Ibuprofen 200mg Soft Gelatine Capsules

PL 14338/0003

UKPAR

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Ibuprofen 200mg Soft Gelatine Capsules

PL 14338/0003

LAY SUMMARY

On 30th June 2010, the MHRA granted Banner Pharmacaps Europe B.V. a Marketing Authorisation (licence) for the medicinal product Ibuprofen 200mg Soft Gelatine Capsules (PL 14338/0003). This product is a general sales list (GSL) medicine used for the relief from rheumatic or muscular pain, backache, neuralgia (sharp pain along nerves), migraine, headache, dental pain, period pain, feverishness, cold and flu symptoms.

Ibuprofen 200mg Soft Gelatine Capsules contain the active ingredient ibuprofen, which belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Ibuprofen 200mg Soft Gelatine Capsules outweigh the risks, hence a Marketing Authorisation has been granted.
Ibuprofen 200mg Soft Gelatine Capsules

PL 14338/0003

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Ibuprofen 200mg Soft Gelatine Capsules (PL 14338/0003) to Banner Pharmacaps Europe B.V. on 30th June 2010. This product is a general sales list (GSL) medicine for the relief of rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

This is a national abridged application for Ibuprofen 200mg Soft Gelatine Capsules submitted under Article 10(1) of Directive 2001/83/EC, as amended. The product claims to be a generic medicinal product of Nurofen Tablets 200mg (PL 00327/0004) that was originally authorised in May 1983 to Crookes Healthcare Limited. The reference product used in the bioequivalence study is Boots Ibuprofen Liquid Capsules 200mg (PL 00327/0118), which was originally licensed in August 1999 to Crookes Healthcare Limited.

Ibuprofen belongs to the class of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). These are effective in relieving pain that occurs in association with relatively common complaints such as influenza, soft tissue injuries and inflammatory conditions affecting joints and tendons. NSAIDs exert analgesic, antipyretic and anti-inflammatory effects, without affecting the underlying pathology to any extent. The anti-inflammatory action of ibuprofen is thought to be due to the peripheral inhibition of prostaglandin synthesis, whilst the analgesic effect results from central and peripheral actions of the S-form.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: 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
Appearance: Ibuprofen is a 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 Pharmacopeia monograph.

All aspects of the manufacture and control of the active substance are covered by European Directorate for the Quality of Medicines (EDQM) certificates of suitability.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuff.

Appropriate stability data have been generated, supporting a suitable retest period when the active substance is stored in the proposed packaging.

DRUG PRODUCT
Other ingredients
In addition to the active substance, the finished product consists of the pharmaceutical excipients macrogol 600, potassium hydroxide, purified water, gelatin, sorbitol and Opacode WB white NS-78-18011.

With the exception of Opacode WB white NS-78-18011, all excipients comply with their respective European Pharmacopoeia monographs. Opacode WB white NS-78-18011 is controlled to a suitable in-house specification, though it should be noted that its components (titanium dioxide (E171), hypromellose and propylene glycol) are all controlled to their European Pharmacopoeia monographs. Suitable Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of gelatin, none of the excipients contained materials of animal or human origin. An EDQM certificate of suitability has been provided for the suppliers of gelatin, showing that it is produced in-line with current requirements concerning the minimisation of transmission of BSE/TSE.
None of the excipients are sourced from genetically modified organisms.

**Pharmaceutical development**
A suitable pharmaceutical development data have been provided for this application. Comparable dissolution and impurity profile are provided for this product versus the reference product used in the bioequivalence study.

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on full-scale batches. The results appear satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for working standards used.

**Container-closure system**
The capsules are packaged in white opaque blister packs, composed of polyvinyl chloride, polyethylene, polyvinylidene chloride and aluminium. These are contained in cardboard outer cartons in pack sizes of 4, 10 or 16 capsules.

Suitable specifications and certificates of analysis have been provided for all packaging components. The primary packaging has been shown to comply with relevant guidelines concerning contact with foodstuff.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been proposed with storage conditions of “Do not store above 25°C” and “Store in the original package”.

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling**
The SPC, PIL and labels are pharmaceutically acceptable.

A Patient Information Leaflet (PIL) has been submitted to the MHRA along with a readability report which refers to the results of consultation with target patient groups (‘user testing’), in accordance with Article 59 2001/83/EEC. The results indicate that the applicant’s PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

A suitable justification has been provided for not submitting a risk management plan for this product.

MAA Form
The MAA form is pharmaceutically satisfactory.

Pharmaceutical expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRE-CLINICAL ASSESSMENT

The toxicological properties of ibuprofen are well-known. Thus, the applicant has not provided any new pre-clinical data and none are required.

The applicant’s pre-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There is no objection to the approval of the product from a pre-clinical viewpoint.
CLINICAL ASSESSMENT

Clinical Pharmacology
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover study to compare the pharmacokinetics of the test product Ibuprofen 200mg Soft Gelatine Capsules versus the reference product Ibuprofen Liquid Capsules 200mg (Crookes Healthcare Limited) in healthy adult volunteers under fasting conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. A single dose was given followed by 240ml water. Blood samples were collected pre- and up to 12 hour post dose. The two treatment arms were separated by a washout period of at least 48 hours.

The results are presented below:

<table>
<thead>
<tr>
<th></th>
<th>( \text{AUC}_{0-\text{inf}} )</th>
<th>( \text{AUC}_{0-t} )</th>
<th>( \text{C}_{\text{max}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio (test/reference)</td>
<td>102.81%</td>
<td>104.65%</td>
<td>101.36%</td>
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<tr>
<td>90% Geometric CI</td>
<td>96.21-109.86%</td>
<td>97.15-112.73%</td>
<td>91.44-112.36%</td>
</tr>
<tr>
<td>Intrasubject CV</td>
<td>12.13%</td>
<td>13.62%</td>
<td>18.96%</td>
</tr>
<tr>
<td>Intersubject CV</td>
<td>27.66%</td>
<td>28.02%</td>
<td>23.71%</td>
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</table>

CI = Confidence Interval; CV = Cumulative Variance;
\( \text{AUC}_{0-\text{inf}} \) area under the plasma concentration-time curve from time zero to infinity
\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours
\( \text{C}_{\text{max}} \) maximum plasma concentration

The 90% confidence intervals for \( \text{C}_{\text{max}} \) and \( \text{AUC} \) for test versus reference product are within the predefined acceptance criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98). The data support the claim that the test product is bioequivalent to the reference product.

Efficacy
No new efficacy data have been submitted and none are required.

Safety
No new safety data have been submitted and none are required.

Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labels are consistent with those for the reference product.

MAA Form
The MAA form is satisfactory.

Conclusion
The grant of a marketing authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Ibuprofen 200mg Soft Gelatine Capsules 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.

PRECLINICAL
No new pre-clinical data were submitted and none are required for an application of this type.

EFFICACY
No new data have been submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between Ibuprofen 200mg Soft Gelatine Capsules and the reference product Ibuprofen Liquid Capsules 200mg (Crookes Healthcare Limited).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new pre-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Ibuprofen 200mg Soft Gelatine Capsules

PL 14338/0003

STEPS TAKEN FOR ASSESMENT

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 04 May 2009</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 21 May 2009</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 16 July 2009 and 13 August 2009</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the quality section on 21 October 2009 and 30 November 2009</td>
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<tr>
<td>5</td>
<td>The application was determined on 30 June 2010</td>
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# Ibuprofen 200mg Soft Gelatine Capsules

**PL 14338/0003**

## STEPS TAKEN AFTER ASSESSMENT

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ibuprofen 200mg Soft Gelatine Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Ibuprofen 200 mg per capsule, soft.
For excipients see 6.1.

3 PHARMACEUTICAL FORM
Capsule, soft
Oval clear capsules printed with a logo in white.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the relief of rheumatic or muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

4.2 Posology and method of administration
For oral administration and short-term use only. Do not chew.

Adults, the elderly and children over 12 years:
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms.
The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

Take one or two capsules (200 mg – 400 mg), up to three times a day as required.

Leave at least four hours between doses and do not take more than 6 capsules (1200 mg) in any 24 hour period.

Children under 12 years:
Not recommended.

4.3 Contraindications
Hypersensitivity to ibuprofen or any of the excipients in the product.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.

Active or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Severe heart failure, renal failure or hepatic failure (See section 4.4).

Last trimester of pregnancy (See section 4.6).

4.4 Special warnings and precautions for use
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration, necessary to control symptoms (See GI and cardiovascular risks below).

The elderly have an increased frequency of adverse reactions to NSAIDs, especially GI bleeding and perforation which may be fatal.

Respiratory:
Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.
Other NSAIDs:
The use of Ibuprofen 200mg Soft Gelatine Capsules with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (See section 4.5).

SLE and mixed connective tissue disease:
Systemic lupus erythematosus and mixed connective tissue disease - increased risk of aseptic meningitis (See section 4.8).

Renal:
Renal impairment as renal function may further deteriorate (See sections 4.3 and 4.8).

Hepatic:
Hepatic dysfunction (see sections 4.3 and 4.8).

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 (2400mg 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. ≤ 1200mg daily) is associated with an increased risk of myocardial infarction.

Impaired female fertility:
There is limited evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

Gastrointestinal:
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn’s disease) – as these conditions may be exacerbated (See section 4.8).

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 NSAIDs 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.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (See section 4.5).

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

Dermatological:
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 200mg Soft Gelatine Capsules should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Patients with rare hereditary problems of fructose intolerance should not take this medicine because of the presence of sorbitol.

**The label will include:**
Read the enclosed leaflet before taking this product.
Do not take if you
- have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding
- are allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg
- are in the last 3 months of pregnancy

Speak to a pharmacist or your doctor before taking this product 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 in the first 6 months of pregnancy

If symptoms persist or worsen, consult your doctor.

**4.5 Interaction with other medicinal products and other forms of interaction**

*Aspirin:* Unless low-dose aspirin (not above 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (See section 4.4).

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).

Other NSAIDs including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (See section 4.4).

**Ibuprofen should be used with caution in combination with:**

*Anticoagulants:* NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).

*Antihypertensives and diuretics:* NSAIDs may diminish the effect of these drugs. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

*Corticosteroids:* Increased risk of gastrointestinal ulceration or bleeding (See section 4.4).

*Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):* increased risk of gastrointestinal bleeding (See section 4.4).

*Cardiac glycosides:* NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

*Lithium:* There is evidence for potential increases in plasma levels of lithium.

*Methotrexate:* There is a potential for an increase in plasma methotrexate.

*Ciclosporin:* Increased risk of nephrotoxicity.

*Mifepristone:* NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

*Tacrolimus:* Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematomata in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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.

4.6 Pregnancy and lactation

Whilst no teratogenic effects have been demonstrated in animal experiments, the use of Ibuprofen 200mg Soft Gelatine Capsules should, if possible, be avoided during the first 6 months of pregnancy.

During the 3rd trimester, ibuprofen is contraindicated as there is a risk of premature closure of the foetal ductus arteriosus with possible persistent pulmonary hypertension. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (See section 4.3).

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

None expected at recommended doses and duration of therapy.

4.8 Undesirable effects

Hypersensitivity reactions have been reported and these may consist of:
(a) Non-specific allergic reactions and anaphylaxis
(b) Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea
(c) Various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)

The following list of adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Hypersensitivity reactions:
Uncommon: Hypersensitivity reactions with urticaria and pruritus.
Very rare: severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). Exacerbation of asthma and bronchospasm.

Gastrointestinal:
The most commonly observed adverse events are gastrointestinal in nature.
Uncommon: abdominal pain, nausea and dyspepsia.
Rare: diarrhoea, flatulence, constipation and vomiting.
Very rare: peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemeses, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis. Exacerbation of colitis and Crohn’s disease (see section 4.4).

Nervous System:
Uncommon: Headache
Very rare: Aseptic meningitis – single cases have been reported very rarely.

Renal:
Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.
Hepatic:
Very rare: liver disorders.

Haematological:
Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Dermatological:
Uncommon: Various skin rashes
Very rare: Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis can occur.

Immune System:
In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (See section 4.4).

Cardiovascular and Cerebrovascular:
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 2400mg 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 ibuprofen 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 drowsiness, occasionally excitement 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, ATC code: M01AE01.

Ibuprofen is a propionic 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 ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.
5.2 Pharmacokinetic properties
Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.

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
There are no preclinical safety data of relevance additional to that contained elsewhere in the SmPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsule contents:
- Macrogol 600
- Potassium hydroxide
- Purified water

Capsule shell:
- Gelatine
- Sorbitol
- Purified water
- Opacode WB white NS-78-18011 (titanium dioxide (E171), hypromellose, propylene glycol)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
A blister pack consisting of opaque, white polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVDC), heat sealed to aluminium foil. The blisters are packed into cardboard cartons.

Package size(s): 4, 10 or 16 capsules per carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 14338/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/06/2010
UKPAR Ibuprofen 200mg Soft Gelatine Capsules

PL 14338/0003

10 DATE OF REVISION OF THE TEXT
30/06/2010
UKPAR Ibuprofen 200mg Soft Gelatine Capsules
PL 14338/0003

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ibuprofen 200mg Soft Gelatine Capsules

Important things that you need to know:

- This medicine is a treatment for several types of pain.
- Do not take this medicine if you have had a stomach ulcer, perforation or bleeding or if you are in the last 3 months of pregnancy.
- If you are pregnant, you should read the section below on 'before taking this medicine' carefully.
- Taking other medicines with Ibuprofen capsules can cause problems. Tell your doctor if you are taking anything else. If you are, you should read Section 2 below on 'before you take Ibuprofen capsules' carefully.
- Do not take more than 6 capsules in 24 hours.
- Do not take this medicine for longer than 10 days unless your doctor tells you to.
- Ibuprofen can cause side effects, although most people do not have serious problems — see the section below on 'side effects'. If you pass bloody or black tarry stools, vomit any blood or dark particles, have difficulty breathing, have unexplained swelling, worsening of asthma or swelling of the face or throat, see your doctor immediately.
- This leaflet was last updated in March 2010. Read all of this leaflet carefully because it contains important information for you.

In this leaflet:

1. What Ibuprofen 200mg Soft Gelatine Capsules are and what they are used for
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1. WHAT IBUPROFEN 200 MG SOFT GELATINE CAPSULES ARE AND WHAT ARE THEY USED FOR

This medicine contains ibuprofen, which belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs).

Your capsules are used to relieve the symptoms of pain, headache, toothache, dental pain, period pain, feverishness, cold or flu symptoms. They are designed to provide effective relief from pain.

2. BEFORE YOU TAKE IBUPROFEN 200 MG SOFT GELATINE CAPSULES

Do not take these capsules if you:

- are allergic to ibuprofen or any of the other ingredients of this product, aspirin or other related painkillers (see and under section 2 and section 6).
- have had a worsening of asthma, allergic rash or itch, nausea when taking similar medicines.
- have or have had two or more episodes of a stomach ulcer, perforation or bleeding.
- ever had stomach bleeding or a perforation due to NSAIDs.
- are already taking other drugs that belong to the NSAIDs group.
- are taking aspirin at doses of above 75 mg daily.
- are in the last 3 months of pregnancy.
- suffer from severe heart, liver or kidney disease.

Please see your doctor or pharmacist before taking this medicine if you:

- are elderly, as you may be more likely to suffer from side effects.
- have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver, kidney or bowel problems.
- are allergic to any other painkiller.
- suffer from systemic lupus and rheumatism or a mixed connective tissue disease (both chronic rheumatic diseases).

- suffer from an allergy.
- suffer from infections of the intestines (ulcerative colitis, Crohn's disease).
- are on low-dose aspirin (up to 75 mg daily).
- are a smoker.
- are in the last 6 months of pregnancy.
- If symptoms persist or worsen, consult your doctor.

Medicines such as ibuprofen 200mg Soft Gelatine Capsules may be associated with a small increase in risk of heart attack or stroke in people with pre-existing heart or blood disorder or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment (10 days).

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.

If you are taking any of the following medicines, please see your doctor before taking the capsules:

- any other painkillers (aspirin or other NSAIDs). Do not take this medicine if you are taking aspirin at doses of above 75 mg daily. If you are on low-dose aspirin (up to 75 mg daily) speak to your doctor or pharmacist before you take Ibuprofen 200mg Soft Gelatine Capsules.
- regular medication for high blood pressure (antihypertensive) or diabetes; these include ACE inhibitors such as captopril, beta-blockers such as atenolol, or angiotensin-receptor antagonists such as losartan.
- blood thinning medicines (anticoagulants); such as aspirin/ acetylsalicylic acid, warfarin, clopidogrel.
- corticosteroids (anti-inflammatories) which can increase the risk of side effects in the stomach including bleeding.
- antidepressant agents (prescription of thrombotic or cardiovascular and cardiovascular disease);
- sodium valproate (anticonvulsant) and lithium (for treatment of depression, bipolar disease and mania).
- corticosteroids (treatment of heart failure and cardiac arrhythmia)
- methotrexate (anti-cancer and immunosuppression).
- zidovudine (HIV/AIDS infection).
- cyclosporine (to prevent rejection after organ transplant).
- mifepristone (emergency contraception).
- tacrolimus (to prevent rejection after organ transplant, treatment of skin diseases).

Pregnancy and breast-feeding

Ask your doctor or pharmacist before taking this medicine if you are in the first 6 months of pregnancy. DO NOT TAKE THE CAPSULES IF YOU ARE IN THE LAST 3 MONTHS OF PREGNANCY.

Ask your doctor or pharmacist before taking any medicine if you are breast-feeding.
UKPAR Ibuprofen 200mg Soft Gelatine Capsules
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Female fertility
Ibuprofen 200mg Soft Gelatine Capsules belong to a group of medicines which may impair fertility in women. This effect is reversible on stopping the medicine. It is unlikely that Ibuprofen 200mg Soft Gelatine Capsules, when used occasionally, will affect your chances of becoming pregnant. However, tell your doctor before taking this medicine if you have problems becoming pregnant.

Driving and using machines
Ibuprofen 200mg Soft Gelatine Capsules are unlikely to have any effect on your ability to drive or use machines.

Important information about some of the ingredients of Ibuprofen 200mg Soft Gelatine Capsules
These capsules contain:
- sodium
  - 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 200mg SOFT GELATINE CAPSULES
Swallow the capsules whole with water. Do not chew.

Adults, the elderly and children over 12 years:
Take one or two capsules (200mg – 400mg), up to three times a day as required.
Leave at least 4 hours between doses and do not take more than 6 capsules in 24 hours.

This medicine is intended for short-term use only. You should take the lowest dose for the shortest time necessary to relieve your symptoms. Do not take this medicine for longer than 10 days unless your doctor tells you to.

If symptoms persist or worsen consult your doctor.

Not suitable for children under 12 years.

If you take more Ibuprofen 200mg Soft Gelatine Capsules than you should
Problem in overdosage are rare, but if you accidentally take more than the recommended dose contact your doctor immediately.

The following symptoms of overdose can occur:
- nausea, vomiting, stomach ache or, rarely, diarrhoea
- Other less frequently occurring symptoms of overdose are:
- ringing in the ears, headache, bleeding of the stomach and intestines, affects of the central nervous system, convulsions, increased concentration of oral water products in the blood (unpredictable reactions), prolonged duration of the bleed, kidney failure, liver damage or worsening of asthma.

If you forget to take Ibuprofen 200mg Soft Gelatine Capsules
Take as soon as you remember. Do not take a double dose to make up for a forgotten dose.

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

4. POSSIBLE SIDE EFFECTS
Like most medicines, Ibuprofen 200mg Soft Gelatine Capsules 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 stools (bowel motions)
- pass black tarry stools
- vomit any blood or dark particles that look like coffee grounds
- difficulty in breathing, unexplained wheezing, worsening of existing asthma
- other allergic type reactions (e.g. swelling of the face or throat, low blood pressure, fast heart rate)

Stop taking the medicine and tell your doctor if you experience any of the following side effects, or anything unusual happens:
- indigestion or heartburn
- abdominal pain (pain in your stomach) or other abnormal stomach symptoms.
- a skin rash (which may be severe), itchy skin or blisters

Medicine such as Ibuprofen 200mg Soft Gelatine Capsules may be associated with a small increased risk of heart attack (myocardial infarction) or stroke.

This medicine may also cause:
- oedema (fluid retention), high blood pressure (hypertension) and heart failure
- headache
- nausea, diarrhoea, constipation, vomiting and indigestion (indigestion)
- skin peeling
- kidney and liver disorders
- blood disorders. The first signs can be fewer, sore spots, mouth ulcers, ‘flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
- malnourishments such as fever and chills, severe headache, nausea, vomiting and stiff neck (in patients with existing autoimmune disorders such as systemic lupus erythematosus).
- worsening of colds or glaucoma (dilation of the blood).

If any of these side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE IBUPROFEN 200mg SOFT GELATINE CAPSULES
Keep all medicines out of the reach and sight of children.
Do not use these capsules after the expiry date printed on the blister or carton. The expiry date refers to the last day of that month.
Keep the capsules in the original pack.
Do not store above 25°C.
In case of poor storage conditions, this product may deteriorate. If you notice any signs of deterioration of the capsules or change in colour, you should discard the capsules.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Ibuprofen 200mg Soft Gelatine Capsules contains
The active ingredient is: Ibuprofen 200mg.
The other ingredients are: magnesium hydroxide, gelatin, soyaflour (E460), purified water, Opadixyl W white W-799-1011 (Collodion NDI 3711, hypromellose, pregelatinised starch). (see also end of Section 2 “Important information about some of the ingredients of Ibuprofen 200mg Soft Gelatine Capsules”.

What Ibuprofen 200mg Soft Gelatine Capsules look like and contents of the pack
Each Ibuprofen 200mg Soft Gelatine Capsule is an oval clear capsule printed in white with a logo.
This product is available in packs of 4, 10 and 16 capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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Ibuprofen 200mg
4 Soft Gelatine Capsules
For the relief of headaches, migraine, backache, period pain, dental pain, neuralgia, muscular pain, rheumatic pain, cold and flu symptoms and feverishness.
Do not store above 25°C. Store in the original pack.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Speak to a pharmacist or your doctor before taking this product 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 in the first 6 months of pregnancy
If symptoms persist or worsen, consult your doctor.

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Soft Gelatine Capsules