SCHEDULING STATUS
S3

1. NAME OF THE MEDICINE
MYPRODOL® SUSPENSION, 10 mg/200 mg/250 mg, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 10 ml contains codeine phosphate 10 mg, ibuprofen 200 mg and paracetamol 250 mg.

Excipient(s) with known effect:
Preservative (sodium benzoate): 0,1 % *m/v*
Sugar free.
Contains sweetener: Sodium cyclamate 90 mg/10 ml, sodium saccharin 12,4 mg/10 ml.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Suspension.
A homogenous, opaque pink suspension with a blackcurrant taste and odour, free from excess visible particles.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
MYPRODOL® SUSPENSION is indicated for the relief of mild to moderate pain of inflammatory origin with or without fever.

4.2 Posology and method of administration
Posology
DO NOT EXCEED THE RECOMMENDED DOSE.
Adults
Two to four medicine measures (10 to 20 ml) four hourly and not more than twenty-four medicine measures in twenty-four hours.

Paediatric population
Refer to section 4.3.

Use the lowest effective dose for the shortest possible duration of treatment.
Consult your doctor if no relief is obtained with the recommended dosage.

Method of administration
For oral administration. Shake the bottle before use.

4.3 Contraindications

MYPRODOL® SUSPENSION is contraindicated in:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Impaired hepatic and renal function.
- Cardiovascular disease.
- Heart failure.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including MYPRODOL® SUSPENSION.
- Active or history of recurrent ulcer/haemorrhage/perforations.
- Contraindicated in 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. It should not be given during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.
- Contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or within fourteen days of stopping such treatment.
- Caution is advised in those patients who are receiving coumarin anticoagulants.
- Patients who are sensitive to aspirin or another nonsteroidal anti-inflammatory medicines (NSAIDs) should not be given MYPRODOL® SUSPENSION.
- Diarrhoea associated with pseudomembranous colitis.
- Patients during an attack of bronchial asthma, uncontrolled asthma, bronchospasm or in heart failure secondary to chronic lung disease.
- Patients with nasal polyps associated with aspirin-induced bronchospasm.
- Patients with bleeding disorders.
- 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 increased risk of developing serious life-threating adverse reactions (see section 4.4).
- The third trimester of pregnancy (28 – 40 weeks) (see section 4.6).
- In women who are breast feeding (see section 4.6).

4.4 Special warnings and precautions for use

The safety of continuous administration of MYPRODOL® SUSPENSION has not been established for a period greater than four weeks.

Paracetamol

This product 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.
Do not use continuously for more than 10 days without consulting a doctor.

- 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 MYPRODOL® SUSPENSION must immediately be discontinued and appropriate treatment instituted (see section 4.8).

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

Renal and hepatic impairment
- Ibuprofen should be used with care in patients with impaired renal function.
- The administration of an NSAID, such as ibuprofen as in MYPRODOL® SUSPENSION, may cause a dose dependant reduction in prostaglandin formation and precipitate renal failure. The habitual concomitant intake of various similar pain medicines further increases this risk. Patients at greatest risk, are those diuretics and the elderly. For these patients, use the lowest effective dose for the shortest possible duration and monitor renal function (see also section 4.3).
- 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.

Cardiovascular effects
- Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with MYPRODOL® SUSPENSION therapy. In view of ibuprofen's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Gastrointestinal bleeding, ulceration and perforation
- Gastrointestinal (GI) bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION, at any time during treatment, with or without warning symptoms or a previous history of serious GI events.
- Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including ibuprofen in MYPRODOL® SUSPENSION, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.
- The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of MYPRODOL® SUSPENSION, in patients with a history of ulcers,

particularly if complicated with haemorrhage or perforation (see section 4.3) and the elderly.

- Patients with a history of gastrointestinal disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.
- When gastrointestinal bleeding or ulceration occurs in patients receiving MYPRODOL® SUSPENSION, treatment with MYPRODOL® SUSPENSION should be stopped.
- MYPRODOL® SUSPENSION should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastroesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.
- Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, selective serotonin-reuptake inhibitors or antiplatelet medicines such as aspirin (see section 4.5).
- The use of MYPRODOL® SUSPENSION with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see section 4.5).
- The concomitant consumption of excessive alcohol with NSAIDs, including ibuprofen, as in MYPRODOL® SUSPENSION, may increase the risk of adverse effects on the gastrointestinal tract, such as GI haemorrhage or the central nervous system possibly due to an additive effect.

Severe skin reactions

- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing medicines, as in MYPRODOL® SUSPENSION.
  MYPRODOL® SUSPENSION should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility

- The use of MYPRODOL® SUSPENSION may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of MYPRODOL® SUSPENSION should be considered (see section 4.6).

Foetal Toxicity

- Use of NSAIDs such as ibuprofen in MYPRODOL® SUSPENSION during the third trimester of pregnancy, may result in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed, and its duration increased (see section 4.3 and 4.6).
- Limit use of NSAIDs, including MYPRODOL® SUSPENSION, between 20 to 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. use of NSAIDs in women around 20 weeks 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 seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.
- If NSAID treatment is necessary between 20 weeks and 30 weeks gestation, limit NSAID use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue NSAID if oligohydramnios occurs and follow up according to clinical practice (see sections and 4.6).

Drug reaction with eosinophilia and systemic symptoms

- Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as MYPRODOL® SUSPENSION. 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 MYPRODOL® SUSPENSION and evaluate the patient immediately.

Respiratory disorders ad hypersensitivity reactions

Caution is required if MYPRODOL® SUSPENSION is administered to patients suffering from, or with a previous history of chronic rhinitis or allergic diseases since NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION, have been reported to precipitate bronchospasm, urticaria or angioedema in such patients (see section 4.3).

Acute asthma attack or respiratory impairment or disease may decrease respiratory drive and increase airway resistance in these patients.

Asthma may be exacerbated (see section 4.3).

Alcoholism, impaired liver function, drug abuse, drug dependence or if the patient is predisposed to drug abuse

Avoid alcohol as there is an increased risk of liver toxicity, especially in alcoholics using high doses of MYPRODOL® SUSPENSION for a prolonged period of time (see section 4.5).

Dehydration

Caution should be used when initiating treatment with MYPRODOL® SUSPENSION in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children, adolescents and the elderly.

Masking of symptoms of underlying infections
The antipyretic, analgesic and anti-inflammatory action of MYPRODOL® SUSPENSION 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 MYPRODOL® SUSPENSION 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.

Allergic conditions
Possibility of cross sensitivity.

Anaemia
Anaemia may be exacerbated.

Bleeding disorders
MYPRODOL® SUSPENSION, like other NSAIDs, can interfere with platelet aggregation and prolong bleeding time in normal patients. Increased risk of bleeding.

General
If taken for pain, including arthritic pain, and the pain persists for longer than 5 days, or if taken for fever and the fever persists for longer than 3 days or if the condition deteriorates or new symptoms develop, the healthcare provider needs to be contacted as additional treatment may be necessary.
Diabetic patients may experience false results with blood glucose tests.

Elderly patients
The elderly have an increased frequency of adverse reactions to NSAIDs including ibuprofen, as in MYPRODOL® SUSPENSION, especially gastrointestinal perforation, ulceration or bleeding (PUBs), which may be fatal (see section 4.2).

Surgery
Possible enhanced bleeding, if surgery is required.

Varicella
In exceptional cases, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. The contributing role of NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION, in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of MYPRODOL® SUSPENSION in case of varicella.

Systemic lupus erythematosus 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 (see below and section 4.8).

Aseptic meningitis
Aseptic meningitis has been observed on occasions in patients on ibuprofen, as in MYPRODOL® SUSPENSION, therapy. Although it is probably more likely to occur in patients with SLE and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Codeine phosphate
MYPRODOL® SUSPENSION should be used with caution in patients with:
- Acute abdominal conditions as diagnosis or clinical course may be obscured.
- Respiratory impairment or disease as MYPRODOL® SUSPENSION may decrease respiratory drive and increase airway resistance in these patients (see section 4.3).
- Cardiac dysrhythmias, as these may be induced or exacerbated.
- Convulsions or history thereof, as these may be induced or exacerbated.
- Gallbladder disease or gallstones as these may cause biliary tract spasm.
- Recent gastrointestinal tract surgery.
- Hypothyroidism, due to an increased risk of respiratory depression and prolonged central nervous system depression.
- Adrenocortical insufficiency
- Impaired liver function
- Prostatic hypertrophy, obstruction, urethral stricture or recent urinary tract surgery, as urinary retention may be precipitated by MYPRODOL® SUSPENSION.
- Shock.
- Inflammatory or obstructive bowel disorders or ulcerative disease of the upper or lower gastrointestinal tract, as the risk of toxic megacolon may be increased.
- The dosage should be reduced in elderly and debilitated patients.
- 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.

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. Abuse or intentional misuse of MYPRODOL® SUSPENSION 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 opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia).

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.

MYPRODOL® SUSPENSION contains sodium benzoate (excipient)
This medicine contains 10 mg sodium benzoate in each 10 ml which is equivalent 0,1 % *m/v*.
Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old) (see section 4.3).
Sodium benzoate may cause local irritation.

MYPRODOL® SUSPENSION contains sodium
This medicinal product contains 26,88 mg sodium per 10 ml, equivalent to 1,344 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
MYPRODOL® SUSPENSION contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interactions with other medicines and other forms of interaction
Care should be taken in patients treated with any of the following medicines as interactions have been reported in some patients.
- *MAOIs:* Possible severe and sometimes fatal reactions may occur (see section 4.3).
- *Central nervous system depressant:* The depressant effects of codeine, as in MYPRODOL® SUSPENSION, 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:* Increased risk of severe constipation and central nervous system depression.
- *Hypotension-producing medicines:* Hypotensive effects may be potentiated.
- *Hepatotoxic medicines:* Increased risk of hepatotoxicity.

- *Enzyme inducing medicines:* Increased risk of hepatotoxicity. Possible decrease in therapeutic effects of paracetamol, as in MYPRODOL® SUSPENSION.
- *Metoclopramide:* Absorption of paracetamol, as in MYPRODOL® SUSPENSION, may be accelerated.
- *Probenecid:* Excretion of paracetamol, as in MYPRODOL® SUSPENSION, may be affected and plasma concentrations altered.
- *Cholestyramine:* Absorption of paracetamol, as in MYPRODOL® SUSPENSION, is reduced if given within one hour of cholestyramine. The concomitant administration of MYPRODOL® SUSPENSION and cholestyramine may reduce the absorption of MYPRODOL® SUSPENSION in the gastrointestinal tract.
- *NSAIDs:* use of two or more NSAIDs concomitantly could result in an increase in side effects.
- *Alcohol, corticosteroids, clopidogrel, ticlopidine, bisphosphonates, oxpentifylline*: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).
- *Antidiabetic medicines:* Hypoglycaemic effects of these medicines may be increased.
- *Sulfonylureas:* MYPRODOL® SUSPENSION may potentiate the effects of sulfonylurea medicines. There have been reports of hypoglycaemia in patients on sulfonylurea medicines receiving ibuprofen as in MYPRODOL® SUSPENSION.
- *Cardiac glycosides such as digoxin:* MYPRODOL® SUSPENSION may exacerbate cardiac failure, reduce GFR and increase serum cardiac glycoside concentrations.
- *Lithium:* Increase in the steady-state concentration of lithium and decreased elimination of lithium.
- *Methotrexate:* MYPRODOL® SUSPENSION may inhibit the tubular secretion of methotrexate, reduce clearance of methotrexate, increase and prolong methotrexate plasma concentration and increase the risk of methotrexate toxicity.
- *Nephrotoxic medicines e.g. ciclosporin:* Increased risk of nephrotoxicity.
- *Mifepristone:* A decrease in the efficacy of the medicine can occur due to the antiprostaglandin properties of ibuprofen, as in MYPRODOL® SUSPENSION. Evidence suggests that coadministration of NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION, on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicines used in the termination of pregnancy.
- *Other analgesics and cyclooxygenase-2 selective inhibitors:* Avoid concomitant use of two or more NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION, including cox-2 inhibitors, as this may increase the risk of adverse effects (see section 4.4).
- *Aspirin (Acetylsalicylic acid):* Concomitant administration of MYPRODOL® SUSPENSION and aspirin is not generally recommended because of the potential of increased adverse effects (see section 4.3).
  Data suggest that ibuprofen, as in MYPRODOL® SUSPENSION, may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly.
- *Anticoagulants:* MYPRODOL® SUSPENSION may enhance the effects of anticoagulants such as warfarin and the possibility of gastrointestinal ulceration or bleeding (see section 4.3).
- *Antiplatelet medicines and selective serotonin reuptake inhibitors (SSRIs):* increased risk of gastrointestinal bleeding.

- *Antihypertensives or beta-blockers or diuretics:* Reduction or reversal of the antihypertensive effect may occur, such as ACE inhibitors, angiotensin-II receptor antagonists, beta-blockers and diuretics.
- Diuretics can also increase the risk of nephrotoxicity of NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION.
- *Bone marrow depressant:* The leucopenic and/or thrombocytopenic effects of these medicines may be increased.
- *Quinolone antibiotics:* NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION, can increase the risk of convulsions associated with quinolone antibiotics. Patients taking MYPRODOL® SUSPENSION and quinolones may have an increased risk of developing convulsions.
- *Aminoglycosides:* MYPRODOL® SUSPENSION may decrease the excretion of aminoglycosides.
- *Tacrolimus:* Possible increased risk of nephrotoxicity when MYPRODOL® SUSPENSION is given with tacrolimus.
- *Zidovudine:* Increased risk of haematological toxicity when MYPRODOL® SUSPENSION is given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen, as in MYPRODOL® SUSPENSION.
- *CYP2C9 Inhibitors:* Concomitant administration of MYPRODOL® SUSPENSION with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate), as in MYPRODOL® SUSPENSION. In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+) ibuprofen exposure by approximately 80 % to 100 % has been shown. Reduction of the MYPRODOL® SUSPENSION dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose MYPRODOL® SUSPENSION is administered with either voriconazole or fluconazole.
- *Herbal extracts:* Ginkgo biloba may potentiate the risk of bleeding with MYPRODOL® SUSPENSION.

4.6 Fertility, pregnancy and lactation

Pregnancy

MYPRODOL® SUSPENSION is not recommended for use by pregnant women (see section 4.3 and 4.4).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. 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 losses 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.

Use of non-steroidal anti-inflammatory medicines (such as ibuprofen) during the third trimester of pregnancy, may result in persistent pulmonary hypertension of the newborn. The onset of

labour may be delayed, and its duration increased (see section 4.4).

Use of NSAIDs, including MYPRODOL® SUSPENSION, 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 MYPRODOL® SUSPENSION dose and duration between 20 and 30 weeks of gestation should be limited.

MYPRODOL® SUSPENSION is contraindicated in the third trimester (28 – 40 weeks).

Breastfeeding
NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION, can appear in the breast milk in very low concentrations.
MYPRODOL® SUSPENSION is contraindicated for use by breastfeeding women (see section 4.3).

Fertility
The use of MYPRODOL® SUSPENSION may impair female fertility and is not recommended in women attempting to conceive (see section 4.4).

4.7 Effects on ability to drive and use machines
MYPRODOL® SUSPENSION has moderate influence on the ability to drive and use machines, as it may cause dizziness, drowsiness and blurred vision.

4.8 Undesirable effects
a. Summary of the safety profile
The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen, as in MYPRODOL® SUSPENSION, administration. Less frequently, gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed.

b. Tabulated summary 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	

Blood and lymphatic system disorders		Agranulocytosis, thrombocytopenia, leukopenia, neutropenia, aplastic anaemia, haemolytic anaemia, pancytopenia	
Immune system disorders		Hypersensitivity reactions, anaphylactic reaction	
Metabolism and nutrition disorders			Hypokalaemia***
Psychiatric disorders		Nervousness, depression, insomnia, anxiety, confusional state	
Nervous system disorders	Dizziness headache	Drowsiness, paraesthesia, somnolence, optic neuritis	
Eye disorders		Blurred vision, other ocular reactions, visual impairment, toxic optic neuropathy	
Ear and labyrinth disorders		Tinnitus.	
Cardiac disorders		Oedema, hypertension, cardiac failure, angina pectoris, cardiac dysrhythmias, myocardial infarction	
Vascular disorders		Hypertension	
Respiratory, thoracic and mediastinal disorders		Asthma, bronchospasm, dyspnoea	

Gastrointestinal disorders	Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, gastrointestinal haemorrhage	Ulcerative stomatitis, gastritis, peptic ulceration, bloating, decreased appetite, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation, pancreatitis	Exacerbation of colitis and Crohn's disease
Hepato-biliary disorders		Abnormalities of liver function tests, hepatitis, jaundice, hepatic function abnormal, hepatic failure	
Skin and subcutaneous tissue disorders	Skin rash	Pruritus, urticaria, purpura, angioedema, severe forms of skin reactions (e.g. erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis)	Photosensitivity reactions, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4), Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders		Impairment of renal function., acute reversible renal failure, nephrotoxicity in variation forms e.g. tubulointerstitial nephritis, nephrotic syndrome and renal failure	Renal tubular acidosis**

Paracetamol:			
SYSTEM ORGAN CLASS	**FREQUENT**	**LESS FREQUENT**	**FREQUENCY UNKNOWN** (cannot be estimated from the available data)
Blood and lymphatic system disorders:		Haematological reactions (including thrombocytopenia, leucopenia, pancytopenia, neutropenia, agranulocytosis)	
Immune system disorders:		Sensitivity reactions resulting in reversible skin rash or blood disorders may occur.	Drug-induced hypersensitivity syndrome (DIHS) (see section 4.4) *
Hepatobiliary disorders		Hepatitis	
Skin and subcutaneous tissue disorders			Fixed drug eruptions (FDE) (see section 4.4) *
Renal and urinary disorders		Renal colic, renal failure	
Codeine phosphate:			
SYSTEM ORGAN CLASS	**FREQUENT**	**LESS FREQUENT**	**FREQUENCY UNKNOWN** (cannot be estimated from the available data)
Nervous system disorders:		Drowsiness, confusion and restlessness. Raised intracranial pressure, vertigo, changes in mood	
Eye disorders:		Miosis.	
Cardiac disorders:		Bradycardia and palpitations, orthostatic hypotension	

Respiratory, thoracic and mediastinal disorders		Respiratory depression	
Gastrointestinal disorders:		Nausea, vomiting, constipation and dry mouth, acute pancreatitis**	
Skin and subcutaneous tissue disorders:		Sweating and facial flushing. Reactions such as urticarial and pruritus may occur.	
Renal and urinary disorders:		Micturition may be difficult and there may be ureteric or biliary spasm.	
General disorders and administrative site conditions:		Hypothermia.	

Post-marketing experience

**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).*

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

***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

Gastrointestinal disorders: A transient sensation of burning in the mouth or throat may occur with MYPRODOL® SUSPENSION.

Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, rarely, erythema multiforme, bullous dermatoses (including Stevens Johnson syndrome and toxic epidermal necrolysis).

Cardiac disorders and vascular disorders: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment, such as ibuprofen as in MYPRODOL® SUSPENSION. Clinical studies suggest that use of ibuprofen, as in MYPRODOL® SUSPENSION, particularly at high dose (2 400 mg/day) may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke (see section 4.4).

Infections and infestations: Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as SLE and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).
Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs, such as ibuprofen as in MYPRODOL® SUSPENSION, has been described. If signs of an infection occur or get worse during use of MYPRODOL® SUSPENSION, the patient is therefore recommended to go to a doctor without delay.

Skin and subcutaneous tissue disorders: In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see section 4.4 "Infections and infestations")

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

4.9 Overdose
Paracetamol:
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 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 drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.
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 arrhythmias have been reported.

Treatment for paracetamol overdosage:

Although evidence is limited, it is recommended that for any adult person who has ingested 5-10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, a single dose of 50 g activated charcoal given. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above).

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.

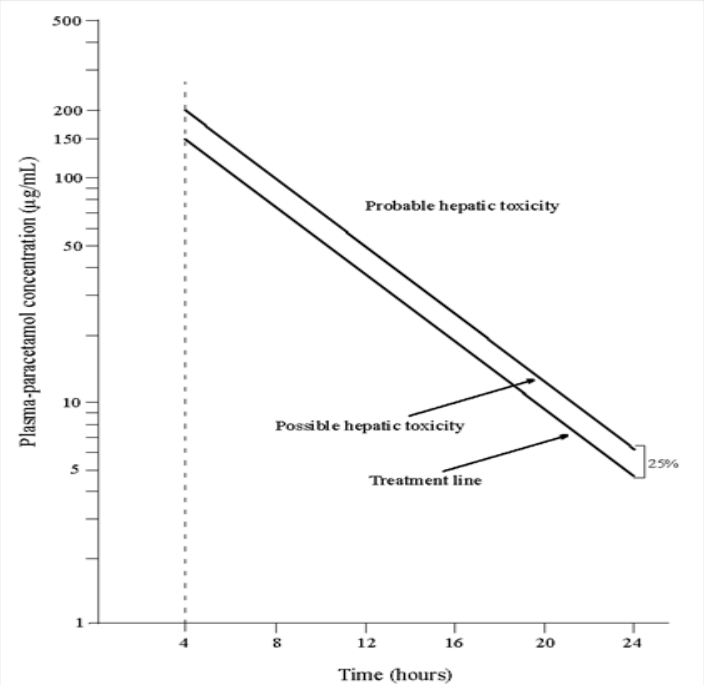
An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen hours. **The volume of 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 4-hour 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.



Ibuprofen:
The most likely symptoms of overdosage are epigastric pain and nausea.
Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults.
However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.
Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.
The most frequently reported symptoms of overdose include gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting), central nervous system symptoms (e.g. lethargy, drowsiness), gastrointestinal haemorrhage, acute renal failure, convulsions and coma.
Central nervous system (CNS) effects include headache, tinnitus, dizziness and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, apnoea, diarrhoea and depression of the CNS and respiratory system have also been reported.
In serious poisoning metabolic acidosis may occur. Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported.
In cases of significant overdose, acute renal failure and liver damage are possible.
Large overdoses are generally well tolerated when no other medicines are being taken.
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).

Treatment in ibuprofen overdosage:
Within one hour of ingestion of a potentially toxic amount, 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. Other measures may be indicated by the patient's clinical condition

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

Treatment in codeine overdosage:
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-ray 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 millilitres of water per 30 grams charcoal.
The optimum dose has not been established, but the usual dose is 25 to 100 grams in adults and adolescents; 25 to 50 grams in children aged 1 to 12 years (or 0,5 to 1 gram/kilogram body weight); and 1 gram/kilogram 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 to 2 milligrams 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 Analgesics combinations
Pharmacotherapeutic group: Codeine and other non-opioid analgesics
ATC code: N02AJ09

Mechanism of action
MYPRODOL® SUSPENSION has an analgesic, anti-inflammatory and antipyretic 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
Ibuprofen
Rapidly absorbed after oral administration.
Paracetamol
Absorption following oral administration is rapid and almost complete.
Codeine phosphate
Readily absorbed from the gastrointestinal tract.

Distribution
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.

Paracetamol
Paracetamol has a half-life of 1 to 4 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.
Codeine phosphate
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 phosphate
Codeine is metabolised in the liver. The cytochrome P450 enzyme 2D6 converts codeine to morphine, one of its metabolites. About 10 % of the dose is demethylated to morphine. Onset of action is 30 to 45 minutes.

Elimination
Ibuprofen
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 3 % of a dose may be excreted unchanged.
Codeine phosphate
Codeine is eliminated via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Blackcurrant NE 53984,
Citric acid anhydrous,
Disodium edetate,
Glycerine,
Kaolin light,
Polyethylene glycol 4000,
Polyvinylpyrrolidone (PVP) K25,
Purified water,
Raspberry red H 1277,
Sodium benzoate (Preservative),
Sodium citrate,
Sodium cyclamate (Sweetener),
Sodium metabisulphite (Antioxidant),
Sodium saccharin 500 (Sweetener),
Sodium dihydrogen phosphate dehydrate,
Xanthan gum TF.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at or below 30 °C in well-closed containers.
Protect from light.

6.5 Nature and contents of container
100 ml amber round glass bottle, with a polypropylene lined (with an expanded polyethylene liner) white screw cap.
200 ml amber round glass bottle, with a polypropylene lined (with an expanded polyethylene liner) white screw cap.
200 ml amber round PVC bottle with a low-density polyethylene white snap-on cap.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road,
Erand Gardens,
1685
Midrand
Customer Care: 0860 ADCOCK 232625

8. REGISTRATION NUMBER(S)
Y/2.8/119

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22 June 1994

10. DATE OF REVISION OF THE TEXT
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