SUMMARY OF PRODUCT CHARACTERISTICS

CIPYNE® Capsules

1. Name of the medicinal product

CIPYNE® Capsules

2. Qualitative and quantitative composition

Each capsule contains: Codeine Phosphate 10mg, Ibuprofen 200mg, Paracetamol 250mg

For full list of excipients, see section 6.1

3. Pharmaceutical form

Size '0' hard gelatin capsule with a green cap printed 'CIP' and a red body printed 'YNE' in black ink.

4. Clinical particulars

4.1 Therapeutic indications

For the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. This product is especially suitable for pain which requires stronger analgesia than ibuprofen, codeine or paracetamol alone.

4.2 Posology and method of administration

Not recommended for children under twelve years of age.

Adults: One to two capsules four hourly and not more than twelve capsules per twenty-four hours. Consult your doctor if no relief is obtained with the recommended dosage.

Elderly: No special dosage modifications are required

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.

4.3 Contraindications

This product is contraindicated:

- In patients with a known hypersensitivity to ibuprofen, codeine, paracetamol or any other excipients.
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs.
- Patients with defects in coagulation.
- In patients with severe hepatic failure, severe renal failure or severe heart failure.

• In concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions.
• In concomitant use with other paracetamol-containing products – increased risk of serious adverse effects.
• During the last trimester of pregnancy due to risk of premature closure of the foetal ductus arteriosus with possible pulmonary hypertension.
In all patients below 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.
• In women during breastfeeding.
• In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

4.4 Special warnings and precautions for use

The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

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

Caution is required in patients with certain conditions:
• *Respiratory disorders:*
In patients suffering from, or with a history of, bronchial asthma or allergic disease NSAIDs have been reported to precipitate bronchospasm.

• *Cardiovascular, renal and hepatic impairment:*
The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients.

• *Cardiovascular and cerebrovascular effects*
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical trial 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 (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg daily) is associated with an increased risk of myocardial infarction.
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating long-term treatment for patients with risk factors for cardiovascular events

(e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

• *Gastrointestinal bleeding, ulceration and perforation:*
Gastrointestinal (GI) bleeding, ulceration and 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 acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).
Patients with a history of GI toxicity, particularly the 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 antiplatelet agents such as acetylsalicylic acid

When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn.
NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

• *SLE and mixed connective tissue disease:*
In patient with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis

• *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 of 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. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

• *Impaired female fertility:*
The use of the product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

<u>CYP2D6 metabolism</u>
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 or very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	**Frequency %**
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%

Special label warnings

Do not take with any other paracetamol, ibuprofen or codeine - containing products. Keep all medicines out of the reach and sight of children.

Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Special leaflet warnings

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage. Keep all medicines out of the reach and sight of children.

4.5 Interaction with other medicinal products and other forms of interaction

This product (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects (see Section 4.3).

This product (like any other ibuprofen containing products and NSAIDs) is contraindicated in combination with:
• Acetylsalicylic acid, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see Section 4.3).
• Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see Section 4.3).

This product (like any other paracetamol containing products) should be used with

caution in combination with:
• Chloramphenicol: Increased plasma concentration of chloramphenicol.
• Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.
• Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
• Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

This product (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:
• Anticoagulants: NSAIDs may enhance the effects of anticoagulants, i.e. warfarin.
• Antihypertensives: NSAIDs may reduce the effects of these drugs.
• Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see Section 4.4).
• Acetylsalicylic acid: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding the 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 use (see section 5.1)
• Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
• Ciclosporin: Increased risk of nephrotoxicity.
• Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see Section 4.4).
• Diuretics: Reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs.
• Lithium: Decreased elimination of lithium.
• Methotrexate: Decreased elimination of methotrexate.
• Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
• 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.
• Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
• Zidovudine: Increased risk of haematological toxicity with 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.
Codeine interacts with monoamine oxidase inhibitors. Therefore caution should be exercised in patients taking monoamine oxidase inhibitors.

Codeine

CNS Depressants

Concurrent use of other opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, or other tranquilizers or alcohol) concomitantly with codeine sulfate tablets may result in additive CNS depression, respiratory depression, hypotension, profound sedation, or coma. Use codeine sulfate with caution and in reduced dosages in patients taking these agents.

Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should NOT be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as codeine sulfate. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics including codeine sulfate, may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Antidepressants
Use of MAO inhibitors or tricyclic antidepressants with codeine sulfate may increase the effect of either the antidepressant or codeine. MAOIs markedly potentiate the action of morphine sulfate, the major metabolite of codeine. Codeine should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

Metabolic Enzymes
Patients taking cytochrome P-450 enzyme inducers or inhibitors may demonstrate an altered response to codeine, therefore analgesic activity should be monitored. Codeine sulfate is metabolized by the cytochrome P-450 3A4 and 2D6 isoenzymes. The concurrent use of drugs that preferentially induce codeine N-demethylation (cytochrome P-450 3A4) may increase the plasma concentrations of codeine's inactive metabolite norcodeine. Drugs that are strong inhibitors of codeine O-demethylation (cytochrome P-450 2D6) may decrease the plasma concentrations of codeine's active metabolites, morphine and morphine-6-glucuronide. The contribution of these active metabolites to the overall analgesic effect of codeine is not fully understood, but should be considered.

4.6 Pregnancy and lactation

Whilst no teratogenic effects have been demonstrated in animal experiments, the use of this medicine should, if possible, be avoided during the first 6 months of pregnancy. During the 3rd trimester, ibuprofen is contraindicated as there is a risk of premature closure of the foetal ductus arteriosus with possible persistent pulmonary hypertension. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. (See section 4.3 Contraindications).

Lactation:
Codeine
Codeine should not be used during breastfeeding (see section 4.3).
At normal therapeutic doses codeine and its active metabolite may be present in breast

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

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

Paracetamol
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible since the medicine contains an NSAID. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Paracetamol

Rare but may include rashes, blood disorders (including thrombocytopenia, leucopenia,neutropenia) reported; hypotension, flushing and tachycardia also reported on infusion; important: liver damage (and less frequently renal damage) following overdosage.

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

Paracetamol

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

b) Regularly consumes alcohol in excess of recommended amounts.

c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Symptoms

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac

arrhythmias and pancreatitis have been reported.

Management
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.
Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).
Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however; the maximum protective effect is obtained up to 8 hours post ingestion. The effectiveness of the antidote declines sharply after this time.
If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.
Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen
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 if there is a co-incident of dehydration. 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.

Codeine
The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms
Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. 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 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The pharmacological actions of ibuprofen, codeine and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has
also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within
the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central
inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.
Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid (81mg), a decreased effect of acetylsalicylic acid 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.

Paracetamol's exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various biochemical studies point to inhibition of central COX 2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

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

5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Concentration in plasma reaches a peak in 30 - 60 minutes. Plasma half-life is 1 - 4 hours. Paracetamol is relatively uniformly distributed throughout most body fluids, plasma protein binding is variable.

Codeine phosphate is well absorbed after oral administration and is widely distributed. About 86% is excreted in the urine in 24 hours, 40 - 70% is free or conjugated morphine and 10 - 20% is free or conjugated norcodeine

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.
Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours.

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

Partially Pregelatinised Starch BP (Starch 1500)
Colloidal anhydrous silica BP (aerosol)
Croscarmellose Sodium BP
Magnesium Stearate

6.2 Incompatibilities

None known.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Do not store above 30 °C. KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

100’s in HDPE round bottles with aluminium waded HDPE screw caps.
30’s in HDPE round bottles with aluminium waded HDPE screw caps

3 x 10s, 10 x 10s and 100 x 10s of PVC-Aluminium blister strips

7. Principal and Manufacturer

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8. Registration number(s)

TBA

9. Category of Distribution

Pharmacy Only

10. Pharmacological Classification

N02AJ09 - Opioids in combination with non-opioid analgesics

11. Last Date of revision

August 2020