1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

MYBUCOD 10 mg/200 mg/350 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of MYBUCOD contains 10 mg Codeine phosphate, 200 mg Ibuprofen, 350 mg Paracetamol.

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

MYBUCOD is a blue, capsule-shaped, film-coated tablet with a break score on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MYBUCOD is indicated for the relief of mild to moderate pain or fever of inflammatory origin for a maximum treatment period of 5 days.

4.2. Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

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

Adults (over the age of 12 years):

Take 1 to 2 tablets 4 hourly.

Do not take more than 6 tablets in 24 hours.

Consult your healthcare professional if you require further treatment after 5 days.

Paediatric population

MYBUCOD is not recommended for children 12 years of age and younger.

Method of administration

For oral administration.

4.3. Contraindications

MYBUCOD is contraindicated in:

- Patients with hypersensitivity to ibuprofen, codeine, paracetamol or to any excipients in MYBUCOD (see section 6.1).
- Patients with acute respiratory depression especially in the presence of cyanosis and excessive bronchial secretion, after operations on the biliary tract, acute alcoholism, head injuries and conditions in which intracranial pressure is raised.
- Patients with heart failure or cardiovascular disease.
- Concurrent use with Monoamine Oxidase Inhibitors (MAOIs) or within 14 days of stopping such treatment (see section 4.5).
- Patients with diarrhoea associated with pseudomembranous colitis.
- Patients with impaired hepatic and renal function (see section 4.4).
- Patients with history of peptic ulcer disease or gastrointestinal perforation, ulceration, or bleeding (PUBs) related to previous NSAIDs, including MYBUCOD.

- Patients with an active or a history of recurrent gastrointestinal ulcer, haemorrhage or perforations.
- Patients sensitive to aspirin or another nonsteroidal anti-inflammatory medicine.
- Patients during an attack of bronchial asthma, uncontrolled asthma or bronchospasm or in heart failure secondary to chronic lung disease.
- Patients with nasal polyps associated with aspirin-induced bronchospasm.
- Patients with bleeding disorders.
- Patients who are receiving coumarin anticoagulants.
- Safety in lactation has not been established.
- Women around 30 weeks gestation and later 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

MYBUCOD should not be administered continuously for longer than 5 days as safety has not been established.

Paracetamol as in MYBUCOD

MYBUCOD contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

Dosages in excess of those recommended may cause severe liver damage.

Alcohol should be avoided. Increased risk of liver toxicity, especially in alcoholics using high doses of MYBUCOD for a prolonged period of time.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with MYBUCOD must immediately be discontinued and appropriate treatment instituted.

Codeine as in MYBUCOD

EXCEEDING THE PRESCRIBED DOSE, TOGETHER WITH PROLONGED AND CONTINUOUS USE OF THIS MEDICATION 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 MYBUCOD. Abuse or intentional misuse of MYBUCOD may result in overdose and/or death.

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

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 drug is stopped.

MYBUCOD should be used with caution in the following:

- Acute abdominal conditions: Diagnosis or clinical course may be obscured.
- Cardiac dysrhythmias: May be induced or exacerbated.
- Convulsions or history thereof: May be induced or exacerbated.
- Alcoholism, drug abuse or dependence: Patient is predisposed to drug abuse. Avoid alcohol - Increased risk of liver toxicity, especially in alcoholics with high doses and prolonged use (see section 4.5).
- Gallbladder disease or gallstones: May cause biliary tract spasm.
- Recent gastrointestinal tract surgery.
- Head injury increased intracranial pressure or intracranial lesions: Risk of respiratory depression and further increase in intracranial pressure. MYBUCOD may also cause sedation and pupillary changes that may obscure the clinical course of head injury.
- Hypothyroidism: Increase risk of respiratory depression and prolonged central nervous system depression.
- Adrenocortical insufficiency.
- Inflammatory or obstructive bowel disorders: Risk of toxic megacolon may be increased.
- Prostatic hypertrophy, obstruction, urethral stricture, or recent urinary tract surgery: As urinary retention may be precipitated by MYBUCOD.
- Risk of severe constipation if used with antidiarrhoeal medicines such as diphenoxylate (see section 4.5).
- Myasthenia gravis.

Ibuprofen as in MYBUCOD

Conditions predisposing to and exacerbated by fluid retention such as compromised cardiac

function, congestive heart disease, pre-existing oedema, hypertension, and renal function impairment: MYBUCOD may cause fluid retention and oedema (See section 4.3).

Special care has to be taken in the following cases:

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

Elderly patients

The elderly have an increased frequency of adverse reactions to NSAIDs including MYBUCOD, 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 is more likely to cause serious consequences.

Gastrointestinal bleeding, ulceration, and perforation

Gastrointestinal 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 gastrointestinal events.

The risk of gastrointestinal bleeding, perforation or ulceration or is higher with increasing doses of MYBUCOD, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly.
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.

The use of ibuprofen, as in MYBUCOD, 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 medications which could increase the risk of ulceration or bleeding, such as corticosteroids, selective serotonin-reuptake inhibitors and anti-platelet medicines such as aspirin (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving MYBUCOD, the treatment should be withdrawn.
MYBUCOD 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 4.8).

Cardiovascular and cerebrovascular effects

Caution 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 MYBUCOD therapy.
In view of MYBUCODs inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients
Caution is required in patients with risk factors for cardiovascular events (e.g. hypertension,

hyperlipidaemia, diabetes mellitus, smoking), and should only be treated with MYBUCOD after careful consideration.

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported (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.

Acute generalised exanthematous pustulosis (AGEP) has been reported.

MYBUCOD 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 MYBUCOD, in case of varicella.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms has been reported in patients taking NSAIDs such as MYBUCOD. 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 MYBUCOD and evaluate the patient immediately.

Hepatic function impairment:

MYBUCOD is metabolised in the liver. Increased risk of hepatotoxicity (see section 4.3 and

4.8). Dosage of MYBUCOD in excess of those recommended may cause severe liver damage.

Renal function impairment

Ibuprofen, as in MYBUCOD, 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.

MYBUCOD 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 MYBUCOD 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 MYBUCOD is generally followed by recovery to the pre-treatment state.

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

Asthma

Asthma may be exacerbated in patients suffering from or with a previous history of bronchial asthma or allergic disease. MYBUCOD may decrease respiratory drive and increase airway resistance in these patients (see section 4.3).

SLE and mixed connective tissue disease

Systemic lupus erythematosus and mixed connective tissue disease -increased risk of aseptic meningitis (see section 4.8).

Aseptic meningitis

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen as contained in MYBUCOD, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever, or disorientation have been observed.

Other precautions

Hypersensitivity reactions have been reported.

MYBUCOD should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

If taking for pain, including arthritic pain, and the pain persists for longer than 5 days, or if taking for fever and the fever persists for longer than 3 days, or if the condition deteriorates or new symptoms develop, a healthcare provider needs to be contacted as additional treatment may be necessary.

The antipyretic, analgesic, and anti-inflammatory action of ibuprofen as contained in MYBUCOD may mask symptoms of the occurrence of 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 MYBUCOD 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.

Diabetic patients may experience a false result with blood glucose test.

Allergic conditions

Possibility of cross sensitivity.

Elderly or debilitated patients:

Dosage should be reduced.

Anaemia

May be exacerbated.

Bleeding disorders

Increased risk of bleeding.

Foetal Toxicity:

Limit use of NSAIDs, including MYBUCOD, between 20 and 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Avoid use of NSAIDs in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.3 and 4.6). If NSAID treatment is necessary between 20 weeks and 30 weeks gestation, limit MYBUCOD use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if MYBUCOD treatment extends beyond 48 hours. Discontinue MYBUCOD if oligohydramnios occurs and follow up according to clinical practice.

Surgery

Possible enhanced bleeding if surgery is required.

Paediatric population

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

4.5. Interaction with other medicines and other forms of interaction

Ibuprofen as in MYBUCOD

Acetylsalicylic acid (aspirin)

Unless low-dose aspirin (not above 75mg daily) has been advised by a doctor, concomitant administration of ibuprofen, as in MYBUCOD, and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low- dose acetylsalicylic acid cannot be excluded.

NSAIDs including cyclooxygenase-2 selective inhibitors:

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

Anticoagulants (e.g warfarin and heparin)

Enhancement of anticoagulant effect and the possibility of gastrointestinal ulceration or bleeding (see section 4.3 and 4.4).

Methotrexate:

Increased and prolonged methotrexate plasma concentration and an increased risk of methotrexate toxicity.

NSAIDs, such as ibuprofen, as in MYBUCOD, inhibit 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 MYBUCOD 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 medicines (e.g clopidogrel and ticlopidine) and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding (see section 4.4).

Antihypertensives, beta blockers and diuretics

NSAIDs, such as ibuprofen, as in MYBUCOD, may reduce the effect of antihypertensives, such as ACE inhibitors, beta blockers, angiotensin-II antagonists and diuretics.

In patients with reduced kidney function (e.g. dehydrated patients or elderly patients with reduced kidney function), the concomitant use of an ACE inhibitor, beta blocker or angiotensin II antagonist with a cyclooxygenase-inhibiting medicines can lead to further impairment of kidney function and through to acute renal failure. This is usually reversible. Such combination should therefore only be used with caution, especially in elderly patients. The patients have to be instructed to drink sufficient liquid and periodic monitoring of the kidney values should be considered for the time immediately after the start of the combination therapy.

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

Diuretics can also increase the risk of nephrotoxicity of MYBUCOD.

Captopril

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

Aminoglycosides

MYBUCOD may decrease the excretion of aminoglycosides and increase their toxicity.

Antidiabetic medicines (e.g sulphonylureas)

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

MYBUCOD may exacerbate cardiac failure, reduce glomerular filtration rate.

Co-administration of MYBUCOD 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 MYBUCOD, either.

Tacrolimus

Possible increased risk of nephrotoxicity when NSAIDs, as in MYBUCOD are given with tacrolimus.

Colestyramine

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

Mifepristone

NSAIDs, such as ibuprofen as contained in MYBUCOD, should not be used for 8-12 days after mifepristone administration as it can reduce the effect of mifepristone.
A decrease in the efficacy of mifepristone can theoretically occur due to the antiprostaglandin properties of MYBUCOD.

Probenecid or sulfinpyrazone

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

Quinolone antibiotics:

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

Zidovudine

Increased risk of haematological toxicity when NSAIDs, such as ibuprofen as contained in MYBUCOD, are given with zidovudine. There is evidence of an increased risk of haemarthrosis and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen, as in MYBUCOD. Blood counts 1 to 2 weeks after starting use are recommended.

Ritonavir

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

Alcohol, bisphosphonates and oxpentifylline

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

Baclofen

Elevated baclofen toxicity.

CYP2C9 Inhibitors

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

Herbal extracts

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

Bone marrow depressants

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

Paracetamol as in MYBUCOD

Enzyme inducing and Hepatotoxic medicines:

Increased risk of hepatotoxicity. Possible decrease in therapeutic effects of paracetamol, as in MYBUCOD.

Metoclopramide

Absorption of paracetamol, as in MYBUCOD, may be accelerated.

Probenecid

Excretion of paracetamol, as in MYBUCOD, may be affected, and plasma concentrations altered.

Colestyramine

Absorption of paracetamol, as in MYBUCOD, is reduced if given within one hour of colestyramine.

Codeine phosphate as in MYBUCOD

MAOIs

Possible severe and sometimes fatal reactions may occur (see section 4.3).

Alcohol or central nervous system depressants

Depressant effects are enhanced.

Anticholinergics

Increased risk of severe constipation.

Antidiarrhoeals (e.g diphenoxylate):

Increased risk of severe constipation and central nervous system depression.

Hypotension-producing medications

Hypotensive effects may be potentiated.

4.6. Fertility, pregnancy and lactation

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

Pregnancy

Ibuprofen as in MYBUCOD

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 a 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.

Second and third trimester

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, leading to oligohydramnios and, in some cases, neonatal renal impairment (see section 4.4)

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.

Because of these risks, the use of MYBUCOD dose and duration between 20 and 30 weeks of gestation should be limited and avoided at around 30 weeks of gestation and later in pregnancy (see section 4.3 and 4.4).

Codeine phosphate as in MYBUCOD

MYBUCOD 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.

Breastfeeding

Codeine as in MYBUCOD

At normal therapeutic doses codeine, as in MYBUCOD, and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breastfed 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 as in MYBUCOD

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

Fertility

Ibuprofen as in MYBUCOD

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

MYBUCOD has minor influence on the ability to drive or operate machinery.

Since adverse events such as drowsiness have been reported in patients receiving MYBUCOD, patients should not drive, use machinery, or perform any tasks that require concentration, until they are certain that MYBUCOD does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

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

The most commonly observed adverse events are gastro-intestinal in nature.

b) *Tabulated list of adverse reactions*

Ibuprofen

System organ class	**Frequent**	**Less frequent**	**Frequency unknown (cannot be estimated from the available data)**
Infections and Infestations		Rhinitis, aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, nausea, vomiting, fever or disorientation.	
Blood and the lymphatic system disorders		Haematopoietic disorders (leucopoenia, pancytopenia, agranulocytosis,	

		thrombocytopenia with or without purpura, aplastic anaemia, haemolytic anaemia, anaemia, neutropenia). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.	
Immune system disorders		Hypersensitivity reactions with urticaria and pruritus, symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). Exacerbation of asthma and bronchospasm.	Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Psychiatric disorders		Confusional state, nervousness, insomnia, depression, anxiety, hallucination.	
Nervous system disorders	Dizziness.	Drowsiness, headache, somnolence, fatigue, agitation, irritability.	
Eye disorders		Blurred vision and other ocular reactions.	
Ear and labyrinth disorders		Tinnitus.	
Cardiac disorders		Angina pectoris, cardiac dysrhythmias, oedema, hypertension, and cardiac failure.	
Respiratory, thoracic and mediastinal disorders		Bronchospasm.	Alveolitis, pulmonary eosinophilia.
Metabolism and nutrition disorders			Hypokalaemia.
Gastrointestinal disorders	Heartburn, dyspepsia, abdominal cramps and pain, nausea, vomiting, flatulence, diarrhoea, constipation.	Peptic ulceration, perforation or gastrointestinal bleeding, sometimes fatal; gastrointestinal ulcers, sometimes with bleeding and perforation, occult blood loss which may lead to anaemia, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, inflammatory bowel disease, complications of colonic diverticula (perforation, fistula), gastritis, oesophagitis, pancreatitis, intestinal strictures, bloating, decreased appetite.	
Hepatobiliary disorders		Abnormalities of liver function tests, hepatitis, jaundice, liver dysfunction, liver damage, especially in long-term use, hepatic failure.	Hepatotoxicity.
Skin and subcutaneous tissue disorders	Skin rash, pruritus.	Severe forms of skin reactions such as bullous reactions, including Stevens-Johnson Syndrome, erythema	Severe cutaneous adverse reactions (SCARs) such as Drug reaction with eosinophilia and systemic

		multiforme and toxic epidermal necrolysis.	symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), Photosensitivity reactions.
Renal and urinary disorders		Impairment of renal function, acute reversible renal failure, oedema, papillary necrosis, nephritic syndrome, interstitial nephritis which can be associated with renal failure.	Renal tubular acidosis (reported in the post-marketing setting typically following prolonged use at higher than recommended doses due to dependence on the codeine component).
Investigations		Increase of blood urea nitrogen, serum transaminases and alkaline phosphatase, decrease in haemoglobin and haematocrit values, inhibition of platelet aggregation, prolonged bleeding time, decrease of serum calcium, increase in serum uric acid.	

Paracetamol

System organ class	Frequent	Less frequent	Frequency unknown (Cannot be estimated from the available data)
Blood and the lymphatic system disorders		Haematological reaction (including thrombocytopenia, leukopenia, pancytopenia, neutropenia and agranulocytosis).	
Hepatobiliary disorders		Hepatitis.	
Renal and urinary disorders		Renal colic, renal failure, sterile pyuria.	
General disorders		Sensitivity reactions resulting in reversible skin rash (which may be accompanied by fever and mucosal lesions) or blood disorders.	Fixed Drug Eruptions (FDE), Drug Induced Hypersensitivity Syndrome (DIHS).

Codeine Phosphate

System organ class	Frequent	Less frequent	Frequency unknown (Cannot be estimated from the available data)
Psychiatric disorders		Euphoria.	
Nervous system disorders		Confusion, vertigo, restlessness, changes in mood, hypothermia, raised intracranial pressure, drowsiness.	
Eye disorders		Changes in miosis, blurred or double vision.	
Cardiac disorders		Bradycardia, palpitations, orthostatic hypotension.	

Vascular disorders		Facial flushing.	
Respiratory, thoracic and mediastinal disorders		Respiratory depression, cough suppression.	
Gastrointestinal disorders		Nausea, vomiting, constipation, dry mouth. Pancreatitis.	
Hepatobiliary disorders		Biliary spasm.	
Skin and subcutaneous tissue disorders		Urticaria, pruritus.	
Renal and urinary disorders		Micturition difficulties, ureteric spasm.	
General disorders and administrative site conditions		Sweating.	

c) Description of selected adverse reactions

Ibuprofen

Acute reversible renal failure has been reported. Ibuprofen, as in MYBUCOD, should be used with care in patients with impaired renal function.

Hypersensitivity reactions have been reported following treatment with ibuprofen, as in MYBUCOD.

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

Codeine phosphate, as in MYBUCOD, should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, impaired liver function, prostatic hypertrophy or shock. It should be used with caution in patients with inflammatory or obstructive bowel disorders.

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

MYBUCOD 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. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

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

4.9. Overdose

Paracetamol

Symptoms

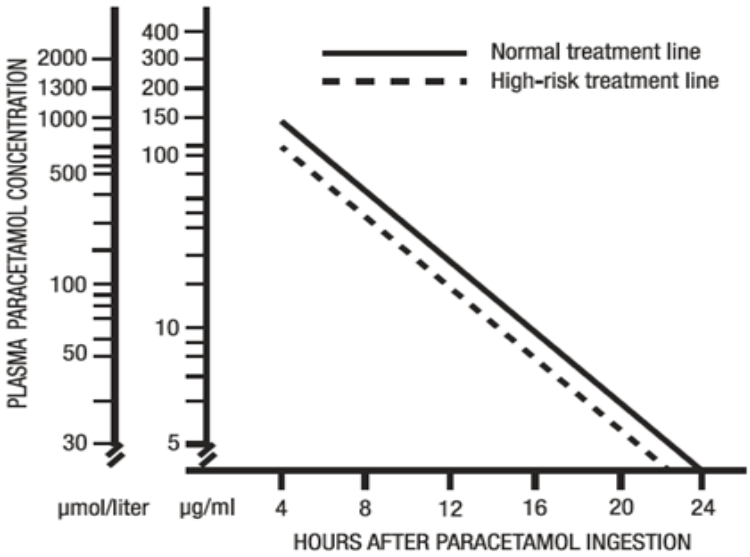
In the first 24 hours, symptoms include pallor, nausea, vomiting, anorexia, and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours, or later after ingestion of paracetamol, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentrations and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma, and death.

Acute renal failure with acute tubular necrosis may develop even the absence of severe liver damage. Abnormalities of glucose metabolism and acidosis may occur. Cardiac dysrhythmias have been reported.

Cerebral oedema and non-specific myocardial depression have occurred.

Figure 1: A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.



Prompt treatment is essential. In the event of overdosage, consult a doctor immediately, or

take the person to a hospital directly. A delay in starting treatment may mean that the antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 g to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Treatment of overdose

Although evidence is limited it is recommended that an adult who has ingested 5 g to 10 g or more of paracetamol (or child who has had more than 140 mg/kg) within the preceding four hours should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuporous or comatose, endotracheal intubation should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. The volume of intravenous fluid should be modified for children.

Although the oral formula is not the treatment of choice, 140 mg/kg dissolved in water as a 5 % solution may be administered initially, followed by 70 mg/kg every four hours for

seventeen doses. If activated charcoal is used, then it should be removed by gastric lavage as it may interfere with absorption of orally administered acetylcysteine and decrease its efficacy.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdose. Levels done before four hours, unless high, may be misleading. Patients at risk of liver damage and hence requiring continued treatment with N-acetylcysteine, can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the treatment nomogram (refer figure 1 above).

Those, whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival. Monitor all patients with significant ingestion for at least ninety-six hours.

Ibuprofen

Symptoms

Gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting, epigastric pain, or more rarely diarrhoea), central nervous system symptoms (e.g. lethargy, drowsiness, occasionally excitation and disorientation), gastrointestinal haemorrhage, acute renal failure, convulsions, and coma.

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. Prolonged use at higher than recommended doses may result in severe hypokalaemia and

renal tubular acidosis. Symptoms may include reduced level of consciousness and generalized weakness (see section 4.4 and section 4.8).

Exacerbation of asthma is possible in asthmatics.

Treatment

Treatment 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 phosphate

Symptoms

Codeine overdose may result in central nervous system and respiratory depression with hypoxia, hypotension, shock, gastric hypomotility with ileus, excitement and convulsions (especially in children) and non-cardiogenic pulmonary oedema. The opiate intoxication syndrome is described as a triad of depressed level of consciousness, miotic pupils, and decreased respiration.

Treatment

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

Plasma codeine levels are not clinically useful.

Support the respiratory and cardiovascular function.

Monitor arterial blood gases and/or pulse oximetry, pulmonary function tests, and chest x-

rays in patients with significant exposure.

Ipecac-induced emesis is not recommended because of the potential for CNS depression and seizures.

Consider pre-hospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway.

Activated charcoal is most effective when administered within one hour of ingestion.

Use a minimum of 240 ml of water per 30 g charcoal.

The optimum dose has not been established, but the usual dose is 25 g to 100 g in adults and adolescents; 25 g to 50 g in children aged 1 to 12 years (or 0,5 g to 1 g/kg body weight); and 1 g/kg in infants up to 1 year old.

Consider naloxone as an antidote in patients with a decreased level of consciousness.

The most frequently recommended initial naloxone dose for codeine overdose is 0,4 mg to 2 mg given as an intravenous bolus in both children and adults.

This dose can also be given subcutaneously in the absence of intravenous access or intratracheally.

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

Paracetamol has analgesic and antipyretic effects. Ibuprofen has analgesic, antipyretic and anti-inflammatory activities.

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.

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

5.2. Pharmacokinetic properties

Absorption

Paracetamol

Absorption following oral administration is rapid and almost complete.

Ibuprofen

Rapidly absorbed after oral administration.

Codeine

Readily absorbed from the gastrointestinal tract.

Distribution

Paracetamol

Paracetamol has a half-life of 1 to 3 hours, time to peak concentration of 0,5 to 2 hours, time to peak effect of 1 to 3 hours and a duration of action of 3 to 4 hours.

Ibuprofen

Onset of action for pain relief is 30 minutes and the time for peak effect for fever is 2 to 4 hours. The half-life of ibuprofen is about 2 hours and the duration of action for fever is 6 to 8 hours or more and is 4 to 6 hours for pain.

Codeine

Half-life is 2,5 to 4 hours. The time to peak effect is 1 to 2 hours. Duration of action is 4 hours.

Biotransformation

Paracetamol

Paracetamol is metabolised in the liver primarily by conjugation.

Codeine

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

Paracetamol

Paracetamol is renally excreted primarily as metabolites and 3 % of a dose may be excreted unchanged.

Ibuprofen

More than 90 % of an ingested dose is excreted in the urine as metabolites or their conjugates.

Codeine

Codeine is eliminated via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Brilliant blue (C.I. 42090), magnesium stearate, methocel, microcrystalline cellulose, Polyvinylpyrrolidone povidone, pregelatinised starch, purified talc.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C in airtight containers.

Protect from light.

Keep in original packaging until required for use.

6.5. Nature and contents of container

30 tablets are packed into a white, round, polypropylene container and sealed with a tamper evident, round, burnt-orange low density polyethylene cap, together with a leaflet and silica gel sachet.

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

8. REGISTRATION NUMBER

36/2.8/0379

9. DATE OF FIRST AUTHORISATION

25 November 2005

10. DATE OF REVISION OF TEXT

26 January 2024

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

Namibia: NS2 10/2.8/0629

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