonate, mono sodium citrate, sodium carbonate and saccharin sodium.
- up to 0.4 mg sucrose, present in saccharose palmitate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet.

Round, white tablet, flat-faced on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is suitable for adults and adolescents over 12 years of age and over 30 kg in weight for the relief of mild to moderate pain such as headache, migraine (with or without aura), minor previously diagnosed osteoarthritis pain, joint pain, backache, rheumatic or muscular pain, dysmenorrhoea, dental pain, feverishness and for the relief of symptoms of colds and influenza.

4.2 Posology and method of administration

For oral use.

For short-term use only.

The minimum effective dose should be used for the shortest time necessary to relieve symptoms. If the medicinal product is required for more than 5 days for pain or 3 days for fever or if the symptoms worsen, the patient should consult a doctor.

The effervescent tablets should be dissolved in a glass of water and the solution drunk immediately after dissolution. Do not swallow effervescent tablets whole.

Suitable for adults, the elderly and adolescents over 12 years of age and over 30 kg in weight:

The single dose is 400 mg (one effervescent tablet).

Adults, the elderly and adolescents over 12 years of age and over 30 kg in weight: 400 mg (one tablet) to be repeated, if

necessary, every 4-6 hours. Do not take more than 1200 mg ibuprofen (3 effervescent tablets) in any 24 hour period.

This product is not recommended for use in children below 12 years old.

The elderly and patients with renal and hepatic impairment should always be treated with the lowest effective dose.

4.3 Contraindications

Hypersensitivity to ibuprofen or any of the excipients.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis or urticaria) in response to acetylsalicylic acid/aspirin or other NSAIDS.

Active or previous peptic ulcer.

Active or history of upper gastrointestinal bleeding or perforation (two or more different episodes of ulceration or bleeding), including that associated with previous NSAID therapy.

Patients with severe hepatic failure, severe renal failure or severe heart failure (see section 4.4).

Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors (see section 4.5).

Use in third trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

The use of Advil Maximum Strength 400mg Effervescent Tablets with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided.

Caution is required in patients with certain conditions:

- systemic lupus erythematosus as well as those with mixed connective tissue disease, due to increased risk of aseptic meningitis (see section 4.8).
- gastrointestinal disorders and chronic inflammatory intestinal disease as these conditions may be exacerbated (ulcerative colitis, Crohn's disease) (see section 4.8).
- oedema, hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur (see section 4.5).
- renal impairment as renal function may deteriorate (see section 4.3 and 4.8).
- hepatic dysfunction (see section 4.3 and 4.8).
- bronchial asthma (see section 4.3 and 4.8).

Bronchospasm, urticaria or angioedema may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration (see gastro-intestinal (GI) and cardiovascular risks below).

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation that may be fatal (see section 4.2).

There is some evidence that medicinal products which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Gastrointestinal effects
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime 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/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 acetylsalicylic acid/aspirin (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Cardiovascular and cerebrovascular effects
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (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.

Dermatological effects
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 the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for 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. Advil Maximum Strength 400mg Effervescent Tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

This medicine contains 4.3 mmol (170 mg) potassium per effervescent tablet. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

This medicine also contains 17.7 mmol (407 mg) sodium per effervescent tablet. To be taken into consideration by patients on a controlled sodium diet.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should not be used in combination with:

- Acetylsalicylic acid/aspirin (above 75 mg daily): as this may increase the risk of adverse reactions (see section 4.3).
- Other NSAIDs: as these may increase the risk of adverse reactions (see section 4.3).

Ibuprofen should be used with caution in combination with:

- Acetylsalicylic acid/aspirin when used as an anti-aggregant, because this may increase the risk of gastrointestinal bleeding and decrease the benefit of taking acetylsalicylic acid/aspirin.

- SSRIs (selective serotonin-reuptake inhibitors): may increase the risk of gastrointestinal bleeding.
- Corticosteroids: may increase the risk of adverse reactions, especially of the gastrointestinal tract (see section 4.4).
- Antihypertensives and diuretics: Diuretics and ACE-inhibitors can increase the nephrotoxicity of NSAIDs. NSAIDs may diminish the effects of these medicinal products, including ACE-inhibitors and beta-blockers. In particular, concomitant use of potassium-sparing diuretics or ACE-inhibitors can result in hyperkalaemia.
- Anticoagulants: NSAIDS may enhance the effects of anticoagulants, such as warfarin and ticlopidine (see section 4.4).
- Lithium, digoxin, phenytoin: there is evidence for potential increase in plasma levels of these medicinal products when co-administered with ibuprofen.
- Methotrexate: there is the potential for increased plasma levels of methotrexate.
- Cyclosporin: inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporin and the risk of cyclosporin-induced nephrotoxicity.
- Zidovudine: there is evidence of an increased risk of haemarthroses and haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid/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).

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 trimesters 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 trimesters 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:
- cardio-pulmonary 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 after very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

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

Lactation:
In limited studies ibuprofen appears in breast milk in very low concentrations.

Fertility:
There is some evidence that medicinal products which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, drowsiness, vertigo or visual disturbances while they are taking ibuprofen, should avoid driving or using machinery. Single administration or short-term use of ibuprofen does not usually warrant the adoption of any special precautions.

4.8 Undesirable effects

Undesirable effects are mostly dose-dependent. In particular the risk of occurrence of gastrointestinal bleeding which is dependent on the dosage range and duration of treatment. The undesirable effects are less frequent when the maximum daily dose is 1200mg.

Hypersensitivity reactions have been reported and these may consist of:

a) Anaphylaxis and non-specific allergic reactions.
b) Respiratory tract reactivity comprising bronchospasm, asthma, aggravated asthma or dyspnoea.
c) Various skin reactions, e.g. rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis and erythema multiforme), angioedema, pruritus and urticaria.

The following list of adverse reactions relates to those experienced with ibuprofen at OTC doses (maximum 1200 mg per day), from short-term use. In chronic conditions, under long-term treatment, additional adverse reactions may occur.

Adverse reactions have been ranked under headings of frequency using the following convention: 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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic disorders	Very rare:	Haematopoietic disorders: pancytopenia, agranulocytosis, aplastic anaemia, hemolytic anaemia, leucopenia, thrombocytopenia, anaemia. First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding.
Immune system disorders	Uncommon:	Hypersensitivity reactions with urticaria and pruritus.
	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. Severe hypersensitivity reactions. Symptoms could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). Exacerbation of asthma and bronchospasm.
Psychiatric disorders	Very rare:	Nervousness
Nervous system disorders	Uncommon:	Dizziness and headache
	Very rare:	Aseptic meningitis

		Cerebrovascular accident
Eye disorders	Very rare:	Visual disturbance
Ear and labyrinth disorders	Very rare:	Tinnitus and vertigo
Cardiac disorders	Very rare:	Cardiac failure
	Not known:	Angina pectoris
Vascular disorders	Very rare:	Hypertension
Respiratory, thoracic and mediastinal disorders	Very rare:	Asthma, bronchospasm, dyspnoea and wheezing
Gastrointestinal disorders	Uncommon:	Abdominal pain, dyspepsia, nausea, abdominal distention, and gastritis.
	Rare:	Diarrhoea, flatulence, constipation and vomiting
	Very rare:	Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena and haematemesis, sometimes fatal, particularly in the elderly. Exacerbation of ulcerative colitis and Crohn's disease (see section 4.4). Mouth ulceration.
Hepatobiliary disorders	Very rare:	Liver disorders, especially in long-term treatment, hepatitis and jaundice
Skin and subcutaneous tissue disorders	Uncommon:	Various skin rashes.
	Very rare:	Severe forms of skin reactions such as erythema multiforme and toxic epidermal necrolysis can occur. Stevens-Johnson Syndrome.
Renal and urinary disorders	Very rare:	Renal failure, interstitial nephritis, renal insufficiency, nephritic syndrome, renal papillary necrosis, hematuria and proteinuria.
General disorders and administration site conditions	Very rare:	Oedema, peripheral oedema.
Investigations	Very rare:	Decreased haematocrit and haemoglobin levels.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses, 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) (see section 4.4).

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut.

The half-life in overdose is 1.5-3 hours.

Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning hyperkalaemia and metabolic acidosis may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal or gastric emptying if the patient presents within 1 hour of ingestion of a potentially toxic amount. If ibuprofen has already been absorbed, alkaline substances may be administered to promote the excretion of acid ibuprofen in the urine. When frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propionic acid derivatives
ATC code: M01 AE01

Ibuprofen is a phenylpropionic acid derivative NSAID that exerts its efficacy via inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swelling and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

The effect of ibuprofen effervescent tablets on pain relief was compared to conventional solid ibuprofen tablets in two randomised trials and to paracetamol effervescent tablets in one randomised trial.

The onset of first perceptible pain relief for ibuprofen effervescent tablets was observed approximately 14 minutes after administration, and in both clinical studies was statistically faster than conventional solid ibuprofen tablets indicating a more rapid onset of analgesic effect. The median time to meaningful pain relief was observed 28-35 minutes after dosing for the ibuprofen effervescent tablets. Total pain relief over 8 hours and time to meaningful relief were shown to be statistically superior for ibuprofen effervescent tablets compared to paracetamol effervescent tablets. The analgesic effect of ibuprofen effervescent tablets (400 mg dose) has been shown to last for at least 8 hours in one study and 7 hours in a second study.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid/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 acetylsalicylic acid/aspirin dosing, 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.

Ibuprofen 400 mg is effective in migraine attacks in relieving both headache and the associated symptoms of photophobia, phonophobia and nausea.

5.2 Pharmacokinetic properties

After oral administration, solubilised ibuprofen is quickly absorbed when the effervescent tablets are administered under fasting conditions. Peak plasma concentrations are achieved within 0.36 hours (approximately 22 minutes) compared to 1.56 hours (approximately 1 hour 33 minutes) with conventional ibuprofen tablets (see Table).
Summary of key pharmacokinetic parameters:

Product	Dose	$AUC_{0\text{-inf}}$ µg.hr/ml	C_{max} µg/ml	t_{max} hr	$t_{1/2}$ hr
Ibuprofen 400mg Effervescent Tablets	1 x 400mg tablet	127.6±28.28	46.7±8.79	0.36±0.11	2.56±0.52
Ibuprofen 200mg Effervescent Tablets	2 x 200mg tablets	133.2±28.64	48.0±8.49	0.35±0.13	2.59±0.48
Ibuprofen 200mg Tablets	2 x 200mg tablets	134.0±26.76	30.8±4.84	1.56±0.82	2.47±0.39
Ibuprofen 200mg Soft Gelatin Capsules	2 x 200mg capsules	130.8±23.75	45.0±8.23	0.58±0.17	2.59±0.52

When taken with food, peak levels are observed after 1-2 hours with conventional film-coated tablets.

Ibuprofen protein binding is approximately 99%. After an oral dose, ibuprofen is 75 – 85% excreted via kidneys during the first 24 hours (mainly in the form of two metabolites), the remainder being eliminated in the faeces following excretion in bile. Excretion is complete within 24 hours.

The half-life of ibuprofen is about 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

5.3 Preclinical safety data

The subchronic and chronic toxicity of ibuprofen in animal experiments consisted mainly of lesions and ulcerations in the gastro-intestinal tract.

In-vitro and *in-vivo* investigations have produced no clinically relevant evidence of ibuprofen having mutagenic effects. In studies in rats and mice, no evidence of carcinogenic effects of ibuprofen was found.

Ibuprofen led to an inhibition of ovulation in rabbits and impaired implantation in various animal species (rabbit, rat, mouse). Experimental studies in rats and rabbits have shown that ibuprofen crosses the placenta. Following administration of maternotoxic doses, an increased rate of malformations (ventricular septal defects) occurred in the progeny of rats.

In animal studies it has been observed that the use of NSAIDs, known to inhibit prostaglandin synthesis, may increase the incidence of dystocia and delayed parturition.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium carbonate (E501)
Sodium carbonate, anhydrous (E500)
Citric acid, anhydrous (E330)
Mono sodium citrate (E331)
Sodium hydrogen carbonate (E500)
Hypromellose (E464)
Saccharin sodium (E954)
Saccharose palmitate (contains sucrose)
Menthol flavour
Grapefruit flavour
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C
Store in the original package to protect from moisture.

6.5 Nature and contents of container

Foil strip, paper/PE/aluminium, in a cardboard outer.

Pack sizes: 2, 4, 8, 10, 12, 16 and 20 effervescent tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0822/163/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th February 2010

10 DATE OF REVISION OF THE TEXT

July 2013