COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ibuprofen 400 mg Capsules, soft (ibuprofen)

NL/H/4469/001/DC

Date: 18 January 2023

This module reflects the scientific discussion for the approval of Ibuprofen 400 mg Capsules, soft. The procedure was finalised in the United Kingdom (UK/H/4613/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Ibuprofen 400 mg Capsules, soft

UK/H/4611/001/DC
UK/H/4613/001/DC

UK licence no: PL 14338/0004-5

Applicant: Banner Pharmacaps Europe BV

LAY SUMMARY

The MHRA granted Banner Pharmacaps Europe BV Marketing Authorisations (licences) for the medicinal products Ibuprofen 400 mg Capsules, soft (PL 14338/0004) and a duplicate licence for the same product with the same name (PL 14338/0005) on 29 November 2011. In the UK Ibuprofen 400 mg Capsules, soft (PL 14338/0004-5) are pharmacy-only medicines.

Ibuprofen 400 mg capsules, soft contain a medicine called ibuprofen. This belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) that work by relieving pain and fever.

Ibuprofen 400 mg Capsules, soft is indicated in adults and adolescents from 40 kg and above (12 years of age and above) for the relief of mild to moderate pain such headache, acute migraine headaches with or without aura, muscular pain, period pain, feverishness and pain associated with a common cold.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of using Ibuprofen 400 mg Capsules, soft outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Product Name	Ibuprofen 400 mg Capsules, Soft
Type of Application	Generic, Article 10.1
Active Substance	Ibuprofen
Form	Soft Capsules
Strength	400 mg
MA Holder	Banner Pharmacaps Europe B.V., De Posthoornstraat 7, Tilburg, 5048 AS, Netherlands.
Reference Member State (RMS)	UK
CMS	UK/H/4611/001/DC (PL 14338/0004): Poland UK/H/4613/001/DC (PL 14338/0005): Czech Republic, Germany, France, the Netherlands, Poland and Sweden
Procedure Number	UK/H/4611/001/DC UK/H/4613/001/DC
End of Procedure	25 October 2011

Module 2
Summary of Product Characteristics

The UK Summary of Product Characteristics (SPC) for Ibuprofen 400 mg capsules, soft (PL 14338/0004 and PL 14338/0005) is as follows:
Differences between the two SmPCs are highlighted in yellow.

1 NAME OF THE MEDICINAL PRODUCT
Ibuprofen 400 mg capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each soft capsule contains 400 mg Ibuprofen.

Excipient with known effect (per capsule):
96 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, soft.

A clear oval transparent soft gelatin capsule.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Ibuprofen 400 mg capsules, soft is indicated in adults and adolescents from ≥40 kg (12 years of age and above) for the symptomatic relief of mild to moderate pain such as headache, acute migraine headaches with or without aura, muscular pain, period pain/dysmenorrhoea, feverishness and pain associated with a common cold

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 duration necessary to relieve symptoms. If the medicinal product is required for more than 4 days for pain or 3 days for fever and migraine headaches or if the symptoms worsen, the patient should consult a doctor.

If people experience mild indigestion it is recommended to take this medicine with food or milk to avoid gastrointestinal problems.

Adults and adolescents from >40 kg in weight (12 years of age and above):
400 mg (one capsule) with water.

400 mg (one capsule) to be repeated, if necessary, with intervals of at least 6 hours. Do not take more than 1200 mg ibuprofen (three capsules) in any 24 hour period.

Special patient groups
The elderly and patients with renal and hepatic impairment should always start treatment with the lowest effective dose.

Paediatric population:
Ibuprofen 400 mg capsules, soft is contraindicated in adolescents under 40 kg body weight and in children, see section 4.3.

Elderly:
No special dose adjustment is required. Because of the possible undesirable-effect profile (see section 4.4), it is recommended to monitor the elderly particularly carefully.

Renal insufficiency:
No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).

Hepatic insufficiency (see section 5.2):
No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).

4.3 Contraindications

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

Patients who have previously shown hypersensitivity reactions (e.g. bronchospasms, asthma, rhinitis, angioedema or urticaria) in response to acetylsalicylic acid or other NSAIDs.

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).

Bleeding diathesis or coagulation disorders.

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

Patients with cerebrovascular or other active bleeding.

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

Patients with unclarified blood-formation disturbances.

Patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

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

Adolescents under 40 kg body weight and children.

4.4 Special warnings and precautions for use

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).
- congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria).
- 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 further deteriorate (see section 4.3 and 4.8).
- hepatic dysfunction (see section 4.3 and 4.8).
- directly after major surgery.
- in patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of Ibuprofen 400 mg capsule, soft (see section 4.3).

- in patients who suffer from hayfever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria (see section 4.3).

- bronchial asthma (see section 4.3 and 4.8).

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

- 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 (see section 4.6).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and gastrointestinal and cardiovascular risks below).

Gastrointestinal effects
The use of Ibuprofen 400 mg capsule, soft with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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 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 aspirin, 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. 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 400 mg capsule, soft, 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).

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs (see also section 4.7).

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. Ibuprofen 400 mg capsule, soft should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues 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 Ibuprofen 400 mg capsule, soft in case of varicella.

Other notes
Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking/administering Ibuprofen 400 mg capsule, soft therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

In prolonged administration of Ibuprofen 400 mg capsule, soft regular checking of the liver values, the kidney function, as well as of the blood count, is required.

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 (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore it should be avoided.

The use of NSAIDs may mask the symptoms of infection.

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance 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 (above 75 mg daily): as this may increase the risk of adverse reactions (see section 4.3).

- Other NSAIDs, including cyclo-oxygenase-2 inhibitors: as these may increase the risk of adverse reactions (see section 4.3 and 4.4).

Ibuprofen should be used with caution in combination with:

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

- Antiplatelet agents and selective serotonin-reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

- Diuretics, ACE inhibitors, betareceptor-blockers and angiotensin-II antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. 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,

betareceptor-blockers 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. 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.

In particular, concomitant use of potassium-sparing diuretics may increase the risk of hyperkalaemia.

- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin and ticlopidin (see section 4.4).

- Lithium, digoxin and phenytoin: there is evidence for potential increase in plasma levels of these medicinal products when co-administered with ibuprofen. If used correctly (maximum dose for 4 days), monitoring of the plasma concentrations of lithium, digoxin or phenytoin is usually not needed.

- Probenecid and sulfinpyrazon: medicinal products that contain probenecid or sulfinpyrazon may delay the excretion of ibuprofen.

- Methotrexate: the administration of Ibuprofen 400 mg capsule, soft within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase of its toxic effect.

- Cyclosporin: inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporin and the risk of cyclosporin-induced nephrotoxicity.

- Tacrolimus: the risk of nephrotoxicity is increased if ibuprofen and tacrolimus are co-administered.

- Zidovudine: there is evidence of an increased risk of haemarthroses and haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

- Sulphonylureas: there is evidence of interactions between NSAIDs and antidiabetic medicinal products (sulphonylureas). Although no specific interactions between ibuprofen and sulphonylureas have been described, blood glucose values should be monitored as a precaution during co-administration of ibuprofen and sulphonylureas.

- Quinolone antibiotics: animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

- Cholestyramine: Concomitant treatment with cholestyramine and ibuprofen results in prolonged and reduced (25%) absorption of ibuprofen. The medicinal products should be administered with at least one hour interval.

- Aminoglycosides: NSAIDs can slow down the elimination of aminoglycosides and increase their toxicity.

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).

4.6 Fertility, Pregnancy and Lactation

Fertility (see section 4.4):

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.

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:

- 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.

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

Lactation:
In limited studies Ibuprofen and its metabolites appear in breast milk in very low concentrations. Since no harmful effects to infants are known to date, it is usually not necessary to interrupt breast-feeding during short-term use of Ibuprofen 400 mg capsule, soft at the recommended doses.

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. This remark applies to a greater extent in combination with alcohol (see section 4.4). Single administration or short term use of ibuprofen does not usually warrant the adoption of any special precautions.

4.8 Undesirable effects
The list of the following undesirable effects comprises all undesirable effects that have become known under treatment with ibuprofen, also those under high-dose long-term therapy in rheumatism patients. The stated frequencies, which extend beyond very rare reports, refer to the short-term use of daily doses up to a maximum of 1200 mg ibuprofen for oral dosage forms and a maximum of 1800 mg for suppositories.

With the following adverse drug reactions, it must be accounted for that they are predominantly dose-dependent and vary interindividually.

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, 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.

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

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.

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.

Infections and infestations	Very rare	Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of nonsteroidal antiinflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal antiinflammatory drugs. If signs of an infection occur or get worse during use of Ibuprofen 400 mg capsule, soft, the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an antiinfective/antibiotic therapy. The symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.
Blood and Lymphatic System Disorders	Very rare	Disturbances to blood formation (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranuloctosis, aplastic anaemia, haematolytic anaemia). The first signs may be fever, sore throat, superficial wounds in the mouth, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding. In such cases the patient should be advised to discontinue the medicine immediately, to avoid any self-medication with analgesics or antipyretics and to consult a physician. The blood count should be checked regularly in long-term therapy.
Immune System Disorders	Uncommon	Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure). The patient is to be instructed to inform a doctor at once and no longer to take Ibuprofen 400 mg capsule, soft in this case.
	Very rare	Severe general hypersensitivity reactions. They may present as face oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, respiratory distress,

		racing heart, drop in blood pressure up to life-threatening shock. If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a doctor is required.
Psychiatric disorders	Very rare	Psychotic reactions, depression, nervousness
Nervous System Disorders	Uncommon	Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
Eye disorders	Uncommon	Visual disturbances
Ear and labyrinth disorders	Rare	Tinnitus
Cardiac Disorders	Very rare	Palpitations, heart failure, myocardial infarction
Vascular disorders	Very rare	Arterial hypertension
Respiratory, thoracic and mediastinal disorders	Very rare	Asthma, bronchospasm, dyspnoea and wheezing.
Gastrointestinal Disorders	Common	Gastro-intestinal complaints such as dyspepsia, pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases.
	Uncommon	Gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis.
	Very rare	Oesophagitis, pancreatitis, formation of intestinal diaphragm-like strictures. The patient is to be instructed to withdraw the medicinal product and to go to a doctor immediately if severe pain in the upper abdomen or melaena or haematemesis occurs.
Hepatobiliary Disorders	Very rare	Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis.
Skin and Subcutaneous Tissue Disorders	Uncommon	Various skin rashes
	Very rare	Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").
Renal and Urinary Disorders	Rare	Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood may also occur rarely.

	Very rare	Formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency. Renal function should therefore be checked regularly.
Investigations	Very rare	Decreased haematocrit and haemoglobin levels.

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 adolescents and adults, the dose response effect is not 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 dizziness, drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning 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 and liver damage 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 if the patient presents within 1 hour of ingestion of a potentially toxic amount. If 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: Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivative, ATC Code: M01A E01.

Ibuprofen is a phenylpropionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever.

Furthermore, ibuprofen reversibly inhibits platelet aggregation.

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 aspirin 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 from the gastro-intestinal tract, peak serum concentrations occurring 1-2 hours after administration of conventional film-coated tablets ibuprofen. However, ibuprofen is more rapidly absorbed from the gastrointestinal tract following the administration of Ibuprofen 400 mg capsule, soft, with peak plasma concentrations occurring approximately 46 minutes after administration in the fasting state.

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

Macrogol 600
Potassium hydroxide
Purified water

Capsule shell
Gelatin
Sorbitol Liquid, Partially Dehydrated (E420)

Capsule printing
Opacode WB black NS-78-17821 *

*The ink contains: Black iron oxide, HPMC 2910/Hypromellose 6cP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters formed of PVC/PE/PVdC/Al packed into cartons.

Each carton may contain 4, 10, 12, 15, 16 or 20 capsules in blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Banner Pharmacaps Europe B.V.
De Posthoornstraat 7
5048 AS Tilburg
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 14338/0004
PL 14338/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2011

10 DATE OF REVISION OF THE TEXT

29/11/2011

Module 3
Patient Information Leaflet

The text version of the PIL was provided and approved as part of this application. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the PIL mock-up has been submitted and approved by the competent authority. The PIL for PL 14338/0005 is identical to the one shown here with the exception to the PL number.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ibuprofen 400 mg capsule, soft

For use in adults and adolescents from 40 kg and above (12 years of age and above)

Ibuprofen

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
Always take this medicine exactly as described in this leaflet.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.
- You must talk to a doctor if you do not feel better or if you feel worse after 4 days for pain or 3 days for fever and migraine headaches.

In this leaflet:

1. What Ibuprofen 400 mg capsule, soft is and what it is used for

Ibuprofen 400 mg capsule, soft contains a medicine called ibuprofen. This belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) that work by relieving pain and fever.

Ibuprofen 400 mg capsule, soft is indicated in adults and adolescents from 40 kg and above (12 years of age and above) for the relief of mild to moderate pain such as headache, acute migraine headaches with or without aura, muscular pain, period pain, feverishness and pain associated with a common cold.

2. What you need to know before you take Ibuprofen 400 mg capsule, soft

Please read the following information.

Do not take Ibuprofen 400 mg capsule, soft if you:
- are allergic to ibuprofen or any of the other ingredients of this medicine (listed in section 6)
- ever suffered shortness of breath, asthma, runny nose, swelling or (itching) rash after you have used acetylsalicyl acid (aspirin) or other related painkillers (NSAIDs)
- have a history of gastro-intestinal bleeding or perforation related to previous NSAID therapy
- have (or have had two or more episodes of) a stomach ulcer or bleeding of the stomach
- suffer from a blood coagulation disorder or if you have another bleeding disorder
- suffer from severe liver, kidney or heart failure
- suffer from cerebrovascular or other active bleeding
- suffer from unclarified blood-formation disturbances
- suffer from severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake)
- are in the last 3 months of pregnancy

- are already taking other NSAID painkillers (including COX 2 inhibitors) or aspirin at doses above 75 mg daily

Do not use Ibuprofen 400 mg capsule, soft in adolescents under 40 kg body weight and in children.

Warnings and precautions
Talk to a pharmacist or your doctor before taking your medicine if you:

- suffer from Systemic Lupus Erythematosus (SLE) - a condition of the immune system affecting connective tissue resulting in joint pain, skin changes and disorders of other organs - or a mixed connective tissue disease
- suffer from serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. The use of Ibuprofen 400 mg capsule, soft should be stopped immediately at the first appearance of skin rash, mucosal lesions, or any other signs of allergic reactions
- have hereditary blood formation disorder (acute intermittent porphyria)
- have or have ever had bowel problems or disease (ulcerative colitis, Crohn's disease)
- have or have had asthma or allergic disease as shortness of breath may occur
- suffer from hayfever, nasal polyps or chronic obstructive respiratory disorders an increased risk of allergic reactions exists. The allergic reactions may present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.
- are elderly, as you may be more likely to suffer from side effects
- suffer from kidney or liver disease
- have just had major surgery
- have swelling (oedema), high blood pressure (hypertension) or a heart disease
- are trying to become pregnant (ibuprofen belongs to a group of medicines, NSAIDs, that may impair fertility in women. The effect is reversible upon stopping the medicine).
- are in the first 6 months of pregnancy
- are taking low dose aspirin (up to 75 mg/day)

Undesirable effects are minimised by using the minimum effective dose for the shortest period of time.

Medicines such as Ibuprofen 400 mg capsule, soft may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment (4 days for pain or 3 days for fever or migraine headaches). If you have heart problems, previous stroke or think you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.
During chicken pox (varicella) it is advisable to avoid use of Ibuprofen 400 mg capsule, soft.

In prolonged administration of Ibuprofen 400 mg capsule, soft regular checking of your liver values, the kidney function, as well as of the blood count, is required.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, you should stop taking this medicine and contact your doctor.

In general the frequent use of (several sorts of) analgesics can lead to lasting severe kidney problems. This risk may be increased under physical strain associated with dehydration. Do not take this medicine if you feel dehydrated.

The use of NSAIDs may mask the symptoms of infection.

Other medicines and Ibuprofen 400 mg capsule, soft
What should you avoid when you are taking this medicine?
Some medicines that are anti-coagulants (against clotting) (e.g. acetylsalicylic acid/aspirin, warfarin, ticlopidin), some medicines against high blood pressure (ACE-inhibitors e.g. captopril, betareceptor

blocking medicines, angiotensin II antagonists), and even some other medicines may affect or be affected by the treatment of ibuprofen. Seek therefore always advice of a doctor before you use ibuprofen with other medicines.

Do not use this medicine if you are taking:
- other NSAID painkillers (including COX-2 inhibitors).
- aspirin above 75 mg daily.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially if it regards one of the following medicines:
- **Low-dose aspirin** (up to 75 mg a day)
- **Diuretics** (drug to help you pass water)
- **Anticoagulants** e.g. warfarin and heparin and **Anti-platelet drugs** such as clopidogrel and ticlopidine (drugs that thin the blood)
- **Antihypertensives** (drugs used to treat high blood pressure e.g. captopril or propranolol)
- **Lithium, digoxin, phenytoin** or **Selective serotonin reuptake inhibitors** (SSRI's e.g. fluoxetine - used to treat mood disorders)
- **Methotrexate** (used to treat rheumatoid arthritis, psoriasis and some cancers)
- **Zidovudine** (used to treat HIV)
- **Corticosteroids** (anti-inflammatory drugs, such as prednisone)
- **Ciclosporin** or **tacrolimus** (used to suppress the body's immune system)
- **Quinolone antibiotics** (used to treat a wide range of infections e.g. ciprofloxacin)
- **Probenecid and sulfinpyrazone** (used to treat gout)
- **Moclobemide** (used to treat depression)
- **Aminoglycosides** (an antibiotic)
- **Cholestyramine** (used to reduce cholesterol)
- **Sulphonylureas** (used to treat diabetes)
- Any other **ibuprofen preparations or NSAID painkillers,** including those you can buy without a prescription.

Seek therefore always advice of a doctor before you use ibuprofen with other medicines.

Ibuprofen 400 mg capsule, soft with food and drink
Ibuprofen 400 mg capsule, soft may be taken on an empty stomach. However, a small number of people might experience mild indigestion with this medicinal product. If you experience mild indigestion, it is recommended to take this medicine with food or milk, to avoid gastrointestinal problems.

Some side effects, such as those affecting the gastrointestinal system can be more likely when alcohol is taken at the same time as Ibuprofen 400 mg capsule, soft.

Pregnancy, breast-feeding and fertility
Tell your doctor if you become pregnant during intake of Ibuprofen 400 mg capsule, soft.
If you are in the first six months of pregnancy talk to your doctor or a pharmacist before using Ibuprofen 400 mg capsule, soft.
Ibuprofen 400 mg capsule, soft passes into breast milk, but may be used during breast-feeding at the recommended doses, for the shortest duration possible.
If you are in the last three months of pregnancy do not use this medicine because it might cause problems to the unborn child or complications during delivery.
This product belongs to a group of medicines (NSAIDs) which might impair fertility in women. This effect is reversible on stopping the medicine. It is unlikely that this medicine, used occasionally, will affect your chances of becoming pregnant however, talk to your doctor before using it if you have problems becoming pregnant.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Do not drive or use machines if you start to experience dizziness, drowsiness, vertigo or visual disturbances.

Important information about some of the ingredients of Ibuprofen 400 mg capsule, soft
This medicine contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking these capsules.

3. How to take Ibuprofen 400 mg capsule, soft

Always take this medicine exactly as described in this leaflet. Check with your doctor or pharmacist if you are not sure.

For oral use.

For short term use only.

The minimum effective dose should be used for the shortest time necessary to relieve symptoms.
You must talk to a doctor if you do not feel better or if you feel worse after 4 days for pain or 3 days for fever and migraine headaches.

Ibuprofen 400 mg capsule, soft should be swallowed unchewed with plenty of liquid.
Ibuprofen 400 mg capsule, soft is contraindicated in adolescents under 40 kg body weight and in children.

The recommended dose for adults and adolescents from 40 kg and above (12 years of age and above) is:
One capsule (400 mg ibuprofen) up to 3 times a day, as required. Take only as much as you need to relieve your symptoms and leave at least 6 hours between each dose.

Do not take more than three capsules (1200 mg ibuprofen) in any 24 hour period.

If you take more Ibuprofen 400 mg capsule, soft than you should
If you accidentally take too many capsules, contact your doctor or hospital immediately. Bring the remaining capsules with you to show to the doctor. The symptoms of taking a lot more capsules than the stated dose (an overdose) include: nausea, stomach pain, vomiting containing either blood or brown grit (like ground coffee), diarrhoea, ringing in the ears, headache, dizziness, drowsiness, confusion, disorientation and rarely, loss of consciousness.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Ibuprofen 400 mg capsule, soft can cause side effects, although not everybody gets them.

If you suffer from any of the following at any time during your treatment STOP TAKING the medicine and *seek immediate medical help*:

- Pass blood in your faeces (stools/motions)
- Pass black tarry stools
- Vomit any blood or dark particles that look like coffee grounds

- Unexplained wheezing, shortness of breath, skin rash (which may be severe and included blister or peeling of the skin), itching or bruising, light-headedness, racing of the heart or fluid retention e.g. swollen ankles, not passing enough water
- Stiff neck, headache, nausea, vomiting, fever and disorientation
- Swelling of the face

STOP TAKING the medicine and *tell your doctor if you experience*:

- Indigestion or heartburn
- Abdominal pain (pains in your stomach) or other abnormal stomach symptoms
- Yellowing of the eyes and/or skin
- Severe sore throat with high fever or unexplained bleeding, bruising and tiredness

The following frequencies are taken as a basis when evaluating side effects:

very common	affects more than 1 user in 10
common	affects 1 to 10 users in 100
uncommon	affects 1 to 10 users in 1,000
rare	affects 1 to 10 users in 10,000
very rare	affects less than 1 user in 10,000

The following are side effects that may be experienced.

Infections
Very rare: Exacerbation of infection-related inflammations (e.g. necrotising fasciitis), aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding. Patients with autoimmune disorders (lupus, mixed connective-tissue disease) appear to be predisposed.

Blood disorders
Very rare: Problems in the blood cell production - first signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding. If this happens you must stop taking this medicine immediately and consult a doctor.

Problems of the immune system
Uncommon: Hypersensitivity reactions with hives and itch, as well as asthma attacks. You must stop taking Ibuprofen 400 mg capsule, soft and inform your doctor at once.
Very rare: Severe hypersensitivity reactions – signs could be: swelling of face, tongue and throat, shortness of breath, palpitations, severe shock. If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a doctor is required.

Psychiatric disorders
Very rare: Psychotic reactions, depression, nervousness

Nervous system disorders
Uncommon: Headache, dizziness, sleeplessness, agitation, irritability and tiredness

Eye disorders
Uncommon: visual disturbances

Ear and balance disorders
Rare: Tinnitus (ringing in the ears)

Cardiac disorders
Very rare: palpitations, heart failure, myocardial infarction

Vascular disorders
Very rare: arterial high blood pressure

Respiratory, thoracic and mediastinal disorders
Very rare: Asthma, shortness of breath and wheezing

Stomach and bowel disorders
Common: Stomach complaints, such as indigestion, acid burn, stomach pain and nausea, diarrhoea, vomiting, flatulence (wind) and constipation, and slight blood losses in stomach and/or bowel that may cause anaemia in exceptional cases.
Uncommon: Perforation or gastrointestinal bleeding, black stools and vomiting of blood, worsening of existing bowel disease (ulcerative colitis or Crohn's disease), gastritis
Very rare: Oesophagitis, pancreatitis, formation of intestinal diaphragm-like strictures

Liver disorders
Very rare: Damage to the liver (first signs could be discoloration of the skin), acute hepatitis

Skin disorders
Uncommon: Various skin rashes
Very rare: Severe forms of skin reactions including rash with redness and blistering, Stevens-Johnson syndrome and dead-tissue. Exceptionally, severe skin infection and soft tissue complications during chicken pox (varicella) infection.

Kidney disorders
Rare: Pain in the flanks and/or abdomen, blood in the urine, and a fever may be signs of damage to the kidneys (papillary necrosis). Elevated urea concentration in blood.
Very rare: Passing less urine than normal, swelling (oedema) and cloudy urine (nephrotic syndrome); inflammatory kidney disease (interstitial nephritis) that my lead to acute kidney failure.

Investigations
Very rare: Low haemoglobin levels (anaemia).

Medicines such as Ibuprofen 400 mg capsule, soft may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

5. How to store Ibuprofen 400 mg capsule, soft

This medicinal product does not require any special storage conditions.

Keep this medicine out of the sight and reach of children.

Do not use Ibuprofen 400 mg capsule, soft after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ibuprofen 400 mg capsule, soft contains

The active substance is ibuprofen.
Each capsule contains 400 mg of ibuprofen

The other ingredients are:
Macrogol 600
Potassium hydroxide
Purified water

Capsule shell
Gelatin
Sorbitol Liquid, Partially Dehydrated (E420)

Capsule printing
Opacode WB black NS-78-17821 *

*The ink contains: Black iron oxide, HPMC 2910/Hypromellose 6cP

What Ibuprofen 400 mg capsule, soft looks like and contents of the pack
Ibuprofen 400 mg capsule, soft is a clear oval transparent soft gelatin capsule.

Ibuprofen 400 mg capsule, soft is available in PVC/PE/PVdC/Al blisters.
Packs of 4, 10, 12, 15, 16 and 20 capsules.

Marketing Authorisation Holder and Manufacturer
Banner Pharmacaps Europe B.V.
De Posthoornstraat 7
5048 AS Tilburg,
The Netherlands

PL 14338/0004

This leaflet was last approved in 10/2011.

Module 4
Labelling

The text version of the labelling has been provided and approved as part of this application. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the label mock-ups has been obtained. The text for the labels is identical for PL 14338/0005 with the exception of the PL number.

Carton

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen 400 mg capsule, soft

Ibuprofen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 400 mg ibuprofen.

3. LIST OF EXCIPIENTS

Contains sorbitol (E420).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, Soft
4 caspsules, soft
10 caspsules, soft
12 caspsules, soft
15 caspsules, soft
16 caspsules, soft
20 caspsules, soft

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. For short term use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Blue box:
Do not take this medicine if you:

- are allergic to ibuprofen or any of the other ingredients of this medicine, aspirin or other related painkillers
- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- you are taking other NSAID painkillers or aspirin with a daily dose above 75 mg

Speak to a pharmacist or your doctor before you take this medicine if you:

- Have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver, kidney or bowel problems,
- Are a smoker

- Are pregnant or trying to become pregnant

Do not exceed the stated dose.

8. EXPIRY DATE

EXP: (month/year)

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Banner Pharmacaps Europe B.V.
De Posthoornstraat 7
5048 AS Tilburg,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

PL 14338/0004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

For use in adults and adolescents from 40 kg and above (12 years of age and above)

DOSAGE:
One capsule (400 mg ibuprofen) up to 3 times per day as required. leave at least 6 hours between doses.
Do not take more than 3 capsules in 24 hours.

You must talk to a doctor if you do not feel better or if you feel worse after 4 days for pain or 3 days for fever and migraine headaches.

FOR SYMPTOMATIC RELIEF OF MILD TO MODERATE PAIN SUCH AS:
- Headache
- Acute migraine headaches with or without aura
- Muscular pain
- Period pain
- Feverishness and pain associated with a common cold

Read the package leaflet before use.

16. INFORMATION IN BRAILLE

Ibuprofen 400 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PE/PVdC/Al blister

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen 400 mg capsule, soft

Ibuprofen

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Banner Pharmacaps Europe B.V.

3. EXPIRY DATE

EXP: (month/year)

4. BATCH NUMBER

Lot:

5. OTHER

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Ibuprofen 400 mg Capsules, soft and its duplicate licence, indicated for adults and adolescents from ≥40 kg (12 years of age and above) for the symptomatic relief of mild to moderate pain such as headache, acute migraine headaches with or without aura, muscular pain, period pain/dysmenorrhoea, feverishness and pain associated with a common cold is approvable. Ibuprofen 400 mg capsules, soft are pharmacy-only (P) medicines in the UK.

These applications were submitted using the decentralised procedure, with the UK as Reference Member State (RMS), and Poland as a Concerned Member State (CMS) for procedure (UK/H/4611/001/DC) and Czech Republic, Germany, France, the Netherlands, Poland and Sweden as CMSs for procedure (UK/H/4613/001/DC).

These applications for Ibuprofen 400 mg capsules, soft (UK/H/4611/001/DC) and its duplicate licence, Ibuprofen 400 mg capsules, soft (UK/H/4613001/DC) were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC as amended and as "generic hybrid" applications, Article 10(3) in Germany and Sweden.

The reference medicinal product authorised for not les than 10 years is Nurofen® tablets 200 mg tablets by Crookes Healthcare Limited, licensed since 1983 in the UK (PL 00327/0004). The capsules' pharmaceutical form was authorised in the UK is Nurofen 400mg Liquicaps (PL 00327/0199-200) as a line-extension to the 200 mg tablet form on 25 January 2008. The reference products have been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired.

Ibuprofen is a phenylpropionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. Ibuprofen reduces inflammatory pain, swellings and fever.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications are based on essential similarity to products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant's Ibuprofen 400 mg Capsules, soft and the reference products Nurofen® 400 mg Liquicaps (PL 00327/0198) first authorised to Crookes Healthcare Limited on 21 July 2006; subsequently the licence underwent a change of ownership procedure on 3 June 2001 and is currently authorised to Reckitt Benckiser (UK) Limited (PL 00063/0653); and Nurofen Ultra Forte 400 mg Liquid Capsule (Reckitt Benckiser, Poland) under fasting conditions. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

The applicant has submitted an Environmental Risk Assessment (ERA) based on data from the published data. A CMS maintains that the information in the published literature is inadequate for the purposes of the ERA. The CMS is of the opinion that there is missing data, which may need to be filled by experimental studies. The CMS has stated that the data that they consider to be missing may be provided as a post-authorisation commitment.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Ibuprofen 400 mg capsules, soft Ibuprofen 400 mg capsules, soft
Name(s) of the active substance(s) (INN)	Ibuprofen 400 mg capsules, soft
Pharmacotherapeutic classification (ATC code)	M01 AE01
Pharmaceutical form and strength(s)	Capsules, soft, 400 mg
Reference numbers for the Mutual Recognition Procedure	UK/H/4611/001/DC UK/H/4613/001/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/4611/001/DC (PL 14338/0004): Poland UK/H/4613/001/DC (PL 14338/0005): Czech Republic, Germany, France, the Netherlands, Poland and Sweden
Marketing Authorisation Number(s)	PL 14338/0004 PL14338/0005
Name and address of the authorisation holder	Banner Pharmacaps Europe B.V., De Posthoornstraat 7, Tilburg, 5048 AS, Netherlands.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

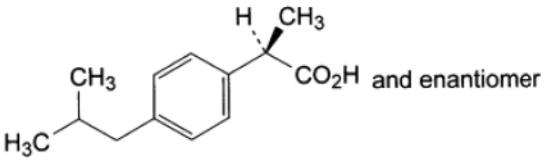
rINN name: Ibuprofen

Chemical name: (2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid.

Molecular formula: $C_{13}H_{18}O_2$

Molecular weight: 206.3 g/mol

Structure



General properties

Description: White crystalline powder or colourless crystals.
Solubility: Practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

The active substance, ibuprofen, is the subject of a European Pharmacopoeia (EP) monograph.

Manufacture

All aspects of the manufacture and control of the active substance ibuprofen are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.

A suitable retest period has been stated, based on stability data from batches of the active substance stored in-line with current requirements and in the proposed packaging.

DRUG PRODUCT

Description and Composition

The drug products are presented as clear oval transparent soft gelatin capsules. Each capsule contains 400 mg ibuprofen.

Other ingredients consist of pharmaceutical excipients, macrogol 600, potassium hydroxide, purified water making up the capsule, gelatin, sorbitol liquid, partially dehydrated (E420) making up the capsule shell and Opacode WB black NS-78-17821 (Black iron oxide, HPMC 2910/Hypromellose 6cP) making up the printing ink on the capsules.

All excipients are commonly used in the pharmaceutical industry and are controlled to Ph.Eur monographs with the exception of Opacode WB black NS-78-17821, which is composed of well-known excipients that are controlled to Ph.Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Appropriate justification for the inclusion of each excipient has been provided.

With the exception of gelatin none of the excipients used contain material derived from animal or human origin. The applicant has provided from each supplier, Certificates of Suitability issued by the European Directorate for the Quality of Medicines (EDQM), confirming that the gelatin has been manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a robust, stable, generic formulation, bioequivalent to the innovator products, Nurofen® 400 mg Liquicaps (PL 00063/0653) authorised in the UK to Reckitt Benckiser and Nurofen Ultra Forte 400 mg Liquid Capsules (Reckitt Benckiser, Poland).

Comparative dissolution profiles were provided for the test and reference products and were found to be similar.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. The validation data demonstrated consistency of the manufacturing process.

Finished Product Specification

Finished product specifications are provided for both release and shelf-life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with

the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container-Closure System
The finished products are licensed for marketing in polyvinylchloride (PVC)/polyvinylidene chloride (PVdC)/aluminium blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The blister strips are packaged in pack sizes of 4, 10, 12, 15, 16 or 20 capsules. The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed however, the MAH has committed to submitting the proposed packaging/labelling for any pack size before it is marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been approved. There are no special storage conditions for this product.

Bioequivalence Studies
The applicant has submitted one bioequivalence study in support of these applications. Bioequivalence has been demonstrated between the applicant's Ibuprofen 400 mg Capsules, soft and the reference products Nurofen® 400 mg Liquicaps (Reckitt Benkiser, UK) and Nurofen Ultra Forte 400 mg Liquid Capsule (Reckitt Benckiser, Poland) under fasting conditions.

An evaluation of the bioequivalence studies can be found in the Clinical Aspects section of this report.

Quality Overall Summary
A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. Final text versions of the PIL and labels have been provided. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the PIL and label mock-ups has been obtained. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test show that the patients/users are able to act upon the information that is contains.

MAA Form
The MAA forms are pharmaceutically satisfactory.

Conclusion
There are no objections to the approval of Ibuprofen 400 mg Capsules, soft from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well-known. Therefore, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

ENVIRONMENTAL RISK ASSESSMENT (ERA)

The applicant has submitted an ERA for ibuprofen based on data in the published literature. The Phase I assessment revealed that the $PEC_{surface\ water}$ was above the 0.01 µg/ml action limit.

In the Phase II assessment, the PEC was refined taking into account the removal of the drug substance through adsorption and degradation. A literature search was conducted regarding the physico-chemical tests and aquatic effects studies. The literature indicated that ibuprofen is readily biodegradable with no persistence. The sorption behaviour (partition coefficient Kd) or adsorption coefficient (Koc) have been reported. Ibuprofen exhibited a low affinity for organic carbon. Acute and chronic toxicity effects of ibuprofen on aquatic organisms were collected from literature. According to the Phase II environmental fate and effect analysis conducted with the data available from the published literature, the applicant concluded that the risk quotient PEC/PNEC is <1 and therefore ibuprofen is unlikely to represent a risk for the environment following its usage in patients.

Overall Summary and Conclusion

The applicant has provided an ERA based on data from the published literature which indicates that ibuprofen is unlikely to pose a risk to the environment following its therapeutic use.
A Concerned Member State maintains that the information in the published literature is inadequate for the purposes of the ERA. The CMS is of the opinion that there is missing data, which may need to be filled by experimental studies. The CMS has stated that the data that they consider to be missing may be provided as a post-authorisation commitment.

NON-CLINICAL OVERVIEW

The non-clinical overall summary was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)

The SmPCs are satisfactory from a non-clinical viewpoint and is consistent with that for the reference products.

In conclusion, the non-clinical aspects can be considered to be resolved, except for the issue of the ERA, which may be resolved as a post authorisation commitment. There are no objections to the approval of Ibuprofen 400 mg Capsules, soft from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

In adults and adolescents from ≥ 40 Kg (12 years of age and above) for the symptomatic relief of mild to moderate pain such as headache, migraine headaches (with or without aura), muscular pain, period pain/dysmenorrhoea, feverishness and pain associated with a common cold.

An adequate clinical overview has been submitted.

The applications are supported by one bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Ibuprofen 400 mg Capsules, soft, to the three reference products, Nurofen® 200 mg Tablets, Nurofen® 400 mg Liquicap and Nurofen Ultra Forte 400 mg Liquid Capsule (Reckitt Benckiser) in healthy adult volunteers under fasting conditions.

Pharmacokinetics

This was a single dose, randomised, four-way crossover comparative oral bioavailability study of the test product, Ibuprofen 400 mg Capsules, soft with three marketed reference formulations all authorised to Crookes Healthcare Limited; Nurofen® 200 mg tablet (2 x 200 mg tablets) Nurofen® 400 mg Liquicap and Nurofen Ultra Forte 400 mg Liquid Capsules in 24 fasting healthy volunteers.

The study was conducted in compliance with current principles of GCP.

Study design

A single dose of medication was given with 240 ml water in each period after fasting overnight and doses were separated by a washout of at least 48 hours. Serial blood collections were made pre-dose and at various time-points up to 12 hours after administration.

Analytical methods

A validated HPLC-UV analytical methodology was used for quantification of ibuprofen from the human plasma samples. Primary variables analysed were: AUC_{0-t}, AUC0-∞, C_{max}, T_{max}

Pharmacokinetic Variables

	Primary	AUC_{0-t}, AUC0-∞, C_{max}, T_{max}, C_t, $AUC_{0-t\ min}$
Additional		$t_{½}$, MRT (Mean residence time) and kel

The applicant, states that as the test formulation is designed for rapid absorption, it might be appropriate to assess bioequivalence with reference Nurofen® 200 mg Tablets (Reckitt Benkiser, UK) a conventional tablet, on the basis of AUC0-t and $AUC_{0-\infty}$ only. The parameters t_{max}, C_t and $AUC_{0-t\ min}$ were used to compare rates of absorption (relative bioavailability).

Statistical methods

Treatment comparisons: ANOVA with 90% CI were carried out for C_{max}, t_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for ibuprofen. ANOVA might also be carried out for C_t and $AUC_{0-t\ min}$.

Acceptance range: 80% – 125% (log-transformed) for AUC0-t and AUC 0-∞, and C_{max}.

Safety criteria included descriptive analysis for adverse Events, pre and post study screening and monitoring of vital signs were conducted.

Results

A vs B

A: Ibuprofen 400 mg Soft Gelatine Capsule, *Banner Pharmacaps Europe BV.*
B: Nurofen® 200 mg tablet, *Reckitt Benckiser, UK.*

	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	T_{max}
Point estimate	116.58%	102.18%	102.22%	66.11%
90% CI	105.32% - 129.03%	97.57% - 107.01%	97.89% - 106.74%	41.80% - 78.64%

Conclusion
The results showed that the test and reference B are equivalent in respect to the extent of absorption but not to the rate of absorption. Although C_{max} lies outside the pre-specified CI acceptance range of 80-125% supportive literature data have shown that this higher C_{max} value does not carry a safety risk.

A vs C

A: Ibuprofen 400 mg Soft Gelatine Capsule, *Banner Pharmacaps Europe BV.*
C: Nurofen® 400 mg Liquicap, *Reckitt Benckiser, UK.*

	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	T_{max}
Point estimate	106.94%	101.01%	101.10%	95.37%
90% CI	97.69% - 117.08%	95.60% - 106.73%	95.64% - 106.88%	71.06% - 119.10%

Conclusion
CI for C_{max} and AUC lie within the acceptance range of 80-125% and therefore the test product and reference C are considered bioequivalent.

A vs D

A: Ibuprofen 400 mg Soft Gelatine Capsule, *Banner Pharmacaps Europe BV.*
D: Nurofen Ultra Forte 400 mg Liquid Capsule, *Reckitt Benckiser, Poland.*

	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	T_{max}
Point estimate	108.24%	102.31%	102.46%	94.62%
90% CI	96.34% - 121.61%	96.49% - 108.48%	96.61% - 108.68%	79.69% - 114.34%

Conclusion
CI for Cmax and AUC lie within the acceptance range of 80-125% and therefore the test product and reference D are considered bioequivalent.

Safety

Data from all 25 volunteers entered for the study were included in the safety evaluation.

There were thirteen mild adverse events (AEs) in nine volunteers. All were considered by the Investigator to be not related or unlikely to be related to the study medication. Laboratory and vital signs results showed no findings of clinical significance.

Study medication was well tolerated.

No pre-dose levels were detected in any period.

Pharmacokinetic conclusion
Conclusion on bioequivalence study:
The results of the bioequivalence study show that the test and reference products (Ibuprofen 400 mg Soft Gelatin Capsule and Nurofen Ultra Forte 400 mg Liquid Capsule) are bioequivalent under fasting conditions, as the confidence intervals for C_{max} and $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ for ibuprofen fall within the acceptance criteria ranges of 80.00-125.00%, in line with current CHMP guidelines.

The results showed that the test and reference product, Nurofen® 200 mg tablet, are equivalent in respect to the extent of absorption but not to the rate of absorption. Although C_{max} lies outside the pre-specified CI acceptance range of 80-125% supportive literature data have shown that this higher C_{max} value does not carry a safety risk.

Bioequivalence has been shown between the applicant's product and the tested reference products.

Pharmacodynamics
No new data have been submitted and none are required for this application.

Clinical efficacy
No new efficacy data have been submitted and none are required for this application.

Clinical safety
No new safety data have been submitted and none are required for this application.

Pharmacovigilance system
The pharmacovigilance system is satisfactory.

Risk Management Plan

No safety concerns requiring additional risk minimization activities have been identified with the reference product. A detailed RMP is not considered necessary for this generic application.

Periodic Safety Update Report (PSUR)

The applicant has applied for a PSUR submission scheme upon approval harmonised with birth date of the first MAA grant in the EEA for Ibuprofen. Ibuprofen is found in the list published by the Heads of Medicines Agencies with an EU Harmonised Birthday (19/2/1969) and related Data Lock Point (DLP). The applicant proposes to submit the first PSUR within 60 days of the next DLP and after maintain the 3 year periodicity of PSUR in line with the originator. The suggestion is acceptable.

BENEFIT RISK ASSESSMENT

The applications contain an adequate review of published clinical data and the bioequivalence has been shown. There are no objections to the approval of Ibuprofen 400 mg Capsules, soft from a clinical point of view.

Expert Report

A satisfactory clinical overall summary is provided, and has been prepared by an appropriately qualified physician. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPCs and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form

The MAA forms are medically satisfactory.

Conclusion

There are no objections to approval of Ibuprofen 400 mg Capsules, soft from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Ibuprofen 400 mg Capsules, soft are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

The applicant has submitted one bioequivalence study in support of these applications. Bioequivalence has been demonstrated between the applicant's Ibuprofen 400 mg Capsules, soft and two reference products Nurofen® 400 mg Liquicaps (Reckitt Benckiser, UK) and Nurofen Ultra Forte 400 mg Liquid Capsule (Reckitt Benckiser, Poland) under fasting conditions.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs and PILs are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's products Ibuprofen 400 mg Capsules, soft and the reference products, Nurofen® 400 mg Liquicap (Reckitt Benckiser, UK) and Nurofen Ultra Forte 400 mg Liquid Capsule (Reckitt Benckiser, Poland) in 24 fasting healthy volunteer are interchangeable. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome