SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient	mg/tablet
Ibuprofen	200 mg
Codeine Phosphate Hemihydrate	12.8 mg

Excipient with known effect	mg/tablet
Sodium Starch Glycolate (Type A)	45 mg (11 mg Sodium)

For the 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 (which contains codeine) 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.

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

Recommended dosage:
Adults, the elderly and children over 12 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 under 12 years: This medicine (which contains codeine) 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 more than 6 tablets in 24 hours.
Leave at least four hours between doses and do not take more than 1200mg ibuprofen in any 24-hour period.

Treatment goals and discontinuation
Before initiating treatment with Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets, treatment duration and treatment goals, should be agreed together with the patient, in accordance with pain management guidelines.

Duration of treatment
Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets should not be used longer than necessary.

The duration of treatment should be as short as possible and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a healthcare professional.

For short term use only. Codeine should be used at the lowest effective dose for the shortest period of 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, 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 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).

In women during breastfeeding (see section 4.6).

In patients with respiratory depression, chronic constipation or raised intracranial pressure.

Concomitant treatment with Monoamine Oxidase Inhibitors (MAOIs) or within 14 days of stopping treatment (see section 4.5).

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

4.4 Special warnings and precautions for use

Do not take Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets concurrently with any other codeine containing compounds.

Ibuprofen

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 (see section 4.2).

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 due to 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 4.8).

There is a risk of renal impairment in dehydrated children and adolescents.

The risk of renal impairment is increased in children, adolescents and elderly, particularly in volume depleted states (e.g. dehydration, which may be due to nausea and vomiting, hypotension, sepsis) and hypovolaemia related to other known effects (e.g. GI haemorrhage).

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses. This risk is increased with the use of codeine/ibuprofen as patients may become dependent on the codeine component (see warning on Opioid use disorder, section 4.8 and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

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 myocardial infarction.

Cases of Kounis syndrome have been reported in patients treated with ibuprofen. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction-associated with constriction of coronary arteries and potentially leading to 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 effects:
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.

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, ulceration or bleeding, such as oral corticosteroids, selective serotonin-reuptake inhibitors, anti-platelet agents such as aspirin or anticoagulants such as warfarin (see section 4.5 Interactions).

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

Dermatological:
Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS syndrome), and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month.

If signs and symptoms suggestive of these reactions appear this medicine should be withdrawn immediately and an alternative treatment considered (as appropriate).

Masking of symptoms of underlying infections:
Ibuprofen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When this medicine is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Codeine
Codeine should be used with caution in patients with hypotension, hypothyroidism or head injury. As with other opioids, codeine should be used with caution in patients taking benzodiazepines or other central nervous system (CNS) depressants, including alcohol. The effects of CNS depressants (including alcohol) may be potentiated by codeine.

Caution is advised in the administration of codeine to patients with adrenocortical insufficiency (including Addison's disease), shock, inflammatory or obstructive bowel disorders, acute abdominal conditions (e.g. peptic ulcer), recent gastrointestinal surgery, gallstones, myasthenia gravis, prostatic hypertrophy, a history of peptic ulcer or convulsions and also in patients with a history of drug abuse.

Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults. Codeine should be used with caution in the elderly and debilitated patients as they may be more susceptible to the respiratory depressant effects.

If you are pregnant or are being prescribed medicines by your doctor, seek this advice before taking this product. Care is advised in the administration of this product in patients with severe renal or severe hepatic impairment (hepatic disease).

Hepatobiliary disorders:
Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets should be administered with caution in patients with pancreatitis and diseases of the biliary tract. Caution in patients with history of cholecystectomy as codeine may cause acute pancreatitis in some patients.

Increased sensitivity to pain (hyperalgesia):

As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Sleep-related breathing disorders:
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage.

Tolerance and opioid use disorder (abuse and dependence):
Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets. Repeated use of Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets may result in overdose and/or death.

Serious clinical outcomes, including fatalities, have been reported in association with abuse and dependence with codeine/ibuprofen combinations, particularly when taken for prolonged periods at higher than recommended doses. These have included reports of gastrointestinal perforations, gastrointestinal haemorrhages, severe anaemia, renal failure, renal tubular acidosis and severe hypokalaemia associated with the ibuprofen component.

The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

The patient should be made aware of the risks and signs of OUD as set out in the package leaflet. If these signs occur, patients should contact their physician.

For patients who experience signs and symptoms of OUD, and/or exhibit drug-seeking behaviour, review of concomitant opioids and psycho-active drugs (like benzodiazepines) and consultation with an addiction specialist may be required.

Withdrawal symptoms, such as restlessness and irritability may occur once the drug is stopped.

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:

Population	Prevalence %
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.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

The label will state:
Front of pack
- For three days use only
- Can cause addiction
- Contains opioid
- Prolonged use can cause serious kidney problems

Back of pack
- 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 must speak to your doctor or pharmacist for advice
- 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

The leaflet (or combined label/leaflet) will state:
'Headlines' section (to be prominently displayed)
- This medicine can only 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

Section 1: What Ibuprofen and Codeine 200 mg/12.8 mg Tablets are and what they are used for

- Succinct description of the indications from 4.1 of the SPC

Section 2: 'What you need to know before you take Ibuprofen and Codeine 200 mg/12.8 mg Tablets

- 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

Section 3: How to take Ibuprofen and Codeine 200 mg/12.8 mg Tablets

- Do not take for more than 3 days. Ibuprofen and Codeine Tablets should be used for 3 days only to relieve symptoms. If no effective pain relief is achieved while taking the medicine, you should seek the advice of a healthcare professional
- 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

Section 4: Possible side effects
Some people may have side-effects when taking this medicine.

Reporting of side effects
If you have any unwanted side-effects you should seek advice from your doctor, pharmacist or other healthcare professional. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.go.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. 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 dose
- 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

The following drug-drug interactions are known to occur in association with the ibuprofen active substance in the product:

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, as this may increase the risk of 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).

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. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the coadministration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

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.

The following drug-drug interactions are known to occur in association with the codeine active substance in the product:

Monoamine Oxidase Inhibitors (MAOIs):
MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Moclobemide:
Risk of hypertensive crisis.

Hydroxyzine:
Concurrent use of hydroxyzine (anxiolytics) with Codeine may result in increased analgesia as well as increased CNS depressant, sedative and hypotensive effects.

Central Nervous System Depressants:
The CNS and respiratory depressant and hypotensive effects of codeine are enhanced by depressants of the central nervous system such as alcohol, general anaesthetics and centrally acting muscle relaxants, hypnotics, sedatives including benzodiazepines, tricyclic antidepressants and antipsychotics including phenothiazines.

The concomitant use of Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Diuretics and Anti-hypertensives:
The hypotensive actions of diuretics and anti-hypertensive agents may be potentiated when used concurrently with opioid analgesics.

Antidiarrhoeal and Anti-peristaltic agents:
Concurrent use of Codeine with antidiarrhoeal and anti-peristaltic agents such as loperamide and kaolin may increase the risk of severe constipation.

Antimuscarinics:

Concomitant use of antimuscarinics or medications with muscarinic action, e.g. atropine and some antidepressants may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

Neuromuscular Blocking Agents:
The respiratory depressant effect caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

Quinidine:
Quinidine can inhibit the analgesic effect of Codeine.

Mexiletine:
Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

Metoclopramide and Domperidone:
Codeine may antagonise the gastrointestinal effects of metoclopramide and domperidone.

Cimetidine:
Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.

Naxolone:
Naxolone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.

Interference with laboratory tests:
Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

Serotonergic drugs:
Serotonin syndrome has been reported during concomitant use of serotonergic drugs including triptans, selective serotonin-reuptake inhibitors (SSRIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), and tricyclic antidepressants, with opioids at recommended dosages.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets is contraindicated in the last trimester of pregnancy (See section 4.3 and 5.3).

Whilst no teratogenic effects have been demonstrated in animal experiments, the use of Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets should, if possible, be avoided during the first 6 months of pregnancy.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios

resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the last trimester, ibuprofen is contraindicated as there is there is a risk of premature constriction/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 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.

Female fertility:
See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Patients may become dizzy or sedated with this medicine. Rare side effects may include convulsions, hallucinations, blurred or double vision and orthostatic hypotension (see section 4.8). If affected, patients should not drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:

  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely.

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).

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 painkiller for headache can make them worse.

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

Adverse events which have been associated with Ibuprofen and Codeine are given below, tabulated by System Organ Class (SOC) and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse Events
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders[1].
Immune System Disorders	Uncommon	Hypersensitivity reactions with urticaria and pruritus.
	Very rare	Severe hypersensitivity reactions. Symptoms could be: facial, tongue and throat swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).
Metabolism and Nutrition Disorders	Not known	Decreased appetite. Hypokalaemia[9].
Psychiatric Disorders	Not known	Depression, hallucination, confusional state, dependence[10], mood altered, restlessness, nightmares.
Nervous System Disorders	Uncommon	Headache.
	Very rare	Aseptic meningitis[2].
	Not known	Dizziness, drowsiness, convulsion, intracranial pressure increased, dyskinesia.

Eye Disorders	Not known	Vision blurred, diplopia.
Ear and Labyrinth Disorders	Not known	Vertigo.
Cardiac Disorders	Not known	Cardiac failure, oedema, bradycardia, palpitations[3]. Kounis syndrome.
Vascular Disorders	Not known	Hypertension, orthostatic hypotension[3].
Respiratory, Thoracic and Mediastinal Disorders	Not known	Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea. Respiratory depression, cough suppression.
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia[4].
	Rare	Diarrhoea, flatulence, constipation and vomiting.
	Very rare	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, and haematemesis[5]. Mouth ulceration and gastritis. Exacerbation of ulcerative colitis and Crohn's disease[6].
	Not known	Dry mouth. Pancreatitis.
Hepatobiliary Disorders	Very rare	Liver disorder.
	Not known	Biliary colic. Sphincter of Oddi dysfunction.
Skin and Subcutaneous Tissue Disorders	Uncommon	Various skin rashes.
	Very rare	Severe forms of skin reactions such as bullous reactions, including Stevens-Johnsons Syndrome, erythema multiforme and toxic epidermal necrolysis can occur.
	Not known	Flushing. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP). Photosensitivity reactions.
Musculoskeletal and	Not known	Muscle rigidity.

Connective Tissue Disorders		
Renal and Urinary Disorders	Very rare	Acute renal failure[7].
	Not known	Ureteric colic, dysuria[8]. Renal tubular acidosis[9]. Acute interstitial nephritis (AIN).
General and Administration Site Conditions	Not known	Hypothermia, hyperhidrosis, irritability, fatigue, malaise.
Investigations	Very rare	Haemoglobin decreased.

Description of Selected Adverse Reactions:
[1]Examples include anaemia, leucopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

[2]Single cases have been reported very rarely. The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). 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).

[3]Reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

[4]The most commonly-observed adverse events are gastrointestinal in nature.

[5]Sometimes fatal, particularly in the elderly.

[6]See section 4.4.

[7]Especially in long-term use, associated with increased serum urea and oedema. Also includes papillary necrosis.

[8]Increased frequency, decrease in amount.

[9]Reported in the post-marketing setting typically following prolonged use at higher than recommended doses due to dependence on the codeine component.

[10]Repeated use of Ibuprofen and Codeine 200mg/12.8mg film-coated Tablets can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalized weakness (see section 4.4 and section 4.8).

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;

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

Management
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

Pharmacotherapeutic Group: Opioids in combination with non-opioid analgesics; **ATC Code:** N02AJ08

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 Glycloate (Type A)
Maize Starch, Pregelatinised
Film Coat:
Hypromellose
Titanium dioxide (E171)
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 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.

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

27/03/2026