SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Solpadeine Migraine Ibuprofen & Codeine Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ibuprofen Ph Eur 200 mg
Codeine Phosphate Hemihydrate Ph Eur 12.8 mg

Excipients with known effect

Each Tablet contains:
200mg of Cellactose 80 (which is a one-body compound consisting of lactose monohydrate (73-77%) and cellulose (23-27%).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White, film-coated capsule-shaped tablets with a white core. Embossed with Solpaflex, C+ or Migraine OR plain on both the sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone.

For such conditions as soft tissue injuries, including sprains, strains and musculo-tendonitis, backache, non-serious arthritic and rheumatic conditions, neuralgia, migraine, headache, dental pain and dysmenorrhoea.

4.2 Posology and method of administration

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

1-2 tablets, up to three times a day as required, preferably with or after food.

Leave at least four hours between doses and do not take more than 6 tablets in any 24 hour period.

Paediatric population:
Children and adolescents aged 12 – 18 years:
1 – 2 tablets, up to three times a day as required, preferably with or after food.

Leave at least six hours between doses and do not take more than 6 tablets in any 24 hour period.

Children aged less than 12 years:
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:
Non-steroidal anti-inflammatory drugs (NSAIDs) should be used with particular caution in elderly patients who are prone to adverse events.

Route of Administration:
For oral administration and short-term use only.

Treatment goals and discontinuation

Before initiating treatment with Solpadeine Migraine Ibuprofen & Codeine Tablets, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment in case of prescription, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Patients should not take more than 1200 mg ibuprofen/76.8 mg codeine (6 tablets) in any 24-hour period.

4.3 Contraindications

Solpadeine Migraine Ibuprofen & Codeine Tablets are contraindicated in

individuals with hypersensitivity to ibuprofen, codeine, opioid analgesics or any of the constituents in the product.

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

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

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

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

Pregnancy (see section 4.6).

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

In women during breastfeeding (see section 4.6)

Respiratory depression, chronic constipation.

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

4.4 Special warnings and precautions for use

Patients should be advised to consult their doctor if their headaches become persistent.

Patients taking other medications should consult a doctor prior to taking this product (see section 4.5).

This medicine contains less than 1 mmol sodium (23 mg) per 2 tablets, that is to say essentially ‘sodium- free’.

Solpadeine Migraine Ibuprofen & Codeine Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactosemal absorption should not take this medicine.

Ibuprofen

Undesirable effects may be minimized 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.

Patients should be advised not to take other ibuprofen containing products.

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

Other NSAIDs:
The use Solpadeine Migraine Ibuprofen & Codeine Tablets with concomitant NSAIDs including cyclo- oxygenase-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 ofaseptic meningitis (see section 4.8).

Renal:
Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8). There is a risk of renal impairment in dehydrated children and adolescents.

Severe hypokalemia 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 generalized weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalemia and metabolic acidosis.

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

Cardiovascular and cerebrovascular effects:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.
Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. 1200 mg daily) is associated with an increased risk of myocardial infarction and/or
arterial thrombotic events. Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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 (see section 4.6).

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).

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 cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients (see section 4.8).

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time 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 ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin- reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

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

Dermatological:

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) and acute generalized 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, ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Masking of symptoms of underlying infections:
Solpadeine Migraine Ibuprofen & Codeine Tablets 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, as with other opioids should be used with caution in patients with impaired respiratory function, hypotension, hypothyroidism, head injury or raised intracranial pressure.
Care should be observed in administering the product to any patient, whose condition may be exacerbated by opioids, including the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy, hypothyroidism and those with inflammatory or obstructive bowel disorders, Addison's disease or myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.

Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.

Patients should be advised not to take other codeine containing products.

Hepatobiliary disorders

Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine/ibuprofen has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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 total opioid dosage.

CYP2D6 metabolism:

Codeine is metabolized by the liver enzyme CYP2D6 into morphine. 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 metabolizer 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 summarized 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%-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 metabolize 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.

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 Solpadeine Migraine Ibuprofen & Codeine Tablets. Repeated use of

Solpadeine Migraine Ibuprofen & Codeine 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 Solpadeine Migraine Ibuprofen & Codeine 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 hemorrhages, severe anaemia, renal failure, renal tubular acidosis and severe hypokalemia 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).

Before initiating treatment with Solpadeine Migraine Ibuprofen & Codeine Tablets and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD as well as serious outcomes. If these signs occur, patients should be advised to contact their physician.

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

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Hyperalgesia:

Hyperalgesia may be diagnosed if the patient misuses this product and uses long term opioid therapy and presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. A dose reduction or treatment review may be indicated.

Drug withdrawal syndrome:

Addiction can cause drug withdrawal syndrome upon abrupt cessation of therapy or dose reduction. The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety,

hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this aspect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

This medicine should be avoided 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 cyclo-oxygenase-2 selective inhibitors:* Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

- *Monoamine oxidase inhibitors (MAOIs):* Opiate analgesics may interact with MAOIs and result in serotonin syndrome. Codeine is not considered a serotonin re-uptake inhibitor or to be associated with the risk of serotonin toxicity when used with MAOIs, however caution is advised (see section 4.4). Avoid concomitant use and for two weeks after stopping MAOIs – there is a possible CNS excitation or depression (hypertension or hypotension).

This medicine should be used with caution in combination with:

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

- *Aminoglycosides:* Reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

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

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

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

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

- *Central nervous system depressants:* Codeine may potentiate the depressive effects of central nervous system depressants including alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants and psychotics such as phenothiazines.

- *Domperidone:* Codeine may antagonize effect on gastrointestinal motility.

- *Hypoglycaemic agents:* Inhibition of metabolism of sulfonylurea, prolonged half-life and increased risk of hypoglycaemia.

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

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

- *Metoclopramide:* Codeine may antagonize effect on gastrointestinal motility.

- *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.

- *CYP2C9 inhibitors*: Caution is recommended with potent CYP2C9 inhibitors (such as fluconazole, sulfinpyrazone and voriconazole) that inhibit ibuprofen metabolism, causing a significant increase in plasma

levels.

- *Probenecid and sulfinpyrazone*: May delay excretion of ibuprofen and potentially increase the adverse effects.

- *Digoxin*: Two studies found that ibuprofen raised serum digoxin concentrations, whereas another found no evidence of an interaction. However, it is recommended to monitor for digoxin adverse effects (e.g. bradycardia) and monitor digoxin concentrations if an interaction is suspected. Adjust the digoxin dose accordingly.

- *Medicines with sedative effects:* The concomitant use of opioids with medicines with sedative effects such as benzodiazepines or related drugs, gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma and increased risk for opioid-related death (see section 4.4). Because of these risks, concomitant administration of these medicines with sedative effects should be reserved to patients for whom alternative treatment options are not possible. If a decision is made to prescribe Solpadeine Migraine Ibuprofen & Codeine Tablets concomitantly with medicines with sedative effects, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ibuprofen:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, Solpadeine Migraine Ibuprofen & Codeine Tablets 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 Solpadeine Migraine Ibuprofen & Codeine Tablets for several days from gestational week 20 onward. Solpadeine Migraine Ibuprofen & Codeine Tablets should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

and may expose the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labor.

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

Codeine:

This product should not be used during pregnancy. The safety of codeine during pregnancy has not been established relative to the possible adverse effect on foetal development. Maternal use of codeine during labor may cause respiratory depression in the child.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.
The patient should be advised of the risk of neonatal opioid withdrawal syndrome, and it should be ensured that appropriate treatment will be available.

Lactation

Ibuprofen:

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

Codeine:

Codeine should not be used during breastfeeding (see section 4.3).
At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant.

However, if the patient is an ultra-rapid metabolizer 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

There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment (see section 4.4).

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

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 taking 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 taken to treat a medical or dental problem and
  - You have taken it according to the information provided with the medicine and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

Adverse reactions reported from extensive post-marketing experience are listed below by System Organ Class and frequency. The following convention has been utilized for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated by available data).

Ibuprofen

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

System Organ Class	Frequency	Adverse Events
Gastrointestinal disorders	Uncommon	Abdominal pain, heartburn 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 ulcerative colitis and Crohn's disease (see section 4.4). Oesophagitis, pancreatitis.
Nervous system disorders	Common	Headache, drowsiness, dizziness, hearing disturbance (tinnitus).
	Very rare	Aseptic meningitis
Renal and urinary disorders	Very Rare	Acute renal failure, papillary necrosis, especially in long- term use, associated with increased serum urea and oedema.
	Not known	Ureteric colic, dysuria
	Not known	Renal tubular acidosis*
Hepatobiliary disorders	Very rare	Liver function disorders, especially in long-term treatment. Hepatitis, including jaundice
Blood and lymphatic system disorders	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.
Skin and subcutaneous tissue disorders	Uncommon	Various skin rashes
	Very rare	Severe cutaneous adverse reactions (SCARs) (including Erythema multiforme, exfoliative dermatitis, Stevens- Johnson Syndrome and toxic epidermal necrolysis.
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalized exanthematous pustulosis(AGEP) and photosensitivity reactions.
Immune system disorders	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).
Cardiac disorders	Not known	Oedema, hypertension,cardiac failure and Kounis syndrome.

Infections and infestation	Not known	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).
Metabolism and Nutrition Disorders	Not known	Decreased appetite
	Not known	Hypokalemia*
Vascular disorders	Not known	Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400 mg daily) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).
Respiratory, thoracic and mediastinal disorders	Very rare	Exacerbation of asthma and bronchospasm.

Codeine

Undesirable effects depend on dose and individual patient metabolism.

System Organ Class	Frequency	Adverse Events
Psychiatric disorders	Not known	Drug dependence* can occur after prolonged use of codeine (see section 4.4).
Gastrointestinal disorders	Not known	Constipation, nausea, vomiting, dyspepsia, dry mouth, pancreatitis and acute pancreatitis in patients with a history of cholecystectomy (see section 4.4).
Nervous system disorders	Not known	Dizziness, worsening of headache with prolonged use, drowsiness.
Hepatobiliary disorders	Not known	Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorder	Not known	Pruritus, sweating.
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome
Renal and urinary disorders	Not known	Difficulty with micturition

Description of Selected Adverse Reactions:

*Renal tubular acidosis and hypokalemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses due to dependence on the codeine component.

**Drug dependence
Repeated use of this medicine 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 of time may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Ibuprofen

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, hypotension and respiratory depression, 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 hypokalemia 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.

Codeine

The effects in over dosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms:

An overdose of codeine is characterized, in the first phase, by nausea and vomiting. An acute depression of the respiratory center can cause cyanosis, slower breathing, drowsiness, ataxia and, more rarely, pulmonary oedema. Respiratory pauses, miosis, convulsion, collapse and urine retention as well as signs of histamine release have been observed as well. Hypotension and tachycardia are possible but unlikely.

Management:

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life, so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, nonsteroids, propionic acid derivatives.

ATC code: M01AE51.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin on the

formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

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 such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Ibuprofen

Absorption

Ibuprofen is rapidly absorbed following administration

Distribution

Ibuprofen is distributed throughout the whole body.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1-2 hours. These times may vary with different dosage forms.
Ibuprofen is extensively bound to plasma protein (90 to 99%). The half-life of ibuprofen is about 2 hours.

Biotransformation

About 90% of ibuprofen is metabolised by the liver to two major metabolites (hydroxy– and carboxy ibuprofen) neither of which has any anti-inflammatory or analgesic activity.

Elimination

The excretion is rapid and complete via kidneys.
In limited studies, ibuprofen appears in the breast milk in very low concentrations.

Codeine

Absorption

Codeine phosphate is well absorbed from the gastrointestinal tract following oral administration. Peak plasma concentrations occur about one-hour post-dose.

Distribution

Codeine is widely distributed throughout most body fluids and exhibits low plasma protein binding with a relative bioavailability (versus parenteral administration) of about 75%.

Biotransformation
The half-life in plasma is about 2.5 - 3 hours, whilst its analgesic effect occurs from 15 minutes up to 4 - 6 hours after oral administration.

Elimination
Codeine and its metabolites are excreted almost entirely via the kidneys (approximately 90%)

Combination of ibuprofen and codeine
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

Both ibuprofen and codeine are well established analgesics with well-documented preclinical safety profiles.

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Hydrogenated vegetable oil
Sodium starch glycollate
Colloidal silicon dioxide
Cellactose 80
Hydroxypropyl methyl cellulose
Polyethylene glycol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years

6.4 Special precautions for storage

Store this medicine in a safe and secure storage space, where other people cannot access it. It can cause serious harm and be fatal to people when it has not been intended for them.

6.5 Nature and contents of container

White opaque polyvinyl chloride (250 m)/aluminium foil (20 m) blister packs containing 4, 6, 12 or 24 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Galpharm Healthcare Limited,
Wrafton,
Braunton,
Devon,
EX33 2DL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16028/0184

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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