SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

LENBUCOD, 10 mg/200 mg/350 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains codeine phosphate 10 mg, ibuprofen 200 mg and paracetamol 350 mg.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

LENBUCOD is a blue, oblong, double convex, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LENBUCOD is indicated for the relief of mild to moderate pain of inflammatory origin, with or without fever, for a maximum period of five days.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSAGE.

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

Adults and children over the age of 12 years:

Take one (1) to two (2) tablets, six (6) hourly if necessary.

Do not take more than six (6) tablets in a 24-hour period.

Consult your health care provider if you require further treatment after five days.

Paediatric population

LENBUCOD is contraindicated in children under the age of 12 years (see section 4.3).

Method of administration

For oral administration.

4.3 Contraindications

LENBUCOD is contraindicated in:

- Hypersensitivity to paracetamol, ibuprofen, codeine or to any of the excipients listed in section 6.1.
- A history of previous hypersensitivity reactions (e.g. urticaria, rhinitis, asthma or angioedema), in response to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).
- A history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including **LENBUCOD**.
- Patients with an active, or a history of recurrent gastrointestinal ulcer, haemorrhage or perforations (two or more distinct episodes of proven ulceration or bleeding).
- Patients with cerebrovascular bleeding or other active bleeding.
- Unclarified disturbances in blood-formation.
- Severe hepatic impairment, severe hepatic failure, or severe renal failure (see section 4.4).
- Cardiovascular disease.

- Severe heart failure (NYHA Class IV), heart failure secondary to chronic lung disease.
- During an attack of bronchial asthma, uncontrolled asthma, acute asthma or bronchospasm.
- Nasal polyps associated with aspirin-induced bronchospasms.
- After operations on the biliary tract, acute alcoholism, head injuries, and conditions where intracranial pressure is raised, respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- Concurrent use with monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping such treatment (see section 4.5).
- Concurrent use with coumarin anticoagulants (see section 4.5).
- Substantial dehydration (caused by vomiting, insufficient fluid intake or diarrhoea).
- The third trimester of pregnancy (from 28 weeks onwards), relating to the risk of oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus due to NSAIDs, and the risk of foetal respiratory complications due to codeine (see sections 4.4 and 4.6).
- In women who are breast feeding (see section 4.6).
- Children under the age of 12 years.
- Children (0 – 18 years of age) who undergo tonsillectomy or adenoidectomy surgery for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4)

4.4 Special warnings and precautions for use

Ibuprofen as in LENBUCOD

Before administering **LENBUCOD**, the benefit-risk ratio should be carefully considered in the following conditions: mixed connective tissue diseases or Systemic Lupus Erythematosus (SLE); congenital disturbances of porphyrin metabolism (e.g. acute intermittent porphyria); and the first and second trimester of pregnancy (see section 4.6).

Special care has to be taken in the following cases:

- Diseases affecting the gastrointestinal system including chronic inflammatory intestinal disease (e.g. ulcerative colitis, Crohn's disease).
- Hypertension.
- Reduced renal function.
- Hepatic dysfunction.
- Disturbed haematopoiesis.
- Blood coagulation defects.
- Hay fever, allergies, chronic swelling of nasal mucosa, adenoids, chronic obstructive airway disease or bronchial asthma.
- Immediately after major surgical interventions.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, such as ibuprofen as contained in **LENBUCOD**, especially gastrointestinal bleeding, perforation or ulceration (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 bleeding, ulceration and perforation

Gastrointestinal bleeding, ulceration or perforation, can occur with all NSAIDs at any stage during the course of treatment (which can be fatal), with or without warning symptoms or having a history of previous gastrointestinal events.

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of **LENBUCOD**, in patients with a history of ulcers, and the elderly. Treatment in these patients should be commenced on the lowest dose available.

It should also be considered to combine therapy with protective medicines such as misoprostol or proton pump inhibitors. Combination therapy should also be used for patients concomitantly using low-dose acetylsalicylic acid (aspirin) (or any other medicines likely to increase gastrointestinal risk (see section 4.5). Patients with a history of gastrointestinal toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.

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

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

When gastrointestinal bleeding or ulceration occurs in patients receiving **LENBUCOD**, treatment with it should be stopped.

LENBUCOD 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 advised in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with **LENBUCOD** therapy. In view of the **LENBUCOD**'s inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

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.

LENBUCOD should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

Drug reaction with eosinophillia and systemic symptoms

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ibuprofen as contained in **LENBUCOD**. 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. Eosinophillia 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 **LENBUCOD** and evaluate the patient immediately.

Hepatic effects

The use of **LENBUCOD** in patients with severe hepatic function impairment is contraindicated due to the increased risk of developing hepatoxicity (see sections 4.3 and 4.8).

Renal effects

Ibuprofen, as in **LENBUCOD**, 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.

LENBUCOD is contraindicated in severe renal function impairment as renal failure may be provoked, especially in patients with pre-existing renal impairment (see section 4.3).

Reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome have been presented on the prolonged administration of ibuprofen in human.

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

Renal impairment as renal function may deteriorate (see sections 4.3 and 4.8). Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses. This risk is increased with the use of codeine/ibuprofen as patients may become dependent on the codeine component (see warning on Opioid use disorder, section 4.8 and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen

induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Asthma

Patients with asthma are advised to consult their health care professional before using **LENBUCOD**, due to possible exacerbation of asthma that may occur.

Masking of symptoms of underlying infections

The antipyretic, analgesic and anti-inflammatory action of **LENBUCOD** may mask the signs and symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When **LENBUCOD** is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In nonhospital settings, the patient should consult a doctor if symptoms persist or worsen.

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, (e.g. stiff neck, nausea, vomiting, headache, fever or disorientation) have been observed.

Aseptic meningitis has been observed in some patients who were using ibuprofen, as in **LENBUCOD** 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.

Other precautions

Severe acute hypersensitivity reactions (for example anaphylactic shock) have been observed. At the first signs of hypersensitivity reaction after taking/administering **LENBUCOD** 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).

Bronchospasm, angioedema or urticaria may be precipitated in patients with a previous history of or are suffering from chronic rhinitis, bronchial asthma, nasal polyps, sinusitis, adenoids or allergic diseases.

Prolonged use of medicines, such as **LENBUCOD**, for headache can make them worse. If this situation is experienced or suspected, medical advice should be obtained, and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medicines.

The habitual intake of analgesics, such as **LENBUCOD**, particularly the combination use of different analgesic substances, may cause permanent renal damage and a risk of renal failure (analgesics nephropathy). **LENBUCOD** may temporarily inhibit platelet aggregation and has been shown to prolong the bleeding time. Therefore, patients with coagulation defects or on anticoagulant therapy should be observed carefully.

LENBUCOD should be used with caution in anaemic patients due to the possible exacerbation of the condition.

Consumption of large amounts of alcohol should be avoided as it may intensify side effects of **LENBUCOD** that affect the gastrointestinal tract or the central nervous system.

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

Use in pregnancy

Foetal Toxicity: Limit use of NSAIDs, including **LENBUCOD**, between 20 to 28 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Use of NSAIDs in women around 20 weeks of gestation and later in pregnancy may cause oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see sections 4.3 and 4.6).

These adverse outcomes are usually observed, on average, after days or weeks of treatment, although oligohydramnios has even been reported as soon as 48 hours after the start of NSAID initiation. By discontinuing treatment, oligohydramnios can often, but not always, be reversed. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. Post-marketing cases have shown that invasive procedures such as exchange transfusion or dialysis were required for some cases of impaired neonatal renal function.

If NSAID treatment is necessary between 20 weeks and 28 weeks gestation, limit **LENBUCOD** use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if **LENBUCOD** treatment extends beyond 48 hours. Discontinue **LENBUCOD** if oligohydramnios occurs and follow up according to clinical practice (see section 4.3 and 4.6).

Paracetamol as in LENBUCOD

LENBUCOD 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.

General precautions

Doses of **LENBUCOD** in excess of those recommended may cause severe liver damage. Use with caution in patients with impaired kidney or liver function, or in patients with alcohol dependence. Large doses should be avoided in patients with hepatic impairment.

Severe cutaneous adverse reactions (SCARs):

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), Drug reaction with eosinophilia and systemic symptoms (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 **LENBUCOD** must immediately be discontinued and appropriate treatment instituted (see Section 4.8).

Alcohol

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

Codeine phosphate as in LENBUCOD:

Opioid use disorder (abuse and dependence)

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

Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as codeine, as contained in **LENBUCOD**. Abuse or intentional misuse of **LENBUCOD** 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 medicine is stopped.

Increased risk of addiction in patients with personal or family history of substance abuse or mental health disorders.

Opioid-induced hyperalgesia (OIH) and allodynia

Opioid pain medicines have been associated with opioid-induced hyperalgesia (OIH), a condition where opioids cause an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia). Increases in pain typically occur following a dose increase and resolve quickly following proper diagnosis and management of the condition. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid

dosage increase, decreased levels of pain upon dosage decrease, or pain from ordinarily non-painful stimuli (allodynia).

General precautions

LENBUCOD should be used with caution in patients with:

- Acute abdominal conditions as the diagnosis or clinical course of the condition may be obscured.
- Acute asthmatic attack or respiratory impairment or disease as **LENBUCOD** may decrease respiratory drive and increase airway resistance in these patients.
- Cardiac dysrhythmias, convulsions (or history thereof), as this may be induced or exacerbated.
- Alcoholism, drug abuse or dependence as they are predisposed to substance abuse. Alcohol consumption should be avoided (see section 4.5).
- Gallstones or gallbladder disease, as this may cause biliary tract spasms.
- Recent surgery of the gastrointestinal tract.
- Hepatic impairment, as **LENBUCOD** is metabolised in the liver (see section 4.3).
- Renal function impairment as the use of **LENBUCOD** may lead to urinary retention. The metabolites of **LENBUCOD** are excreted via the kidneys, renal impairment can cause accumulation resulting in an increase in adverse effects.
- Hypothyroidism may increase risk of respiratory depression and prolonged central nervous system depression.
- Adrenocortical insufficiency.
- Inflammatory or obstructive bowel disorders (e.g. chronic ulcerating colitis), 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 **LENBUCOD**.
- Shock.

- Risk of severe constipation if used with certain anti-diarrhoeal medicines including diphenoxylate (see section 4.5).
- Myasthenia gravis.

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

The dosage should be reduced in elderly or debilitated patients.

Paediatric population

LENBUCOD is contraindicated in children under 12 years of age (see section 4.2 & section 4.3).

Children with compromised respiratory function:

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

4.5 Interactions with other medicines and other forms of interaction

Ibuprofen as in LENBUCOD

Concomitant use of ibuprofen and the following medicines should be avoided.

Acetylsalicylic acid (aspirin)

Concomitant administration of ibuprofen, as in **LENBUCOD** and acetylsalicylic acid (aspirin) is not generally recommended because of the potential of increased adverse effects. Data suggests that the concomitant use may competitively inhibit the effect of low dose

acetylsalicylic acid (aspirin) on platelet aggregation. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that the long-term and regular concomitant use can reduce the cardio protective effect of low-dose acetylsalicylic acid (aspirin) cannot be excluded. No clinically relevant effect is considered to be likely for occasional **LENBUCOD** use.

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 **LENBUCOD**, 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.

Anti-coagulants

LENBUCOD may enhance the effects of anti-coagulants such as warfarin or heparin (see section 4.4). It is recommended that the coagulation state of the patients must be monitored during combination treatment.

Methotrexate

The combined use of methotrexate with **LENBUCOD**, may lead to an increased and prolonged plasma concentration of methotrexate. The concomitant administration of ibuprofen within 24 hours before or after the administration of methotrexate can lead to an increase in the toxic effects due to the increased methotrexate plasma concentration. The risk for methotrexate toxicity is increased.

NSAIDs, such as ibuprofen, as in **LENBUCOD**, inhibits the tubular secretion of methotrexate and certain metabolic interactions can occur resulting in reduced clearance of methotrexate. Therefore, combination therapy of **LENBUCOD** and high doses of methotrexate should be

avoided. It is advised to monitor for potential risks of medication interactions, even on low dose treatment with methotrexate especially in patients with impaired renal function.

Concomitant use of ibuprofen and the following medicines should be taken only with caution:

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 and ulceration (see section 4.4).

Antihypertensives, beta blockers and diuretics

NSAIDs, such as ibuprofen, as in **LENBUCOD**, may reduce the antihypertensive effect of 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 medicine can lead to further impairment of kidney function and may result in acute renal failure. This is usually reversible. The combination of these therapies should therefore only be used with caution, especially in elderly patients. Patients should be advised to consider periodic monitoring of the kidney values and drink sufficient amounts of liquid with the onset of combination therapy.

The concomitant administration of **LENBUCOD** 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 **LENBUCOD**.

Captopril

Studies have shown that ibuprofen, as in **LENBUCOD**, counteracts the increased sodium excreting effects of captopril.

Aminoglycosides

LENBUCOD may decrease the excretion of aminoglycosides, and increase their toxicity.

Antidiabetic medicines (e.g. sulphonylureas)

The hypoglycaemic effects of antidiabetic medicines may be increased.

Monitoring of blood glucose levels is advised in the case of simultaneous treatment

Digoxin, phenytoin and lithium

LENBUCOD may exacerbate cardiac failure, decrease the rate of glomerular filtration and increase levels of cardiac glycoside (digoxin) in the plasma.

Combined administration of **LENBUCOD** with digoxin, phenytoin or lithium can increase the serum level of these medicines. Checking the serum lithium level, serum digoxin and serum phenytoin levels are generally not required on correct use (over 3 or 4 days maximum).

Ciclosporin and tacrolimus

Concomitant administration of ciclosporin and certain NSAIDs leads to the risk of developing nephrotoxicity and kidney damage. This effect cannot be ruled out for the combination of ciclosporin and ibuprofen, as in **LENBUCOD**, either.

Cholestyramine

Combination therapy of cholestyramine and ibuprofen, as in **LENBUCOD**, causes a prolonged and reduced (25 %) absorption of ibuprofen. These medicines should be administered at least one hour apart.

Mifepristone

The use of NSAIDs, including ibuprofen as in **LENBUCOD**, within an interval period of eight to twelve days after mifepristone administration, can reduce the effect of mifepristone.

The reduction in mifepristone efficacy is theoretically associated with the antiprostaglandin properties of **LENBUCOD**.

Probenecid or sulfinpyrazone

May cause a delay in the elimination of ibuprofen as in **LENBUCOD**. The uricosuric action of these medicines is decreased.

Quinolone antibiotics

LENBUCOD can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs, such as ibuprofen as in **LENBUCOD**, and quinolones may have a higher risk of developing convulsions.

Zidovudine

When NSAIDs, such as ibuprofen as in **LENBUCOD**, are given with zidovudine, there is an increased risk of haematological toxicity. In HIV positive haemophiliacs receiving concurrent treatment with these medicines, there is evidence of an increased risk of haemarthrosis and haematoma. It is advised to monitor blood counts of patients one to two weeks after starting combination therapy.

Ritonavir

May elevate the plasma concentrations of NSAIDs, such as ibuprofen as in **LENBUCOD**.

Bone marrow depressants

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

Alcohol, bisphosphonates and oxpentifylline

The risk of bleeding and ulceration is increased with co-administration of **LENBUCOD** and alcohol, bisphosphonates or oxypentifylline.

Baclofen

Elevated baclofen toxicity.

CYP2C9 Inhibitors

Ibuprofen (CYP2C9 substrate), and co-administration of medicines such as voriconazole and fluconazole (CYP2C9 inhibitors) increases the exposure to ibuprofen (as in **LENBUCOD**). In a study with voriconazole and fluconazole (CYP2C9 inhibitors) an increased S (+) ibuprofen, as in **LENBUCOD**, exposure by approximately 80 % to 100 % has been shown. Reduction of the **LENBUCOD** dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose **LENBUCOD** is administered with either voriconazole or fluconazole.

Herbal extracts

The concomitant use with Ginkgo biloba may potentiate the risk of bleeding effects of NSAID's (e.g., ibuprofen as in **LENBUCOD**).

Paracetamol as in LENBUCOD

Enzyme inducing and hepatotoxic medicines:

There is an increased risk of hepatotoxicity as well as a possible decrease in therapeutic effects of paracetamol (as in **LENBUCOD**).

Metoclopramide

The absorption of paracetamol (as in **LENBUCOD**) may be accelerated.

Cholestyramine

The absorption of paracetamol (as in **LENBUCOD**) is reduced if given within one hour of cholestyramine.

Probenecid

The excretion of paracetamol (as in **LENBUCOD**) may be affected, and plasma concentrations altered.

Codeine phosphate as in LENBUCOD

Monoamine oxidase inhibitors (MAOIs)

Sometimes fatal reactions may occur in patients taking MAOIs concomitantly and also within 14 days of stopping treatment with MAOIs (see section 4.3).

Alcohol or central nervous system depressants

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

Anticholinergics

Increased risk of severe constipation.

Antidiarrhoeals

May increase the risk of developing severe constipation and central nervous system depression.

Hypotension-producing medicines

May potentiate the hypotensive effects.

4.6 Fertility, pregnancy and lactation

LENBUCOD is not recommended for use by women in early pregnancy and is contraindicated in the third trimester (28 weeks of gestation onwards). **LENBUCOD** is contraindicated in breastfeeding women. (see sections 4.3 and 4.4).

Pregnancy

*Ibuprofen as in **LENBUCOD***

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.

During the first and second trimester of pregnancy, **LENBUCOD** should not be given unless clearly necessary. If **LENBUCOD** is used by a woman attempting to conceive, or during the

first and second trimester of pregnancy, the dose should be kept as low, and duration of treatment as short, as possible.

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

- cardiopulmonary toxicity (with premature closure of the foetal ductus arteriosus in utero, and in persistent pulmonary hypertension of the new-born,
- renal dysfunction, which may progress to renal failure with oligo-hydramniosis (see section 4.4).

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

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in the onset of labour may be delayed and its duration increased.

Use of NSAIDs, including **LENBUCOD**, can cause premature closure of the foetal ductus arteriosus and foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, the use of **LENBUCOD** dose and duration between 20 and 28 weeks of gestation should be limited and avoided in the third trimester (28 weeks of gestation and later) (see sections 4.3 and 4.4).

*Codeine phosphate as in **LENBUCOD***

LENBUCOD 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.

Codeine is contraindicated in the third trimester of pregnancy (see section 4.3).

Breastfeeding

Ibuprofen as in ***LENBUCOD***

Ibuprofen, as in **LENBUCOD**, is excreted in human 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.

Codeine phosphate as in ***LENBUCOD***

LENBUCOD contains codeine phosphate. Breast-fed infants of mothers taking codeine may be at an increased risk of toxicity from its metabolite morphine.

LENBUCOD is contraindicated in breastfeeding women (see section 4.3).

Fertility

Ibuprofen as in ***LENBUCOD***

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

LENBUCOD has a minor influence on the ability to drive or use machines. Adverse reactions such as dizziness, drowsiness and visual disturbances have been reported (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

Ibuprofen as in LENBUCOD

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, heamatemesis, 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 **LENBUCOD**, 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 **LENBUCOD**.

b. Tabulated summary of adverse reactions

*Ibuprofen as in **LENBUCOD***		
SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Less frequent	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 lymphatic system disorders	Less frequent	Haematopoietic disorders (leucopoenia, pancytopenia, agranulocytosis, thrombocytopenia with or without purpura, aplastic anaemia, haemolytic anaemia, anaemia, neutropenia). The first symptoms or signs

		may include: fever, sore throat, surface mouth ulcers, flu-like symptoms, severe fatigue, nasal and skin bleeding
	Frequency unknown	Neutropenia
Immune system disorders	Less frequent	Hypersensitivity reactions such as urticaria, pruritus, purpura and exanthema 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
Metabolism and nutrition disorders	Frequency unknown	Hypokalaemia**
Psychiatric disorders	Less frequent	Confusional state, nervousness, insomnia, depression, anxiety, hallucination
Nervous system disorders	Frequent	Dizziness
	Less frequent	Drowsiness, headache, somnolence, fatigue, agitation, irritability
	Frequency unknown	Paraesthesia
Eye disorders	Less frequent	Blurred vision, other ocular reactions
	Frequency unknown	Visual impairment, toxic optic neuropathy
Ear and	Less frequent	Tinnitus

labyrinth disorders	Frequency unknown	Impaired hearing, vertigo
Cardiac disorders	Less frequent	Heart failure may be precipitated in compromised patients, angina pectoris, cardiac dysrhythmias, palpitations, myocardial infarction, acute pulmonary oedema
	Frequency unknown	Oedema, hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Rhinitis, bronchospasm
	Frequency unknown	Alveolitis, pulmonary eosinophilia
Gastrointestinal disorders	Frequent	Gastrointestinal disorders, such as heartburn, dyspepsia, abdominal cramps and pain, nausea, vomiting, flatulence, diarrhoea, constipation
	Less frequent	Peptic ulcers, perforation or gastro-intestinal bleeding, sometimes fatal; gastrointestinal ulcers, sometimes with bleeding and perforation (see section 4.4), 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

Hepato-biliary disorders	Less frequent	Abnormalities of liver function tests, hepatitis, jaundice, liver dysfunction, liver damage, especially in long-term use, hepatic failure
	Frequency unknown	Hepatotoxicity
Skin and subcutaneous tissue disorders	Frequent	Skin rash, pruritus
	Less frequent	Photosensitivity reaction, severe forms of skin reactions (erythema multiforme, exfoliative dermatitis, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, alopecia, necrotising fasciitis
	Frequency unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Less frequent	Impairment of renal function, acute reversible renal failure, haematuria, renal papillary necrosis in long-term use (see section 4.4), development of oedema especially in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis which can be associated with renal failure
	Frequency unknown	Renal tubular acidosis**
General	Frequency	Malaise

disorders and administration site conditions	unknown	
Investigations	Less frequent	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 as in **LENBUCOD***		
SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Blood and lymphatic system disorders	Less frequent	Haematological reaction (including agranulocytosis, thrombocytopenia, neutropenia, pancytopenia, leukopenia)
Immune system disorders	Frequency unknown	Drug-induced hypersensitivity syndrome (DIHS) (see section 4.4)*
Hepato-biliary disorders	Less frequent	Hepatitis, pancreatitis
Skin and subcutaneous tissue disorders	Less frequent	Hypersensitivity reactions resulting in reversible skin rash (which may be accompanied by fever and mucosal lesions) or blood disorders dermatitis, erythematous or urticarial rash accompanied by fever and mucosal lesions
	Frequency unknown	Fixed drug eruptions (FDE) (see section 4.4)*

Renal and urinary disorders	Less frequent	Renal colic, renal failure, sterile pyuria
*Codeine phosphate as in **LENBUCOD***		
SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Psychiatric disorders	Less frequent	Euphoria
Nervous system disorders	Less frequent	Confusion, drowsiness, restlessness, changes in mood, vertigo, raised intracranial pressure
Eye disorders	Less frequent	Miosis, blurred or double vision
Cardiac disorders	Less frequent	Bradycardia, palpitations, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory depression
Gastrointestinal disorders	Less frequent	Nausea, vomiting, constipation, dry mouth, acute pancreatitis*
Hepato-biliary disorders	Less frequent	Biliary spasm
Skin and subcutaneous tissue disorders	Less frequent	Sweating, facial flushing, urticaria, pruritus

Renal and urinary disorders	Less frequent	Micturition difficulties, ureteric spasm
General disorders and administration site conditions	Less frequent	Hypothermia

*post-marketing experience:

Less frequent increased risk of abdominal pain, including pancreatitis has been reported.

The following side effects have been reported and frequencies are unknown: Fixed drug eruptions (FDE) and drug-induced hypersensitivity syndrome (DIHS) (see section 4.4).

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

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 **LENBUCOD**. These may consist of (a) nonspecific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types, 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 autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

Paracetamol

Concomitant administration with flucloxacillin

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see sections 4.4 and 4.5)

Codeine phosphate

Codeine phosphate, as in **LENBUCOD**, should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, 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

Frequency, type and severity of adverse reactions in children (12 years and older) are expected to be the same as in adults.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

4.9 Overdose

Treatment is symptomatic and supportive (see section 4.4).

*Ibuprofen as in **LENBUCOD***

Most patients who have ingested significant amounts of ibuprofen (as in **LENBUCOD**), will manifest symptoms within four to six hours.

Symptoms

The most frequently reported symptoms of overdose include nausea, abdominal pain, lethargy, vomiting, blurred vision, drowsiness and other central nervous system (CNS) symptoms (such as headache, dizziness, tinnitus, convulsion, and loss of consciousness). Symptoms of overdose that have also been reported include nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea, diarrhoea and depression of the CNS and respiratory system have also been 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.

In more serious poisoning, toxicity is seen in the central nervous system, with symptoms such as vertigo, dizziness, drowsiness, occasionally excitation and loss of consciousness or coma.

Children may also develop myoclonic cramps. In serious poisoning metabolic acidosis may occur, hypothermia and hyperkalaemia may also 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 generalised weakness (see section 4.4 and section 4.8).
Respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Treatment

Patients should be treated symptomatically as required and supportive and the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Within one hour of ingestion of a potentially toxic amount oral administration of activated charcoal should be considered.
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.
Frequent or prolonged convulsions should be treated with intravenous diazepam or lorazepam.
Other measures may be indicated by the patient's clinical condition.
If ibuprofen has already been absorbed, alkaline substances should be administered to promote the excretion of the acid ibuprofen in the urine.

Bronchodilators should be given for asthma. No specific antidote is available.

Paracetamol as in ***LENBUCOD***

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. 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 – 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours 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, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration 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 in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Treatment

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.**

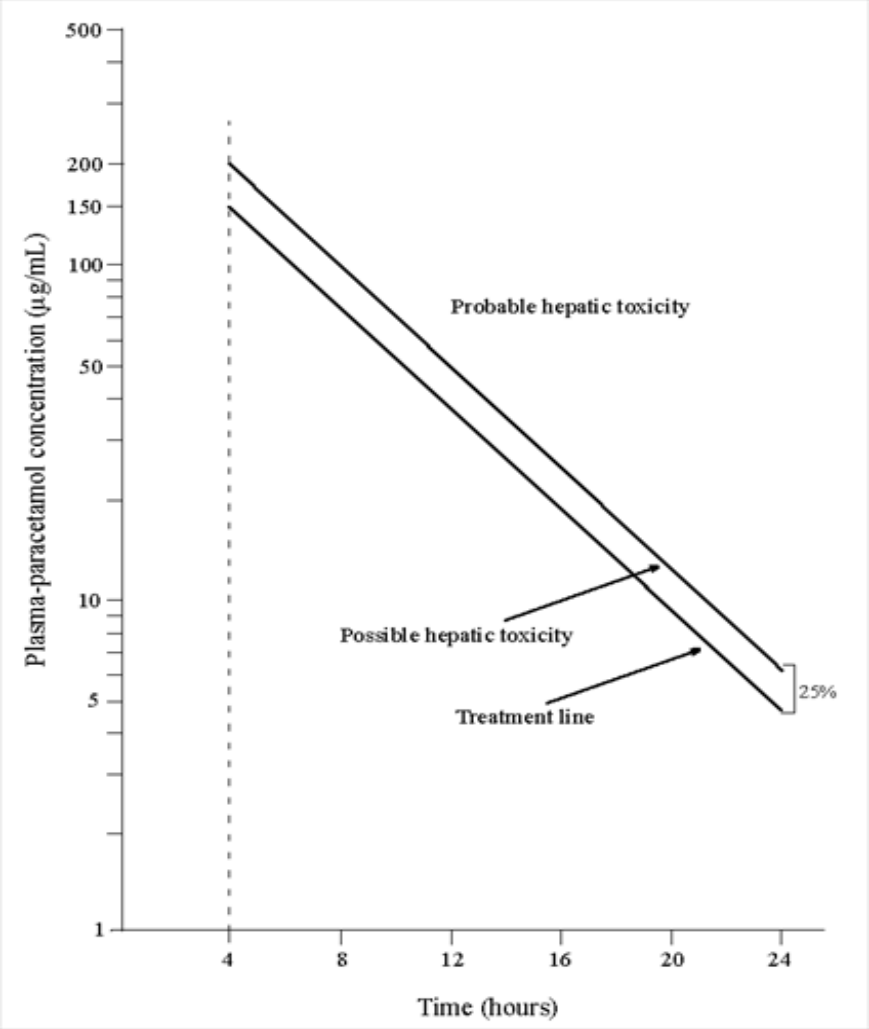
Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours 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 nomogram below. The nomogram should be used only in relation to a single acute ingestion.

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 ingestions for at least ninety-six hours.

A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion (Reference: Martindale).



Codeine phosphate as in ***LENBUCOD***

Symptoms

Respiratory depression is the most important feature of overdosage and occurs with circulatory failure and deepening coma. Pin-point pupils, hypotension and hypothermia, excitement and convulsions, especially in children, and non-cardiogenic pulmonary oedema occur.

Treatment

Immediate attention should be given to maintaining adequate respiration. Naloxone should be given intravenously in a dose of 0,4 mg every two to three 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 anti-inflammatory agent (NSAID) and 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.

Paracetamol has analgesic and antipyretic effects.

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

5.2 Pharmacokinetic properties

Absorption

Ibuprofen

Absorbed from the gastrointestinal tract after oral administration.

Paracetamol

Absorption following oral administration is rapid and almost complete.

Codeine phosphate

Codeine is readily absorbed from the gastrointestinal tract.

Distribution

Ibuprofen

The half-life of ibuprofen is about two hours.

Paracetamol

Paracetamol has a half-life of one to three hours, and time to peak concentration of 0,5 to 2 hours.

Codeine phosphate

Its half-life is 2,5 to 4 hours.

Biotransformation

Paracetamol

Paracetamol is metabolised in the liver primarily by conjugation.

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. The time to peak effect is one to two hours.

Elimination

Ibuprofen

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

Paracetamol

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

Codeine phosphate

Codeine is eliminated via the kidneys.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide,

colour FD&C blue no. 1 aluminium lake,

microcrystalline cellulose PH102,

pregelatinised starch,

stearic acid,

glycerol monocaprylocaprate,

macrogol (PEG) polyvinyl alcohol graft copolymer,

polyvinyl alcohol,

talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

LENBUCOD (30 tablets) is packed in a white high-density polyethylene (HDPE) bottle, fitted with a white polypropylene (PP) closure, which is sealed with a heat induction liner.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand

1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

56/2.8/0960

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 March 2024

10. DATE OF REVISION OF THE TEXT

02 July 2025