

Public Assessment Report

Decentralised Procedure

Ibuprofen and Codeine 200mg/12.8mg film-coated tablets

Procedure No: UK/H/2628/001/DC
UK Licence No: PL 00014/0662

The Boots Company PLC

LAY SUMMARY

On 08 September 2010, Ireland and the UK agreed to grant a Marketing Authorisation to The Boots Company PLC for the medicinal product Ibuprofen and Codeine 200mg/12.8mg film-coated tablets (PL 00014/0662; UK/H/2628/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 03 November 2010.

This is a pharmacy (P) medicine that is used for the short-term treatment of acute moderate pain such as headaches, rheumatic and muscular pain, backache, migraine, period pain, dental pain and neuralgia that is not relieved by aspirin, ibuprofen or paracetamol alone.

This medicine contains the active ingredients ibuprofen and codeine phosphate hemihydrate. These belong to a group of medicines called analgesics which act to relieve pain. Ibuprofen is also a non-steroidal anti-inflammatory medicine (NSAID) and acts to reduce swelling

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 4
Module 2: Summary of Product Characteristics	Page 5
Module 3: Product Information Leaflet	Page 14
Module 4: Labelling	Page 19
Module 5: Scientific Discussion	Page 26
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6	Steps taken after initial procedure

Module 1

Product Name	Ibuprofen and Codeine 200mg/12.8mg film-coated tablets
Type of Application	Generic, Article 10.1
Active Substances	Ibuprofen Codeine phosphate hemihydrate
Pharmacotherapeutic classification (ATC code)	Ibuprofen combinations (M01A E51)
Form	Film-coated Tablet
Strength	200mg/12.8mg
MA Holder	The Boots Company PLC, 1 Thane Road West, Nottingham, NG2 3AA, UK
Reference Member State (RMS)	UK
Concerned Member State (CMS)	Ireland
Procedure Number	UK/H/2628/001/DC
Timetable	Day 210 – 08 September 2010

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen and Codeine 200mg/12.8mg 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**

For the short term treatment of acute moderate pain which is not relieved by 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.

Recommended dosage:

Adults and children over 12 years: One or two tablets every four to six hours.

Children under 12 years: Not recommended.

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 more than 6 tablets in 24 hours.

Leave at least four hours between doses.

Do not take for more than 3 days continuously without medical review.

The minimum effective dose should be used for the shortest time necessary to relieve symptoms. 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 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 (See section 4.4, special warnings and precautions for use).

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

Hypersensitivity to codeine, respiratory depression, chronic constipation.

Use of codeine containing products is contraindicated in mothers who are breastfeeding unless prescribed by a doctor.

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 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 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. ≤ 1200 mg 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 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, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (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.

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

- Some people may have side effects when taking this medicine. If you have any unwanted side effects you should seek advice from your doctor, pharmacist or other healthcare professional. Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side-effects via the internet at www.yellowcard.gov.uk; alternatively you can call Freephone 0800 100 3352 (available between 10am-2pm Monday-Friday) or fill in a paper form available from your local pharmacy

'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:**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).

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.

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 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 Pregnancy and lactationFemale 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:*Ibuprofen*

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

Codeine

Codeine is excreted in breast milk. In nursing mothers who are ultra-rapid metabolisers of codeine, higher than expected serum and breast milk morphine levels can occur. Morphine toxicity in babies can cause excessive somnolence, hypotonia, miosis and difficulty breastfeeding or breathing. In severe cases respiratory depression and death can occur. In severe cases, naloxone may be appropriate to reverse the effects. The lowest effective dose should be used, for the shortest possible time.

Nursing mothers should be informed about carefully monitoring the infant during treatment for any signs and/or symptoms of morphine toxicity such as increased drowsiness or sedation, difficulty breastfeeding, breathing difficulties, miosis and decreased tone, and seeking immediate medical care if such symptoms or signs are noticed. The nursing mother should be informed about monitoring for signs and symptoms of maternal opioid toxicity as well. Should such signs/symptoms be noted in mother or baby, the mother should immediately stop taking all codeine-containing products and seek medical advice.

Codeine-containing products must not be used while breastfeeding unless prescribed by a doctor.

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 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).

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.

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 narcotic analgesic acting on central opiate receptors, although its pharmacological effects are thought to be due largely to its biotransformation to morphine. The combination of a well tolerated peripheral analgesic with a centrally acting analgesic provides optimum pain relief with a lower potential for producing side-effects.

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 400 mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81 mg), 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

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

The Boots Company PLC
1 Thane Road west
Nottingham.
NG2 3AA
Trading as BCM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00014/0662

- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
03/11/2010
- 10 DATE OF REVISION OF THE TEXT**
03/11/2010



Information for the user

Ibuprofen and Codeine 200 mg/12.8 mg Tablets

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription to treat minor conditions. However, you still need to take it carefully to get the best results from it.

- This medicine can only be used for the short term treatment of acute moderate pain such as headaches, rheumatic and muscular pain, backache, migraine, period pain, dental pain and neuralgia that is not relieved by aspirin, ibuprofen or paracetamol alone
- This medicine should only be taken when necessary
- **You should only take this product for a maximum of 3 days** at a time. If you need to take it for 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
- Keep this leaflet, you may need to read it again
- Ask your pharmacist if you need more information or advice

What this medicine is for

This medicine contains Ibuprofen and Codeine which belong to a group of medicines called analgesics which act to relieve pain. Ibuprofen, a non-steroidal anti-inflammatory medicine (NSAID), also acts to reduce swelling (inflammation).

It can be used for the short term treatment of acute moderate pain such as headaches, rheumatic and muscular pain, backache, migraine, period pain, dental pain and neuralgia that is not relieved by aspirin, ibuprofen or paracetamol alone.

Before you take this medicine

- **This medicine contains codeine which can cause addiction** (physiological and psychological dependence) if you take it continuously for more than 3 days. This can give you withdrawal symptoms from the medicine (such as restlessness and irritability) when you stop taking it. If you find you need to take this medicine all the time, it is important to talk to your doctor
 - **If you take a painkiller for headaches for more than 3 days** it can make them worse
- This medicine can be taken by adults and children of 12 years and over. However, some people should not take this medicine or should seek the advice of their pharmacist or doctor first.

Do not take:

- **If you have a stomach ulcer, perforation or bleeding**, or have had one twice or more in the past
- **If you have had perforation or a bleeding stomach** after taking a non-steroidal anti-inflammatory medicine (you may have been sick and it contained blood or dark particles that look like coffee grounds, passed blood in your stools or passed black tarry stools)
- **If you are allergic** to ibuprofen, codeine, or any other ingredients of the product, aspirin or other non-steroidal anti-inflammatory medicines (you have ever had asthma, runny nose, itchy skin or swelling of the lips, face or throat after taking these medicines)
- **If you are taking aspirin with a daily dose above 75 mg**, or other non-steroidal anti-inflammatory medicines
- **If you have severe heart, kidney or liver failure**
- **If you have difficulty breathing** or breathing problems
- **If you have constipation** on a regular basis or are continually constipated

- **If you are pregnant**, and in the last 3 months of pregnancy
- **If you are breastfeeding**, unless your doctor tells you to

! Talk to your pharmacist or doctor:

- If you have asthma, a history of asthma or other allergic disease, bowel problems or Crohn's disease
- If you have other kidney, heart or liver problems (see "Do not take")
- If you have a connective tissue disorder such as SLE (Systemic Lupus Erythematosus)
- If you have low blood pressure or an underactive thyroid
- If you have a head injury or a condition where there is raised pressure in the head
- If you are taking monoamine oxidase inhibitors (for depression), or have taken them in the last 14 days
- If you are elderly – you may get more side effects (see back of leaflet)
- If you are taking any other painkillers or receiving regular treatment from your doctor
- If you have had a stroke, or have heart problems, high blood pressure, diabetes, high cholesterol, or you smoke – see '**Risk of heart attack or stroke**' below
- If you are pregnant, and in the first 6 months of pregnancy

Other important information

Risk of heart attack or stroke: Ibuprofen may increase the risk if you take large amounts for a long time. The risk is small. Take the lowest amount for the shortest possible time to reduce this risk.

Pregnancy: During the last 3 months of pregnancy do not take this medicine. During the first 6 months of pregnancy talk to your pharmacist or doctor.

Breastfeeding: If breastfeeding do not take this medicine, unless your doctor tells you to.

Women of childbearing age: If you take this medicine, it may reduce your ability to become pregnant. This effect will be reversed when you stop taking the medicine.

Do not drink alcohol (wine, beer, spirits) whilst taking this medicine. Alcohol may make you feel more drowsy.

Driving and using machines: This medicine may cause drowsiness, dizziness or blurred vision. You should not drive or use machines until you are sure you are not affected.

If you take other medicines

Before you take these tablets, make sure that you tell your pharmacist about ANY other medicines you might be using at the same time, particularly the following:

- Other painkillers (including NSAIDs)
- Aspirin 75 mg (to prevent heart attacks or strokes) – the protection may be reduced when you take ibuprofen
- Medicines to thin your blood (e.g. warfarin)
- Mifepristone (for termination of pregnancy) – do not take ibuprofen if you have taken mifepristone in the last 12 days
- Water tablets (diuretics), or medicines to treat high blood pressure, medicines for heart problems
- Corticosteroids (used for many conditions such as pain, swelling, allergy, asthma, rheumatism and skin problems)
- Lithium (for bipolar disorder)
- Methotrexate (for cancer, psoriasis, rheumatism, Crohn's disease)
- Zidovudine (for HIV infection)

- Quinolone antibiotics (for infections)
- Medicines for depression (including SSRIs)
- Ciclosporin or tacrolimus (given after transplant surgery, or for psoriasis or rheumatism)

If you are unsure about interactions with any other medicines, talk to your pharmacist. This includes medicines prescribed by your doctor and medicine you have bought for yourself, including herbal and homeopathic remedies.

✓ How to take this medicine

Check the foil is not broken before use. If it is, do not take that tablet.

Age	How many to take	How often to take them
Adults and children of 12 years and over	One or two	Every 4 to 6 hours, if you need to. Don't take more than 6 tablets in 24 hours.
Take the lowest amount for the shortest possible time to relieve your symptoms		

Swallow each tablet with water.

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.

Do not give to children under 12 years.

Do not take more than the amount recommended above.

If your symptoms worsen at any time, or do not go away within 3 days, you must speak to your doctor or pharmacist.

! If you take too many tablets: Talk to a doctor straight away. Take your medicine and this leaflet with you.

Possible withdrawal effects when stopping treatment

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

Most people will not have problems, but some people may have side effects when taking this medicine. If you are elderly you may be more likely to have some of these side effects.

If you have any unwanted side effects you should seek advice from your doctor, pharmacist or other healthcare professional.

Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side effects via the internet at www.yellowcard.gov.uk; alternatively you can call Freephone 0800 100 3352 (available between 10 am - 2 pm Monday-Friday) or fill in a paper form available from your local pharmacy.

! If you get any of these serious side effects, stop taking the tablets. See a doctor at once:

- You are sick and it contains blood or dark particles that look like coffee grounds
- Pass blood in your stools or pass black tarry stools
- Stomach problems including pain, indigestion or heartburn
- Allergic reactions such as itchy, red, raised skin rash (which can sometimes be severe and include peeling and blistering of the skin), swelling of the face, tongue, neck or throat, worsening of asthma, difficulty in breathing, fast heart rate, feeling faint or dizzy
- Meningitis (e.g. stiff neck, fever, disorientation)
- Kidney problems, which may lead to kidney failure (you may feel breathless, very tired or weak, have no appetite, or have swollen ankles)

These other effects are less serious.

If they bother you talk to a pharmacist:

- Feeling sick or being sick
- Headache, blurred vision, drowsiness – do not drive or use machines if you feel drowsy or have blurred vision
- High blood pressure, heart failure (you may be tired, have difficulty breathing or swollen legs)
- Fluid retention, which may cause swelling of the limbs
- Difficulty breathing, problems clearing catarrh or phlegm from the chest
- Rarely, sore mouth, diarrhoea, wind, constipation, yellow skin or eyes, upper abdominal pain, worsening of colitis or Crohn's disease
- Very rarely, tiredness or severe exhaustion, changes in the blood which may cause unusual bruising or unexplained bleeding and an increase in the number of infections that you get (e.g. sore throats, mouth ulcers, flu-like symptoms)
- A small increased risk of heart attack or stroke if you take large amounts for a long time

If any side effect becomes severe, or you notice any side effect not listed here, please tell your pharmacist or doctor.

! How do I know if I am addicted?

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

How to store this medicine

These film-coated tablets do not require any special storage conditions. Keep this medicine in a safe place out of the sight and reach of children, preferably in a locked cupboard.

Use by the date on the foil or end flap of the carton. After this date return any unused product to your nearest pharmacy for safe disposal.

What is in this medicine

Each film-coated tablet contains Codeine Phosphate Hemihydrate 12.8 mg, Ibuprofen 200 mg, which are the active ingredients.

As well as the active ingredients, the film-coated tablets also contain microcrystalline cellulose, sodium starch glycolate, pregelatinised maize starch, hypromellose. The tablet coating contains hypromellose, titanium dioxide (E171), talc.

The pack contains 16 or 32 white capsule-shaped tablets embossed with H+.

Who makes this medicine

Manufactured for the Marketing Authorisation holder The Boots Company PLC Nottingham NG2 3AA, UK by Custom Pharmaceuticals Ltd Conway Street Hove East Sussex BN3 3LW, UK
Leaflet prepared September 2010

If you would like any further information about this medicine, please contact The Boots Company PLC Nottingham NG2 3AA, UK

Other formats

To request a copy of this leaflet in Braille, large print or audio please call free of charge:

0800 198 5000 (UK only)

Please be ready to give the following information:

Product name: Ibuprofen and Codeine 200 mg/12.8 mg Tablets

Reference Number: 00014/0662

This is a service provided by the Royal National Institute of Blind People.

PM/20/358

The following Own Label supplier(Almus) leaflet for Ibuprofen and Codeine 200mg/12.8mg film-coated tablets is included as a representative leaflet. The other leaflets (in Burgopack portrait and Burgopack landscape) for the Almus Own Label supplier are consistent with this leaflet:



Information for the user

Ibuprofen and Codeine 200 mg/12.8 mg Tablets

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription to treat minor conditions. However, you still need to take it carefully to get the best results from it.

- This medicine can only be used for the short term treatment of acute moderate pain such as headaches, rheumatic and muscular pain, backache, migraine, period pain, dental pain and neuralgia that is not relieved by aspirin, ibuprofen or paracetamol alone
- This medicine should only be taken when necessary
- **You should only take this product for a maximum of 3 days** at a time. If you need to take it for 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
- Keep this leaflet, you may need to read it again
- Ask your pharmacist if you need more information or advice

What this medicine is for

This medicine contains Ibuprofen and Codeine which belong to a group of medicines called analgesics which act to relieve pain. Ibuprofen, a non-steroidal anti-inflammatory medicine (NSAID), also acts to reduce swelling (inflammation).

It can be used for the short term treatment of acute moderate pain such as headaches, rheumatic and muscular pain, backache, migraine, period pain, dental pain and neuralgia that is not relieved by aspirin, ibuprofen or paracetamol alone.

Before you take this medicine

- **This medicine contains codeine which can cause addiction** (physiological and psychological dependence) if you take it continuously for more than 3 days. This can give you withdrawal symptoms from the medicine (such as restlessness and irritability) when you stop taking it. If you find you need to take this medicine all the time, it is important to talk to your doctor
 - **If you take a painkiller for headaches for more than 3 days** it can make them worse
- This medicine can be taken by adults and children of 12 years and over. However, some people should not take this medicine or should seek the advice of their pharmacist or doctor first.

Do not take:

- **If you have a stomach ulcer, perforation or bleeding**, or have had one twice or more in the past
- **If you have had perforation or a bleeding stomach** after taking a non-steroidal anti-inflammatory medicine (you may have been sick and it contained blood or dark particles that look like coffee grounds, passed blood in your stools or passed black tarry stools)
- **If you are allergic** to ibuprofen, codeine, or any other ingredients of the product, aspirin or other non-steroidal anti-inflammatory medicines (you have ever had asthma, runny nose, itchy skin or swelling of the lips, face or throat after taking these medicines)
- **If you are taking aspirin with a daily dose above 75 mg**, or other non-steroidal anti-inflammatory medicines
- **If you have severe heart, kidney or liver failure**
- **If you have difficulty breathing** or breathing problems
- **If you have constipation** on a regular basis or are continually constipated

- **If you are pregnant**, and in the last 3 months of pregnancy
- **If you are breastfeeding**, unless your doctor tells you to

! Talk to your pharmacist or doctor:

- If you have asthma, a history of asthma or other allergic disease, bowel problems or Crohn's disease
- If you have other kidney, heart or liver problems (see "Do not take")
- If you have a connective tissue disorder such as SLE (Systemic Lupus Erythematosus)
- If you have low blood pressure or an underactive thyroid
- If you have a head injury or a condition where there is raised pressure in the head
- If you are taking monoamine oxidase inhibitors (for depression), or have taken them in the last 14 days
- If you are elderly – you may get more side effects (see back of leaflet)
- If you are taking any other painkillers or receiving regular treatment from your doctor
- If you have had a stroke, or have heart problems, high blood pressure, diabetes, high cholesterol, or you smoke – see '**Risk of heart attack or stroke**' below
- If you are pregnant, and in the first 6 months of pregnancy

Other important information

Risk of heart attack or stroke: Ibuprofen may increase the risk if you take large amounts for a long time. The risk is small. Take the lowest amount for the shortest possible time to reduce this risk.

Pregnancy: During the last 3 months of pregnancy do not take this medicine. During the first 6 months of pregnancy talk to your pharmacist or doctor.

Breastfeeding: If breastfeeding do not take this medicine, unless your doctor tells you to.

Women of childbearing age: If you take this medicine, it may reduce your ability to become pregnant. This effect will be reversed when you stop taking the medicine.

Do not drink alcohol (wine, beer, spirits) whilst taking this medicine. Alcohol may make you feel more drowsy.

Driving and using machines: This medicine may cause drowsiness, dizziness or blurred vision. You should not drive or use machines until you are sure you are not affected.

If you take other medicines

Before you take these tablets, make sure that you tell your pharmacist about ANY other medicines you might be using at the same time, particularly the following:

- Other painkillers (including NSAIDs)
- Aspirin 75 mg (to prevent heart attacks or strokes) – the protection may be reduced when you take ibuprofen
- Medicines to thin your blood (e.g. warfarin)
- Mifepristone (for termination of pregnancy) – do not take ibuprofen if you have taken mifepristone in the last 12 days
- Water tablets (diuretics), or medicines to treat high blood pressure, medicines for heart problems
- Corticosteroids (used for many conditions such as pain, swelling, allergy, asthma, rheumatism and skin problems)
- Lithium (for bipolar disorder)
- Methotrexate (for cancer, psoriasis, rheumatism, Crohn's disease)
- Zidovudine (for HIV infection)

- Quinolone antibiotics (for infections)
- Medicines for depression (including SSRIs)
- Ciclosporin or tacrolimus (given after transplant surgery, or for psoriasis or rheumatism)

If you are unsure about interactions with any other medicines, talk to your pharmacist. This includes medicines prescribed by your doctor and medicine you have bought for yourself, including herbal and homeopathic remedies.

✓ How to take this medicine

Check the foil is not broken before use. If it is, do not take that tablet.

Age	How many to take	How often to take them
Adults and children of 12 years and over	One or two	Every 4 to 6 hours, if you need to. Don't take more than 6 tablets in 24 hours.
Take the lowest amount for the shortest possible time to relieve your symptoms		

Swallow each tablet with water.

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.

Do not give to children under 12 years.

Do not take more than the amount recommended above.

If your symptoms worsen at any time, or do not go away within 3 days, you must speak to your doctor or pharmacist.

! If you take too many tablets: Talk to a doctor straight away. Take your medicine and this leaflet with you.

Possible withdrawal effects when stopping treatment

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

Most people will not have problems, but some people may have side effects when taking this medicine. If you are elderly you may be more likely to have some of these side effects.

If you have any unwanted side effects you should seek advice from your doctor, pharmacist or other healthcare professional.

Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side effects via the internet at www.yellowcard.gov.uk; alternatively you can call Freephone 0800 100 3352 (available between 10 am – 2 pm Monday-Friday) or fill in a paper form available from your local pharmacy.

! If you get any of these serious side effects, stop taking the tablets. See a doctor at once:

- You are sick and it contains blood or dark particles that look like coffee grounds
- Pass blood in your stools or pass black tarry stools
- Stomach problems including pain, indigestion or heartburn
- Allergic reactions such as itchy, red, raised skin rash (which can sometimes be severe and include peeling and blistering of the skin), swelling of the face, tongue, neck or throat, worsening of asthma, difficulty in breathing, fast heart rate, feeling faint or dizzy
- Meningitis (e.g. stiff neck, fever, disorientation)
- Kidney problems, which may lead to kidney failure (you may feel breathless, very tired or weak, have no appetite, or have swollen ankles)

These other effects are less serious.

If they bother you talk to a pharmacist:

- Feeling sick or being sick
- Headache, blurred vision, drowsiness – do not drive or use machines if you feel drowsy or have blurred vision
- High blood pressure, heart failure (you may be tired, have difficulty breathing or swollen legs)
- Fluid retention, which may cause swelling of the limbs
- Difficulty breathing, problems clearing catarrh or phlegm from the chest
- Rarely, sore mouth, diarrhoea, wind, constipation, yellow skin or eyes, upper abdominal pain, worsening of colitis or Crohn's disease
- Very rarely, tiredness or severe exhaustion, changes in the blood which may cause unusual bruising or unexplained bleeding and an increase in the number of infections that you get (e.g. sore throats, mouth ulcers, flu-like symptoms)
- A small increased risk of heart attack or stroke if you take large amounts for a long time

If any side effect becomes severe, or you notice any side effect not listed here, please tell your pharmacist or doctor.

! How do I know if I am addicted?

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

How to store this medicine

These film-coated tablets do not require any special storage conditions. Keep this medicine in a safe place out of the sight and reach of children, preferably in a locked cupboard.

Use by the date on the foil or end flap of the carton. After this date return any unused product to your nearest pharmacy for safe disposal.

What is in this medicine

Each film-coated tablet contains Codeine Phosphate Hemihydrate 12.8 mg, Ibuprofen 200 mg, which are the active ingredients. As well as the active ingredients, the film-coated tablets also contain microcrystalline cellulose, sodium starch glycolate, pregelatinised maize starch, hypromellose. The tablet coating contains hypromellose, titanium dioxide (E171), talc.

The pack contains 16 or 32 white capsule-shaped tablets embossed with I+.

Who makes this medicine

Manufactured for Almus Pharmaceuticals Ltd, Epsom, KT17 1BH by Custom Pharmaceuticals Ltd, Conway Street, Hove, East Sussex, BN3 3LW, UK. MA Holder: BCM, Nottingham, NG2 3AA, UK. Leaflet prepared September 2010. Almus® is a registered trademark

If you would like any further information about this medicine, please contact Almus Pharmaceuticals Ltd, Epsom, KT17 1BH

Other formats

To request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000 (UK only)

Please be ready to give the following information:

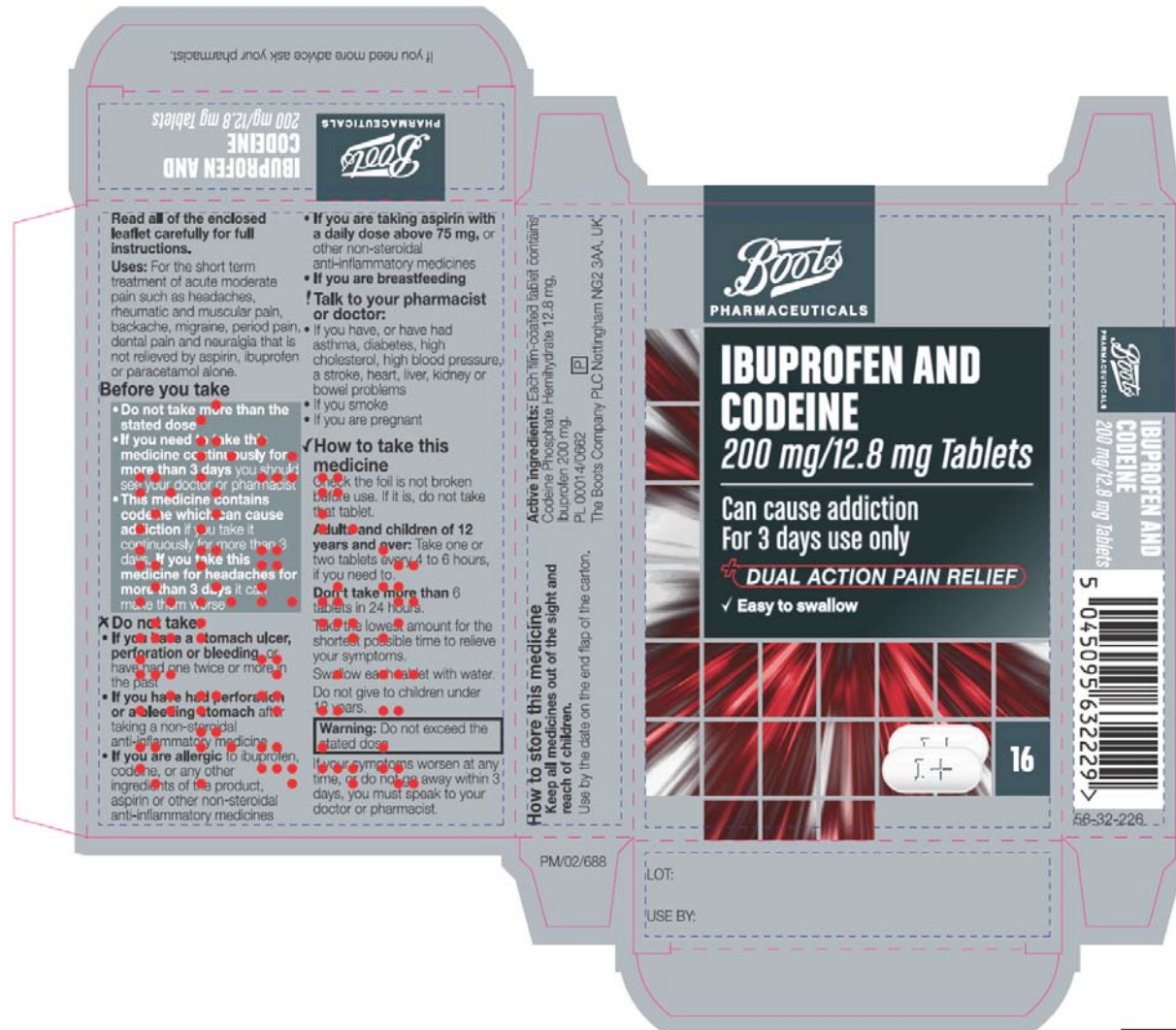
Product name: Almus Ibuprofen and

Codeine 200 mg/12.8 mg Tablets

Reference Number: 00014/0662

This is a service provided by the Royal National Institute of Blind People.

Module 4



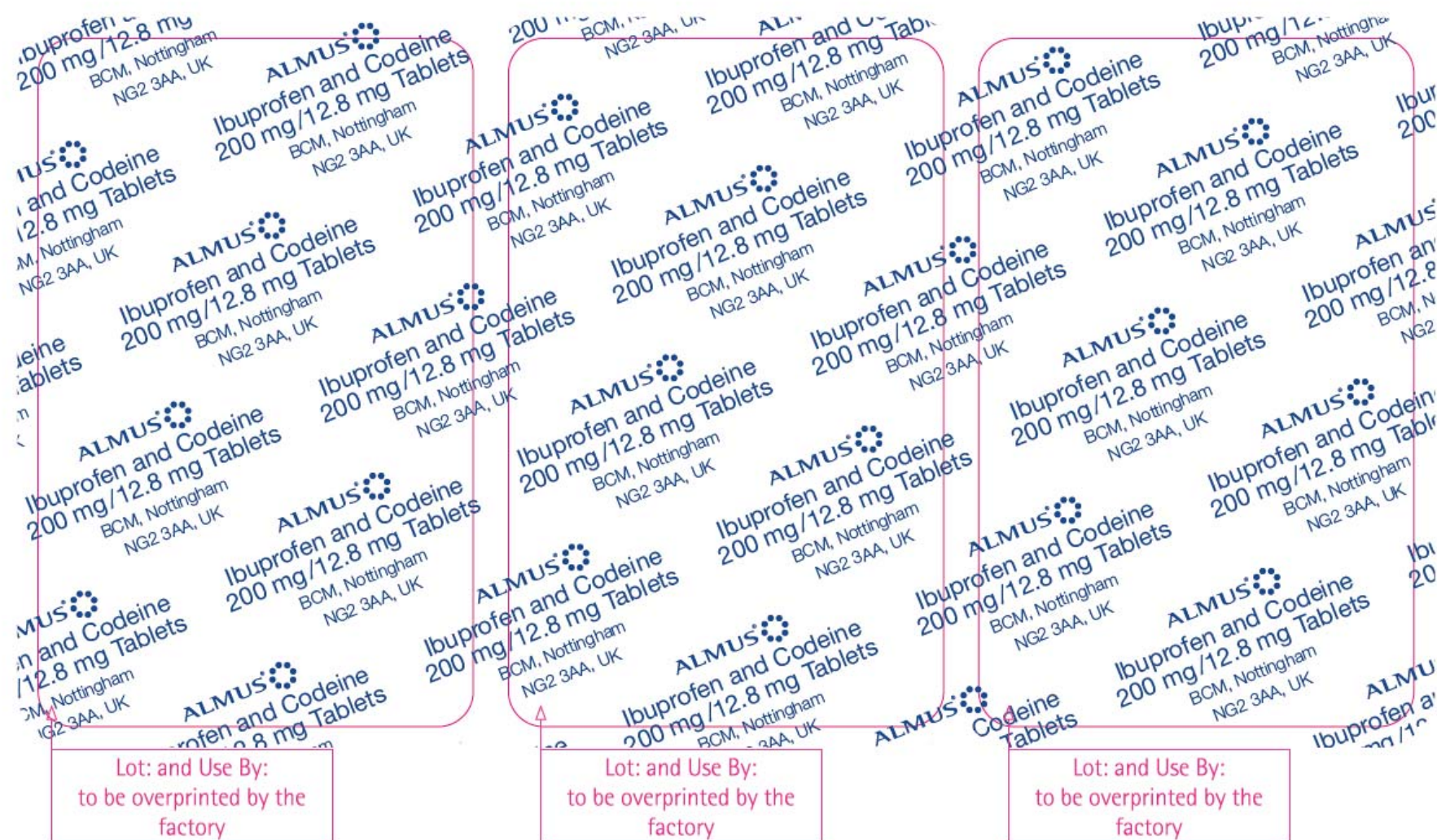




The following Own Label supplier (Almus) labelling for Ibuprofen and Codeine 200mg/12.8mg film-coated tablets is included as representative labelling for the product. The other labelling (in Burgopack portrait and Burgopack landscape) for the Almus Own Label product is consistent with this labelling







Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the application for Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets (PL 00014/0662; UK/H/2628/001/DC) could be approved. The product is a pharmacy (P) medicine used for the short-term treatment of acute, moderate pain (such as rheumatic and muscular pain, backache, migraine, headache, neuralgia, period pain and dental pain), which is not relieved by paracetamol, ibuprofen or aspirin alone.

The application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS).

The application was submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be a generic medicinal product of Nurofen Plus (Crookes Healthcare Limited), which has been approved in the UK since 16 May 1994.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). It is a potent inhibitor of prostaglandin synthesis, via inhibition of cyclo-oxygenase 1 and 2. It exhibits well-established analgesic, anti-inflammatory and antipyretic effects. Codeine, an opiate analgesic, inhibits the release of the pain threshold-lowering neuropeptide, Substance P, from the dorsal horn and peripheral nerve terminals. Some of its analgesic activity may be due to the conversion of a small proportion of the administered dose to morphine. The combination of ibuprofen and codeine is reported to result in improved pain control compared with each active administered as monotherapy.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of originator product that has been licensed for over 10 years.

A single-dose, fasting, bioequivalence study was submitted to support the application. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 08 September 2010. After a subsequent national phase, a licence was granted in the UK to The Boots Company PLC on 03 November 2010.

II. ABOUT THE PRODUCT

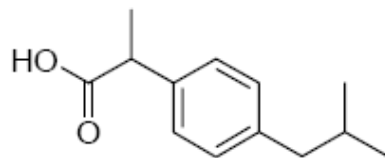
Name of the product in the Reference Member State	Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets
Name(s) of the active substance(s) (INN)	Ibuprofen Codeine phosphate hemihydrate
Pharmacotherapeutic classification (ATC code)	Ibuprofen combinations (M01A E51)
Pharmaceutical form and strength(s)	Film-coated tablets 200 mg/12.8mg
Reference numbers for the Mutual Recognition Procedure	UK/H/2628/001/DC
Reference Member State	United Kingdom
Member State concerned	Ireland
Marketing Authorisation Number	PL 00014/0662
Name and address of the authorisation holder	The Boots Company plc 1 Thane Road West Nottingham NG2 3AA UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE – IBUPROFEN

INN: Ibuprofen
Chemical name: 2-(4-Isobutylphenyl)propionic acid.
Structure:



Molecular formula: $C_{13}H_{18}O_2$
Molecular weight: 206.3
Appearance: A white crystalline powder or colourless crystals. Practically insoluble in water; freely soluble in acetone, in dichloromethane and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides and carbonates.

Ibuprofen is the subject of a European Pharmacopoeia monograph.

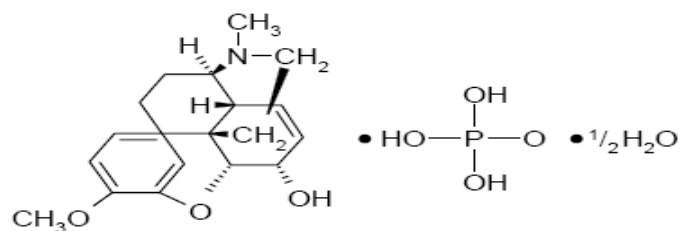
All aspects of the manufacture and control of the active substance ibuprofen are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

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

ACTIVE SUBSTANCE – CODEINE PHOSPHATE HEMIHYDRATE

INN: Codeine phosphate hemihydrate
Chemical name: 7,8-didehydro-4,5 α -epoxy-3-methoxy-17methylmorphinan-6 α -ol phosphate (1:1) (salt) hemihydrate.

Structure:



Molecular formula: $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$
Molecular weight: 406.4
Appearance: White or almost white crystalline powder or small colourless crystals. Freely soluble in water, slightly soluble in alcohol,

Codeine phosphate hemihydrate is the subject of a European Pharmacopoeia monograph.

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

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, hypromellose, sodium starch glycolate (Type A), pregelatinised maize starch, titanium dioxide (E171) and talc. Appropriate justifications for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Certificates of analysis are provided for each excipient showing compliance with their respective monograph/specification.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to manufacture a safe, efficacious product that could be considered a generic medicinal product of the originator product Nurofen Plus (Crooks Healthcare Limited, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

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

In-process controls are appropriate considering the nature of the product and the method of manufacture.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the specification. Certificates of analysis have been provided for all working standards used.

Container-Closure System

The tablets are packaged in white polyvinylchloride/polyvinylidene/aluminium blisters in pack sizes of 6, 8, 10, 12, 14, 16, 18, 20 and 24, (maximum otc ['over the counter'] pack size in Ireland), 28, 30 and 32 (maximum otc ['over the counter'] pack size in the UK). Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size of the product.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials suitable for contact with food.

Stability of the product

Finished product stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with no special storage conditions.

Bioequivalence

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

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

The SmPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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.

MAA form

The MAA form is satisfactory.

Expert report

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

Conclusion

The grant of a Marketing Authorisation is recommended

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen and codeine phosphate hemihydrate are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' non-clinical pharmacology, pharmacokinetics and toxicology.

The Marketing Authorisation Holder has provided an adequate justification for not submitting an Environmental Risk Assessment.

The grant of a Marketing Authorisation is recommended.

III.3 CLINICAL ASPECTS

Pharmacokinetics

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

A randomised, single-dose open-label, two-period, crossover study comparing the rate and extent of absorption of ibuprofen and codeine from the test product Ibuprofen and Codeine 200mg/12.8mg film-coated tablets (The Boots Company PLC, UK) and the reference product Nurofen Plus (Crookes Healthcare Limited, UK) in healthy male and female subjects under fasting conditions.

Subjects were dosed with either treatment (two tablets) after at least a 10-hour fast. Blood sampling was performed pre- and up to 12 hours post dose in each treatment period. The washout period between the two treatment arms was at least 72 hours. Pharmacokinetic parameters were measured from plasma and statistically analysed. The pharmacokinetic results (presented as ratios and 90% confidence intervals) are presented below:

Table 1
Pharmacokinetic parameters (arithmetic mean $\pm$ standard deviation, ratio and confidence intervals [CI]) for ibuprofen

Treatment	AUC _{0-t} $\mu\text{g/ml/h}$	AUC _{0-∞} $\mu\text{g/ml/h}$	C _{max} $\mu\text{g/ml}$
Test	119.91 $\pm$ 30.97	122.95 $\pm$ 31.62	36.07 $\pm$ 7.68
Reference	125.16 $\pm$ 28.96	128.33 $\pm$ 29.62	39.47 $\pm$ 8.36
*Ratio (90% CI)	95.39% (90.85-100.15)	95.42% (90.93-100.12)	91.40% (85.96-97.19)

AUC_{0- ∞} area under the plasma concentration-time curve from time zero to infinity

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours

C_{max} maximum plasma concentration

*In-transformed values

Table 2
Pharmacokinetic parameters (arithmetic mean $\pm$ standard deviation, ratio and confidence intervals [CI]) for codeine

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml
Test	206.82 $\pm$ 63.30	234.60 $\pm$ 70.34	65.08 $\pm$ 19.30
Reference	226.09 $\pm$ 70.72	251.62 $\pm$ 75.09	76.42 $\pm$ 27.55
*Ratio (90% CI)	92.17% (86.58-98.13)	93.78 (88.68-99.17)	87.02 (80.10-94.53)

AUC_{0- ∞} area under the plasma concentration-time curve from time zero to infinity

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours

C_{max} maximum plasma concentration

*In-transformed values

The 90% confidence intervals of the log-transformed parameters AUC_{0-t} and C_{max}, for both ibuprofen and codeine, lie within the accepted limits. Thus, the data support the claim that the test product is bioequivalent to the reference product.

Efficacy

No new data on the efficacy have been submitted and none are required for this type of application.

Safety

No new or unexpected safety issues were raised by the bioequivalence data.

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.

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

The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

Clinical 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.

Conclusion

The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets 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 this application..

EFFICACY

Bioequivalence has been demonstrated between the applicant's Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets and the reference product Nurofen Plus (Crookes Healthcare Limited, UK).

SAFETY

The safety profile of ibuprofen and codeine phosphate hemihydrate, both individually and in combination, is well-known. No new or unexpected safety concerns were raised during the bioequivalence study.

PRODUCT LITERATURE

The approved SmPC is satisfactory and consistent with that for the reference product.

The final PIL and labelling text are satisfactory and consistent with those for the reference product and with the approved SmPC.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that this product is a generic medicinal product of the reference product Nurofen Plus Tablets (Crookes Healthcare Limited, UK). Extensive clinical experience with ibuprofen and codeine phosphate hemihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome