1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

IBUCOD 10 mg/ 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of IBUCOD contains 10 mg of codeine phosphate and 200 mg of Ibuprofen.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

IBUCOD is a white, round, biconvex uncoated tablet with clean edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IBUCOD is indicated for:

- short term use in the management of mild to moderate pain and fever of inflammatory origin, in adults and children 12 years and older, for a maximum treatment period of 5 days.

4.2 Posology and method of administration

Posology

Adults

One to two tablets three times a day, if necessary. Do not take more than 6 tablets in a 24 hour period.

To be taken preferably with or after food.

If no relief is obtained with the suggested dose, a doctor must be consulted.

Use the lowest effective dose for the shortest possible duration of treatment.

Do not use for longer than 5 days.

Paediatric population

IBUCOD is not indicated for children under 12 years of age.

Method of administration

For oral administration

4.3 Contraindications

IBUCOD is contraindicated in:

- Patients with hypersensitivity to ibuprofen or codeine or to any of the excipients in IBUCOD (see section 6.1).
- Patients with active or history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs.
- Patients with asthma or bronchospasm, should not be given IBUCOD during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.
- Patients with cardiovascular disease and/or heart failure.
- Patients with hepatic or renal failure.

- Patients with hypersensitivity to aspirin or another non-steroidal anti-inflammatory medicines. This is because of the possibility of cross-sensitivity due to structural relationships, which exists among non-steroidal anti-inflammatory (NSAIDs) medicines; acute allergic reactions may be more likely to occur in patients who have exhibited allergic reactions, such as worsening of asthma, rhinitis or urticaria to these compounds.
- Patients with nasal polyps associated with aspirin-induced bronchospasm.
- Patients with acute respiratory depression in the presence of cyanosis and excessive bronchial secretion.
- Patients who are receiving warfarin.
- Concurrent use with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping such treatment.
- Diarrhoea associated with pseudomembranous colitis.
- Head injuries and conditions in which intracranial pressure is raised.
- Acute alcoholism.
- Safety in lactation has not been established.
- Women around the third trimester in pregnancy due to the risks of oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

Ibuprofen as contained in IBUCOD

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).

Special care has to be taken in the following cases:

- Hypertension.
- Disturbed haematopoiesis.
- Blood coagulation defects.
- Allergies, hay fever, chronic swelling of nasal mucosa, adenoids, chronic obstructive airway disease.
- Immediately after major surgical interventions.

Elderly:

IBUCOD should be given with care to the elderly.

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Elderly patients are more likely to develop adverse hepatic or renal effects, and if gastrointestinal ulceration or bleeding occurs it is more likely to cause serious consequences.

Gastrointestinal effects

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, such as ibuprofen as in IBUCOD, at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of IBUCOD, in patients with a history of ulcers and the elderly.

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

Other NSAIDs

The use of ibuprofen, as in IBUCOD, with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).

Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, selective serotonin reuptake inhibitors or anti-platelet medicines such as acetylsalicylic acid (see section 4.5).

When gastrointestinal perforation, ulceration or bleeding (PUBs), occurs in patients receiving IBUCOD, treatment with IBUCOD should be stopped.

IBUCOD should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated (see section 4.3 and 4.8).

Cardiovascular and cerebrovascular effects

Appropriate caution, monitoring and advice are required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with IBUCOD therapy.

In view of IBUCOD's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with IBUCOD after careful consideration.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. 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. Acute generalised exanthematous pustulosis (AGEP) has been reported. IBUCOD should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. It is advisable to avoid use of IBUCOD, in case of varicella.

Angioedema and hypersensitivity reactions have been reported.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ibuprofen as contained in IBUCOD. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute, viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue IBUCOD and evaluate the patient immediately.

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Aseptic meningitis

Symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed.

Aseptic meningitis has been observed on occasions in patients on ibuprofen, as in IBUCOD, therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus (SLE) and related connective tissue diseases, it has been reported in patients who do not have an underlying

chronic disease. Patients with collagen disease may be at increased risk of developing aseptic meningitis.

Eyes

IBUCOD should be discontinued in patients who experience blurred or diminished vision, or changes in colour vision.

Hepatic impairment

Hepatic function impairment which may increase risk of hepatotoxicity (see section 4.8).

Renal impairment

Ibuprofen, as in IBUCOD, may cause the retention of sodium, potassium and fluid in patients who have not previously suffered from renal disorders because of its effect on renal perfusion. This may cause oedema or even lead to cardiac insufficiency or hypertension in predisposed patients.
IBUCOD is contraindicated in renal function impairment as renal failure may be provoked, especially in patients with pre-existing renal impairment (see section 4.3).
There have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome. Cases of renal toxicity have also been observed in patients in whom prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of IBUCOD may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, hepatic dysfunction, those taking

diuretics and ACE inhibitors and the elderly. Discontinuation of IBUCOD is generally followed by recovery to the pre-treatment state.

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

Severe hypokalaemia and renal tubular acidosis

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen, as contained in IBUCOD, 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 include reduced level of consciousness and generalized weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Asthma

Asthma may be exacerbated (see section 4.3).

Masking of symptoms

The antipyretic, analgesic and anti-inflammatory action of IBUCOD may mask symptoms of the occurrence or worsening 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 IBUCOD is administered for pain or fever in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Other medicines

IBUCOD should not be taken without consulting a doctor or pharmacist if antihypertensives, diuretics, lithium and methotrexate are taken and when taking other pain relievers such as aspirin and other NSAIDs. Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration.

Other precautions

Severe acute hypersensitivity reactions (e.g., anaphylactic shock) are observed. At the first signs of hypersensitivity reaction after taking IBUCOD, therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Allergic conditions with a possibility of cross sensitivity with other NSAIDs, including aspirin (see section 4.3 and 4.5).

The habitual intake of analgesics, such as IBUCOD, particularly the combination use of different analgesic medicines, may cause permanent renal damage and a risk of renal failure (analgesics nephropathy). IBUCOD may temporarily inhibit platelet aggregation and has been shown to prolong the bleeding time.

IBUCOD should be used with caution in patients with anaemia, as anaemia may be exacerbated.

Consumption of alcohol should be avoided since it may intensify side effects of IBUCOD, especially if affecting the gastrointestinal tract or the central nervous system.

Patients on IBUCOD should report to their doctor signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or oedema.

Foetal Toxicity

Regular use of NSAIDs such as ibuprofen as contained in IBUCOD, during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus, *in utero,* and possibly, in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased. The use of IBUCOD in pregnancy is contraindicated (see section 4.3 and 4.6).

Codeine phosphate as in IBUCOD

Dependency

Exceeding the prescribed dose, together with prolonged and continuous use of IBUCOD, may lead to dependency and addiction.

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 codeine, as in IBUCOD. Abuse or intentional misuse of IBUCOD may result in overdose and/or death(see section 4.9). 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.

Patients should be informed about the risks and signs of OUD as well as serious clinical outcomes. If these signs occur, patients should be advised to contact their doctor.

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

IBUCOD should be used with caution in patients with personal or family history of substance abuse or mental health disorders.

Opioid-Induced Hyperalgesia or Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain (hyperalgesia), or an increase in sensitivity to pain (allodynia). This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect.

Symptoms of OIH include increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). The pain experienced may be at the same location of the underlying pain or can be more generalised or widespread in nature. These symptoms may suggest the occurrence of OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety).

General precautions

IBUCOD should be used with caution in patients with:

- Acute abdominal conditions as the diagnosis or clinical course may be obscured.
- Respiratory impairment or disease, as IBUCOD may decrease respiratory drive and increase airway resistance in these patients.
- Cardiac dysrhythmias, as these may be induced or exacerbated.
- Convulsions or history thereof, as these may be induced or exacerbated.
- Alcoholism, drug abuse or dependence, as these patients are predisposed to IBUCOD abuse.
- Gallbladder disease or gallstones as this may cause biliary tract spasm.
- Recent gastrointestinal tract surgery.
- Hypothyroidism may increase risk of respiratory depression and prolonged central nervous system depression.
- Adrenocortical insufficiency.
- Inflammatory or obstructive bowel disorders as risk of toxic megacolon may be increased.
- Prostatic hypertrophy, obstruction, urethral stricture or recent urinary tract surgery as urinary retention may be precipitated by IBUCOD.
- May cause or aggravate constipation if used with antidiarrhoeal medicines such as diphenoxylate (see section 4.5).
- Myasthenia gravis.
- Impaired liver functions or shock

Consult your doctor if pain or fever persists or gets worse, if new symptoms occur or if redness and swelling is present, as these could be signs of a serious condition. Consult a doctor if no relief is obtained from the recommended dosage.

Elderly

IBUCOD dose should be reduced in elderly and debilitated patients. The effects of alcohol and other sedatives may be potentiated.

Paediatric population

IBUCOD is not indicated for children under 12 years of age (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Ibuprofen as in IBUCOD

Concomitant use of ibuprofen and the following medicines should be avoided

Aspirin (acetylsalicylic acid)

Concomitant administration of ibuprofen, as in IBUCOD, and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Data suggest that ibuprofen, as in IBUCOD, 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 these data to the clinical situation, the possibility that regular, long-term use of IBUCOD may reduce the cardio protective effect of low-dose acetylsalicylic acid cannot be excluded.

Other NSAIDs including cyclooxygenase-2 selective inhibitors

As a result of synergistic effects, the concurrent use of several NSAIDs can increase the risk of gastrointestinal ulcers and haemorrhage. Co-administration of ibuprofen, as in IBUCOD, with other NSAIDs should therefore be avoided (see section 4.4).

Use of two or more NSAIDs concomitantly could result in an increase in side effects.

Anticoagulants

IBUCOD may enhance the effects of anti-coagulants such as heparin or warfarin (see section 4.3).

Methotrexate:

There is evidence for the potential increased and prolonged methotrexate plasma concentration and an increased risk of methotrexate toxicity. NSAID, such as ibuprofen, as in IBUCOD, inhibits the tubular secretion of methotrexate and certain metabolic interactions can occur resulting in decreased clearance of methotrexate. The administration of Ibuprofen within 24 hours before or after the administration of methotrexate can lead to an elevated concentration of methotrexate and an increase in its toxic effects. Therefore, concomitant use of IBUCOD and high doses of methotrexate should be avoided. Also, the potential risk of interactions in low dose treatment with methotrexate should be considered, especially in patients with impaired renal function. In combined treatment, renal function should be monitored.

Ibuprofen should be taken only with caution in combination with the following medicines

Corticosteroids:

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs) (see section 4.4).

Anti-platelet agents (e.g. clopidogrel and ticlopidine) and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs) (see section 4.4).

Antihypertensives, beta blockers and diuretics:

NSAIDs, such as ibuprofen, as in IBUCOD, may reduce the effect of anti-hypertensives, such as ACE inhibitors, beta-blockers, angiotensin-II antagonists and diuretics. There may be an increased risk of hyperkalaemia. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and medicines 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.

The concomitant administration of IBUCOD and potassium-sparing diuretics or ACE-inhibitors can result in hyperkalaemia. Careful monitoring of potassium levels is necessary.

Diuretics may increase the risk of nephrotoxicity of NSAIDs.

Captopril

Studies indicate that ibuprofen, as in IBUCOD, counteracts the effect of captopril of increased sodium excretion.

Aminoglycosides:

NSAIDs *such as ibuprofen, as in IBUCOD*, may decrease the excretion of aminoglycosides and increase their toxicity.

Antidiabetic agents (sulfonylurea):

Hypoglycaemic effects of these medicines may be increased.

In the case of simultaneous treatment, monitoring of blood glucose levels is recommended

Digoxin phenytoin and lithium

NSAIDs, such as ibuprofen, as in IBUCOD, may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma digoxin levels.

Co-administration of IBUCOD with digoxin, phenytoin or lithium preparations can increase the serum level of these medicines. Checking the serum lithium level, serum digoxin and serum phenytoin levels is generally not required on correct use (over 3 or 4 days maximum).

Ciclosporin

The risk of nephrotoxicity and kidney damage by ciclosporin is increased by the concomitant administration of certain NSAIDs. This effect cannot be ruled out for the combination of ciclosporin and ibuprofen, as in IBUCOD, either.

Tacrolimus:

Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Colestyramine

Concomitant treatment with colestyramine and ibuprofen, as in IBUCOD, results in prolonged and reduced (25 %) absorption of ibuprofen. The medicines should be administered with at least one hour interval.

Mifepristone:

IBUCOD should not be used for eight to twelve days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
A decrease in the efficacy of mifepristone can theoretically occur due to the antiprostaglandin properties of IBUCOD.

Probenecid or sulfinpyrazone

May cause a delay in the elimination of ibuprofen, as in IBUCOD. The uricosuric action of these substances is decreased.

Quinolone antibiotics:

NSAIDs, such as ibuprofen, as in IBUCOD, can increase the risk of convulsions associated with quinolone antibiotics. Patients taking IBUCOD and quinolones may have an increased risk of developing convulsions.

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(+) positive haemophiliacs receiving concurrent treatment with zidovudine and IBUCOD. Blood counts 1 to 2 weeks after starting use together are recommended

Ritonavir

May increase the plasma concentrations of NSAIDs, such as ibuprofen, as in IBUCOD.

Alcohol, bisphosphonates or oxypentifylline

The risk of gastrointestinal bleeding and ulceration is increased when used with alcohol, bisphosphonates or oxypentifylline.

Baclofen

Elevated baclofen toxicity.

CYP2C9 Inhibitors

Concomitant administration of IBUCOD with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors) an increased S (+) ibuprofen, as in

IBUCOD, exposure by approximately 80 % to 100 % has been shown. Reduction of the IBUCOD dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high doses of IBUCOD are administered with either voriconazole or fluconazole.

Herbal extracts

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs, such as ibuprofen as in IBUCOD.

Bone marrow depressants:

The leucopenic and/or thrombocytopenic effects of these medicines may be increased.

Investigations:

Interference with thyroid function tests by lowering serum thyroid hormone concentrations.

Codeine phosphate as in IBUCOD

Codeine may affect the activity of other medicines by delaying their absorption.

Monoamine oxidase inhibitors (MAOI):

Fatal reactions may occur in patients taking MAOI's and also within 14 days of stopping such treatment (see section 4.3).

Alcohol or central nervous system depressants:

The depressant effects of opioid analgesics, such as codeine as in IBUCOD are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, tricyclic anti-depressants and phenothiazines. Alcohol should be avoided during treatment with IBUCOD as the psychomotor performance can be significantly reduced.

Anticholinergic medicines:

Increased risk of constipation and urinary retention.

Antidiarrhoeals (e.g. diphenoxylate):

Increased risk of severe constipation and central nervous depression.

Antimuscarinics or medications with muscarinic action

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.

Cimetidine and other medicines which are known to influence the hepatic metabolism

May enhance the effect of IBUCOD

Neuromuscular blocking medicine

The respiratory depressant effect caused by neuromuscular blocking medicine may be additive to the central respiratory depressant effects of opioid analgesics.

Quinidine

Analgesic effect of codeine, as contained in IBUCOD, can be inhibited.

Mexiletine

Codeine, as in IBUCOD may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

Metoclopramide, cisapride and domperidone.

Codeine, as contained in IBUCOD, may antagonise the gastrointestinal effects.

Naloxone and naltrexone

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids, as contained in IBUCOD.

Laboratory tests and gastric emptying studies

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.

Hypotension producing medications:

Hypotensive effects may be potentiated.

4.6 . Fertility, pregnancy and lactation

IBUCOD is not recommended for use by pregnant or breastfeeding women (see section 4.3 and 4.4)

Pregnancy

Ibuprofen as in IBUCOD

First trimester:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. 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.

Second and third trimester:

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

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

At the end of pregnancy, the mother and the neonate may be exposed 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 labour.

Codeine phosphate as in IBUCOD

IBUCOD contains codeine phosphate, a narcotic analgesic. Use of narcotic analgesics during pregnancy is associated with foetal adverse effects which include physical dependence and withdrawal, retardation of growth and neonatal respiratory depression with high doses.

An association between abnormalities of the respiratory tract and the use of codeine during the first three months of pregnancy was found in humans. Evidence for other malformations was also found in epidemiological studies with narcotic analgesics, including codeine. Codeine may therefore only be used during pregnancy, especially during the first three months, if clearly indicated and after a careful benefit-risk assessment.
In case of imminent birth or preterm birth, the use of codeine is contraindicated since codeine crosses the placental barrier and can cause neonatal respiratory depression.

Lactation

Ibuprofen as in IBUCOD

Ibuprofen is excreted in the breast milk in low concentrations. With therapeutic doses during short term treatment the risk for influence on infant

seems unlikely. If, however, longer treatment is prescribed, early weaning should be considered. IBUCOD should not be used during breastfeeding

Codeine phosphate as in IBUCOD

Breastfed infants of mothers taking codeine may be at an increased risk of toxicity from its metabolite morphine.

Fertility

Ibuprofen as in IBUCOD

There is some evidence that medicines which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

IBUCOD has a minor influence on the ability to drive or use machines. Since adverse reactions such as drowsiness, and blurred vision have been reported in patients taking IBUCOD, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that IBUCOD does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena,

haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Gastritis has been observed, less frequently.

Clinical studies suggest that use of ibuprofen, as in IBUCOD, particularly at a high dose (2 400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Oedema, hypertension, and cardiac failure have been reported in association with NSAID treatment, such as ibuprofen, as in IBUCOD.

In view of the IBUCOD's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients (see section 4.3 and section 4.4).

b) Tabulated list of adverse reactions

Ibuprofen as in IBUCOD

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestation		Aseptic meningitis(especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation.	
Blood and the lymphatic system disorders		Neutropenia, thrombocytopenia with or without purpura, agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia, pancytopenia. The first symptoms or signs may include: fever, sore throat, surface mouth ulcers, flu-like symptoms, severe fatigue, nasal and skin bleeding, unexplained bleeding and bruising.	Eosinophilia.
Immune system disorders		Hypersensitivity reactions such as fever, angioedema, urticaria, pruritus, purpura and exanthema	Non-specific allergic reaction and anaphylaxis, respiratory tract reactivity

		as well as asthma attacks (sometimes with hypotension), severe hypersensitivity reactions. The symptoms may include: facial oedema, swelling of the tongue, internal laryngeal swelling with constriction of the airways, dyspnoea, tachycardia, fall of blood pressure to the point of life- threatening shock.	comprising asthma, aggravated asthma, bronchospasm or dyspnoea, exfoliative dermatoses, bullous dermatoses.
Psychiatric disorders		Nervousness, insomnia.	Confusion, anxiety, depression, hallucination.
Nervous system disorders	Dizziness.	Drowsiness, headache.	Optic neuritis, paraesthesia, somnolence.
Eye disorders		Blurred vision, other ocular reactions, changes in visual colour perception, and toxic amblyopia.	Visual impairment, toxic optic neuropathy.
Ear and labyrinth disorders		Tinnitus.	Impaired hearing, vertigo.
Cardiac disorders		Heart failure may be precipitated in compromised patients, angina pectoris, cardiac dysrhythmias palpitations, myocardial infarction, acute pulmonary oedema.	Oedema, cardiac failure.
Vascular disorders		Hypertension.	
Respiratory, thoracic and mediastinal disorders		Rhinitis, provocation of bronchospasm in patients with asthma.	Alveolitis, pulmonary eosinophilia.
Gastrointestinal disorders	Nausea, abdominal cramps, abdominal pain.	Peptic ulcers, Perforation or gastrointestinal haemorrhage, sometimes fatal particularly in the elderly, bloating, constipation, vomiting decreased appetite, diarrhoea, flatulence melaena, haematemesis, pancreatitis, dyspepsia.	Ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.
Hepatobiliary disorders		Hepatitis, jaundice.	Abnormalities of liver function tests, hepatic failure, hepatotoxicity.
Skin and subcutaneous tissue disorders	Skin rash, pruritus.	Bullous reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis.	Photosensitivity reactions, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) (see section 4.4), Acute generalised exanthematous pustulosis (AGEP).
Renal and urinary disorders		Impaired renal function, acute reversible renal failure, renal tubular acidosis, hypokalaemia, interstitial nephritis, nephrotic syndrome, haematuria, cystitis, papillary necrosis, especially in long- term use, associated with increased serum urea and oedema.	
Investigations		Decreased haemoglobin levels.	

Codeine

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Psychiatric disorders		Dysphoria, mood changes, restlessness, confusion.	Euphoria, hallucination, nightmares.
Nervous system disorders	Seizures, addiction tolerance, dependence, headache malaise, sleep disturbances.	Confusion, drowsiness, restlessness, changes in mood, vertigo, raised intracranial pressure.	Dyskinesia.
Eye disorders		Changes in miosis, blurred or double vision	.
Cardiac disorders		Bradycardia, palpitations, orthostatic hypotension, tachycardia.	
Vascular disorder		Postural hypotension, hypothermia.	
Respiratory, thoracic and mediastinal disorders		Respiratory depression.	Cough suppression.
Gastrointestinal disorders	Constipation.	Nausea, vomiting, dry mouth pancreatitis.	
Hepatobiliary disorders		Biliary spasm; liver disorder.	Biliary colic.
Skin and subcutaneous tissue disorders		Sweating, facial flushing, urticaria, pruritus, rashes.	
Renal and urinary disorders		Micturition difficulties, ureteric spasm or retention, dysuria (increased frequency, decrease in amount).	
Musculoskeletal and connective tissue disorders:			Muscle rigidity.
General disorders and administrative site conditions		Hypothermia.	
Investigations		Haemoglobin decreased.	

c) *Description of selected adverse reactions*

Ibuprofen

Acute reversible renal failure has been reported.

Hypersensitivity reactions have been reported following treatment with ibuprofen, as in IBUCOD. These may consist of (a) non-specific allergic

reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types of pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The pathogenic mechanism of medicine-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 medicine intake, and disappearance of symptoms after medicine discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen, in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

Codeine phosphate

The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, and phenothiazines.

The prolonged use of high doses of codeine has produced dependence of the morphine type.

d) Paediatric population

IBUCOD is not recommended for use for children under twelve years of age (see section 4.2).

e) Other special populations

The dosage should be reduced in elderly and debilitated patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/+27 (0)11 239-6200

4.9 Overdose

Ibuprofen

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

Symptoms

The frequently reported symptoms of overdose include nausea, vomiting, abdominal pain**,** lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea, diarrhoea and depression of the CNS and respiratory system have also been rarely reported. Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension,

bradycardia and tachycardia have been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other medicines are being taken.

Treatment

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered.

If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Other measures may be indicated by the patient's clinical condition. Give bronchodilators for asthma. Electrolytes may be corrected by intravenous infusion, if necessary.

There is no specific antidote to ibuprofen, as in IBUCOD.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Codeine phosphate

Symptoms

Patients may experience central nervous system and respiratory depression with hypoxia, circulatory failure and deepening coma, hypotension, shock, gastric hypomotility with ileus and non-cardiogenic pulmonary oedema. The opiate intoxication syndrome is described as a triad of depressed level of consciousness, miotic pupils, and decreased respirations.

Pinpoint pupils, hypotension and hypothermia, excitement and convulsions, especially in children, and non-cardiogenic pulmonary oedema occur.

Treatment

Treatment is based more on clinical presentation than on specific laboratory data, except when complications have occurred.

Immediate attention should be given to maintaining adequate respiration.

Naloxone should be given intravenously in a dose of 0,4 mg every 2 to 3 minutes until improvement occurs or to a maximum of 10 mg. Children may be given 0,01 mg/kg initially followed by a dose of 0,1 mg/kg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.8 Analgesic combinations

Pharmacotherapeutic group: Codeine and other non-opioid analgesics

ATC code: N02AJ09

Mechanism of action

Ibuprofen is a non-steroidal compound with anti-inflammatory agent and has analgesic and antipyretic activities.

Ibuprofen lysine is the lysine salt of ibuprofen, 2-(isobutylphenyl) propionic acid.

Following oral administration, ibuprofen lysine dissociates to ibuprofen and lysine.

Ibuprofen exerts its anti-inflammatory action peripherally in inflamed tissue by reducing prostaglandin activity and by inhibiting synthesis and/or actions of other local mediators of the inflammatory response, by competitive or reversible inhibition of the two isoforms of cyclooxygenase.

Codeine is an opioid analgesic and is metabolised to morphine, which in turn, exerts an analgesic effect.

5.2 Pharmacokinetic properties

Absorption

Ibuprofen

Ibuprofen has peak serum concentrations occurring approximately 35 minutes after proteins. It is absorbed from the gastrointestinal tract after oral administration.

Codeine phosphate

Codeine is readily absorbed from the gastrointestinal tract.

Distribution

Ibuprofen

The elimination half-life is approximately two hours. Ibuprofen is extensively bound to plasma proteins.

Codeine phosphate

Its half-life is 2,5 to 4 hours. The time to peak effect is 1 to 2 hours.

Biotransformation

Ibuprofen

Ibuprofen is metabolised in the liver to produce two major inactive metabolites, hydroxylated and a carboxylated compound.

Codeine phosphate

Codeine is metabolised in the liver. The cytochrome P450 enzyme 2D6 converts codeine to morphine, one of its metabolites. About 10 % of the dose is demethylated to morphine. Onset of action is 30 to 45 minutes.

Elimination

Ibuprofen

Both the inactive metabolites and small amount of unchanged ibuprofen are excreted by kidneys.

Codeine phosphate

Codeine is eliminated via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, microcrystalline cellulose, pregelatinized starch, silicon dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use

6.5 Nature and contents of container

18 and 30 tablets are packed in a white polypropylene container sealed with a push-on polyethylene cap, together with a silica gel sachet, a white foam insert and a leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

Hotline: 0800 122 912 / +27 11 239 6200

8. REGISTRATION NUMBER

33/2.8/0430

9. DATE OF FIRST AUTHORISATION

14 November 2002

10. DATE OF REVISION OF TEXT

09 September 2026

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

Namibia: NS2 04/2.8/2015