

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Boots Pharmaceuticals Ibuprofen and Codeine 200mg / 12.8 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

<u>Active ingredient</u>	<u>mg/tablet</u>
Ibuprofen	200 mg
Codeine Phosphate Hemihydrate	12.8 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film Coated Tablet (Tablet)
White capsule-shaped tablet embossed with ‘I +’

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicine is indicated in patients older than 12 years of age.
For the short term treatment of acute moderate pain which is not considered to be relieved by other analgesics (e.g. paracetamol, ibuprofen or aspirin) alone, such as: rheumatic and muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea.

4.2 Posology and method of administration

For oral administration and short-term use only.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Recommended dosage:

Adults over 18 years: One or two tablets every four to six hours.
Do not take more than 6 tablets in 24 hours.
Leave at least four hours between doses.

Children aged 12 years to 18 years: The recommended dose for children 12 years and older is one or two tablets every 6 hours when necessary up to a maximum of 6 tablets in 24 hours.

Children under 12 years: This medicine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Elderly:

No special dosage modifications are required for elderly patients, unless renal or hepatic function is impaired, in which case dosage should be assessed individually.

Do not take for more than 3 days continuously without medical review.
The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 3 days.

4.3 Contraindications

Hypersensitivity to ibuprofen, codeine 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 upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Severe hepatic failure, renal failure or heart failure (NYHA Class IV) (See section 4.4, special warnings and precautions for use).

Last trimester of pregnancy (See section 4.6 Pregnancy and lactation).

Respiratory depression, chronic constipation.

In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life threatening adverse reactions (see section 4.4).

In women during breastfeeding (see section 4.6).

In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

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 section 4.2, Posology and method of administration and GI and cardiovascular risks below).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal 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 this medicine 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 Undesirable effects).

Renal:

Renal impairment as renal function may further deteriorate (See section 4.3 and Section 4.8)

Hepatic:

Hepatic dysfunction (See section 4.3 and Section 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 studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should be made before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

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 Undesirable effects).

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids, selective serotonin-reuptake inhibitors, anti-platelet agents such as aspirin or anticoagulants such as warfarin. In patients receiving anticoagulant therapy, prothrombin time should be monitored daily for the first few days of combined treatment (see section 4.5 Interactions).

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. This medicine should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Codeine should be used with caution in those with hypotension and/or hypothyroidism. The tablets should be used with caution in patients with raised intracranial pressure or head injury. The effects of CNS depressants (including alcohol) may be potentiated by codeine.

Codeine is a narcotic analgesic. No more than the stated dose of this medicine should be taken. Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped. It is important to consult a doctor if a patient experiences the need to use this product all the time.

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

<u>Population</u>	<u>Prevalence %</u>
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Post operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

The label will state:

Front of pack

- Can cause addiction
- For three days use only

Back of pack

Read the enclosed leaflet before taking this product.

- List of indications as agreed in 4.1 of the SPC
- If you need to take this medicine continuously for more than 3 days you should see your doctor or pharmacist
- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. If you take this medicine for headaches for more than 3 days it can make them worse

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

Speak to a pharmacist or your doctor before taking if you:

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

If symptoms persist or worsen, consult your doctor.

The leaflet (or combined label/leaflet) will state:

'Headlines' section (to be prominently displayed)

- This medicine can be used for.....(indications)
- You should only take this product for a maximum of 3 days at a time. If you need to take it for a longer than 3 days you should see your doctor or pharmacist for advice
- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. This can give you withdrawal symptoms from the medicine when you stop taking it
- If you take this medicine for headaches for more than 3 days it can make them worse

'What this medicine is for' section

- Succinct description of the indications from 4.1 of the SPC

'Before you take this medicine' section

- This medicine contains codeine which can cause addiction if you take it continuously for more than 3 days. This can give you withdrawal symptoms from the medicine when you stop taking it
- If you take a painkiller for headaches for more than 3 days it can make them worse

'How to take this medicine' section

- Do not take for more than 3 days. If you need to use this medicine for more than 3 days you must speak to your doctor or pharmacist
- This medicine contains codeine and can cause addiction if you take it continuously for more than 3 days. When you stop taking it you may get withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms

'Possible side effects' section

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: <http://www.hpra.ie/>; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

'How do I know if I am addicted?' section

If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to your doctor:

- You need to take the medicine for longer periods of time
- You need to take more than the recommended amount
- When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should not be used in combination with:

Acetylsalicylic acid (aspirin):

Unless low-dose aspirin (not above 75mg daily) has been advised by a doctor, Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (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).

Codeine:

Interacts with monoamine oxidase inhibitors. Therefore caution should be exercised in patients taking monoamine oxidase inhibitors.

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 Special warnings).

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.

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 haematoma 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 Fertility, pregnancy and lactation

Female fertility:

See section 4.4 regarding female fertility

Pregnancy:

Whilst no teratogenic effects have been demonstrated in animal experiments, the use of this medicine 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 Contraindications).

Lactation:

Codeine

Codeine should not be used during breastfeeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Ibuprofen

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

4.7 Effects on ability to drive and use machines

Patients may become dizzy or sedated with this medicine. If affected, patients should not drive or operate machinery.

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)

Ibuprofen:

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, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis.

Exacerbation of colitis and Crohn's disease (see section 4.4).

Nervous System:

Uncommon: Headache, blurred vision

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 studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4 Special warnings and precautions for use)

Codeine

Side effects to codeine include constipation, respiratory depression, cough suppression, nausea and drowsiness.

Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

Prolonged use of a pain killer for headache can make them worse.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: <http://www.hpra.ie/>; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period, may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Symptoms of overdose with ibuprofen include;

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as 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

Symptoms of overdose with codeine include;

Nausea and vomiting are prominent features. Respiratory depression, excitability, convulsions, hypotension and loss of consciousness may occur with large codeine overdose.

The stomach should be emptied. If severe CNS depression has occurred, artificial respiration, oxygen and parenteral naloxone may be needed. Imbalance in electrolyte levels should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics, has been shown to be effective in acute nociceptive pain.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 hours before or within 30 minutes after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

The elimination half-life of both ibuprofen and codeine is approximately three hours, and both drugs are given three to four times daily. The combination of the two drugs is therefore appropriate from a pharmacokinetic viewpoint; the tablet exhibits normal release characteristics for both active substances.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Cellulose, Microcrystalline
Hypromellose
Sodium Starch Glycolate (Type A)
Maize Starch, Pregelatinised

Film Coat:

Hypromellose
Titanium dioxide (E171)

Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

White 250 micron PVC/60gsm PVdC/20 micron hard temper aluminium foil.

Pack sizes: 6, 8, 10, 12, 14, 16, 18, 20, 24 (max otc pack IE), 28, 30, 32 (max otc pack UK)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

The Boots Company PLC
1 Thane Road West
Nottingham
NG2 3AA
United Kingdom
Trading as BCM

8 MARKETING AUTHORISATION NUMBER

PA004/066/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th December 2010

10 DATE OF REVISION OF THE TEXT

June 2016