1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

MYBULEN SUSPENSION 200 mg/ 10 mg/ 250 mg per 10 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml of MYBULEN SUSPENSION contains 200 mg ibuprofen, 10 mg codeine phosphate and 250 mg paracetamol.

Preservative: Sodium benzoate 0,1 % *m/v*

Contains sugar: Sorbitol 3,26 g per 10 ml

Contains sweetener: Sodium cyclamate 50 mg per 10 ml, saccharin sodium 7 mg per 10 ml

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension

MYBULEN SUSPENSION is a pink, homogenous suspension with a fruity, blackcurrant odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MYBULEN SUSPENSION is indicated for the relief of mild to moderate pain of inflammatory origin with or without fever for a maximum treatment period of 5 days.

4.2 Posology and method of administration

Posology

AGE	DOSAGE	MAXIMUM DAILY DOSE
Adults and children over the age of 12 years:	Take 10 ml to 20 ml (two to four medicine measures) four hourly.	Do not exceed 60 ml (12 medicine measures) in a 24-hour period.
Children 3 to 5 years:	Take 2,5 ml to 5 ml (half to one medicine measure) three to four times daily.	Do not exceed 1 ml/kg of body weight in a 24-hour period (maximum of 20 ml).
Children 6 to 12 years:	Take 5 ml to 10 ml (one to two medicine measures) three to four times daily.	Do not exceed 1 ml/kg of body weight in a 24-hour period (maximum of 40 ml).

Consult your healthcare provider if no relief is obtained with the recommended dosage.

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

DO NOT EXCEED THE RECOMMENDED DOSE.

Paediatric population

For children below 3 years of age, no recommendation on a posology can be made.

Method of administration

For oral administration.

Shake the bottle before use.

4.3 Contraindications

MYBULEN SUSPENSION is contraindicated in:

- Patients with hypersensitivity to ibuprofen, paracetamol, codeine phosphate or to any excipients in MYBULEN SUSPENSION (see section 6.1).
- Patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, after operations on the biliary tract, acute alcoholism, head injuries and conditions in which intracranial pressure is raised.
- Patients taking Monoamine Oxidase Inhibitors (MAOIs) or within 14 days of stopping such treatment (see section 4.5).
- Patients who are receiving coumarin anticoagulants (see section 4.5).
- Diarrhoea associated with pseudomembranous colitis.
- Patients with impaired hepatic and renal function (see section 4.4).
- Patients with heart failure or cardiovascular disease.
- Patients with an active or a history of recurrent ulcer/haemorrhage/perforations.
- Patients with a history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including MYBULEN SUSPENSION.
- Patients who are sensitive to aspirin or another nonsteroidal anti-inflammatory medicines (NSAIDs).
- 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.
- Newborn babies (up to 4 weeks old) as it contains sodium benzoate (see section 4.4) and may increase jaundice.
- Safety in lactation has not been established (see section 4.6).
- Women around 30 weeks gestation and later in pregnancy due to the risks of

oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

Paracetamol

MYBULEN SUSPENSION 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 of MYBULEN SUSPENSION in excess of those recommended may cause severe liver damage.

DEPENDENCE MAY DEVELOP WITH PROLONGED USE OF HIGH DOSES.

High anion gap metabolic acidosis (HAGMA)

Caution is advised if MYBULEN SUSPENSION is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of MYBULEN SUSPENSION. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Ibuprofen

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

Respiratory disorders and hypersensitivity reactions

Caution is required if MYBULEN 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 MYBULEN 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).

Renal and hepatic impairment

The administration of an NSAID, such as ibuprofen as in MYBULEN SUSPENSION, may cause a dose dependent 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 taking 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).

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

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 include reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as codeine. Abuse or intentional misuse of MYBULEN 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.

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 MYBULEN SUSPENSION therapy (see section 4.3). In view of MYBULEN SUSPENSION's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

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

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 MYBULEN SUSPENSION for a prolonged period of time (see section 4.5).

Gastrointestinal bleeding, ulceration and perforation

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

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

Patients with a history of gastrointestinal disease, particularly when 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, selective serotonin-reuptake inhibitors or antiplatelet medicines such as aspirin (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving MYBULEN SUSPENSION, treatment with MYBULEN SUSPENSION should be stopped.

MYBULEN 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.

The use of MYBULEN 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 MYBULEN 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.

Dehydration

Caution should be used when initiating treatment with MYBULEN 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 MYBULEN 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 MYBULEN 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

MYBULEN 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 MYBULEN SUSPENSION, especially gastrointestinal perforation, ulceration or bleeding (PUBs), which may be fatal (see section 4.2).

Surgery

Possible enhanced bleeding, if surgery is required.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients with paracetamol containing medicines, such as MYBULEN SUSPENSION (see section 4.8). If a patient develops SCARs, treatment with MYBULEN SUSPENSION must immediately be discontinued and appropriate treatment instituted. 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.

Drug reaction with eosinophilia and systemic symptoms

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs, such as MYBULEN 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. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue MYBULEN SUSPENSION and evaluate the patient immediately.

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 MYBULEN SUSPENSION, in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of MYBULEN 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 MYBULEN 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.

Impaired female fertility

The use of MYBULEN 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 MYBULEN SUSPENSION should be considered (see section 4.6).

Foetal Toxicity

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

Codeine phosphate

Dependency

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

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

Use in patients with a history of mental health disorders

There is an increased risk of addiction to MYBULEN SUSPENSION when it is used in patients with a personal or family history of substance abuse or mental health disorders.

General precautions

MYBULEN 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 MYBULEN 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.
- Prostatic hypertrophy, obstruction, urethral stricture or recent urinary tract surgery, as urinary retention may be precipitated by MYBULEN 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 depressant effects of codeine, as in MYBULEN SUSPENSION, are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, and phenothiazines (see section 4.5).

Elderly

The dosage should be reduced in elderly or debilitated patients.

Paediatric population

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

Excipients

MYBULEN SUSPENSION contains sorbitol and may have a laxative effect. Patients with the rare hereditary condition of sorbitol intolerance should not take MYBULEN SUSPENSION. The additive effect of concomitantly administered medicines containing sorbitol and dietary intake of sorbitol should be taken into account. The content of sorbitol in medicines for oral use may affect the bioavailability of other medicines for oral use administered concomitantly.
MYBULEN SUSPENSION contains less than 1 mmol sodium per 10 mL, that is to say essentially 'sodium-free'.
MYBULEN SUSPENSION 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).
MYBULEN SUSPENSION contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction 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 MYBULEN SUSPENSION, are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, and phenothiazines.
- *Anticholinergics, antimuscarinics or medicines with antimuscarinic action:* Increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.
- *Antidiarrhoeals and antiperistaltic medicines:* Increased risk of severe constipation and central nervous system depression.
- *Neuromuscular blocking medicines*: The respiratory depressant effects may be additive to the central respiratory depressant effects of MYBULEN SUSPENSION.
- *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 MYBULEN SUSPENSION.
- *Metoclopramide or domperidone:* Absorption of paracetamol, as in MYBULEN SUSPENSION, may be accelerated.
- *Probenecid:* Excretion of paracetamol, as in MYBULEN SUSPENSION, may be affected and plasma concentrations altered.
- *Colestyramine:* Absorption of paracetamol, as in MYBULEN SUSPENSION, is reduced if given within one hour of colestyramine. The concomitant administration of MYBULEN SUSPENSION and colestyramine may reduce the absorption of MYBULEN SUSPENSION in the gastrointestinal tract.
- *Anticoagulants:* Enhancement of anticoagulant effects of anti-coagulants such as

warfarin and the possibility of gastrointestinal ulceration or bleeding (see section 4.3).

- *Alcohol, corticosteroids, clopidogrel, ticlopidine, bisphosphonates, oxpentifylline:* Increased risk of gastrointestinal perforation, bleeding and ulceration (see section 4.4).
- *Antidiabetic medicines:* Hypoglycaemic effects of these medicines may be increased.
- *Sulfonylureas:* MYBULEN SUSPENSION may potentiate the effects of sulfonylurea medicines. There have been reports of hypoglycaemia in patients on sulfonylurea medicines receiving ibuprofen as in MYBULEN SUSPENSION.
- *Cardiac glycosides such as digoxin:* MYBULEN 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:* MYBULEN 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 MYBULEN SUSPENSION. Evidence suggests that coadministration of NSAIDs, such as ibuprofen as in MYBULEN 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 MYBULEN SUSPENSION, including cox-2 inhibitors, as this may increase the risk of adverse effects (see section 4.4).
- *Aspirin (Acetylsalicylic acid):* Concomitant administration of MYBULEN 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 MYBULEN SUSPENSION, may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly.

- *Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs):* Increased risk of gastrointestinal bleeding with MYBULEN SUSPENSION (see section 4.4).
- *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 MYBULEN SUSPENSION.
- *Bone marrow depressant:* The leucopenic and/or thrombocytopenic effects of these medicines may be increased.
- *Quinolone antibiotics:* NSAIDs, such as ibuprofen as in MYBULEN SUSPENSION, can increase the risk of convulsions associated with quinolone antibiotics. Patients taking MYBULEN SUSPENSION and quinolones may have an increased risk of developing convulsions.
- *Aminoglycosides:* MYBULEN SUSPENSION may decrease the excretion of aminoglycosides.
- *Hydroxyzine*: Analgesia as well as increased CNS depressant and hypotensive effects may be increased.
- *Quinidine*: The analgesic effect of MYBULEN SUSPENSION may be inhibited.
- *Mexiletine*: The absorption of mexiletine and thus reduce the antiarrhythmic effect.
- *Cimetidine*: The metabolism of MYBULEN SUSPENSION is inhibited resulting in increased plasma concentrations.

- *Naloxone*: Naloxone antagonises the analgesic, CNS and respiratory depressant effects of MYBULEN SUSPENSION. Naltrexone also blocks the therapeutic effect of MYBULEN SUSPENSION.
- *Flucloxacillin:* Caution should be taken when MYBULEN SUSPENSION is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).
- *Tacrolimus:* Possible increased risk of nephrotoxicity when MYBULEN SUSPENSION is given with tacrolimus.
- *Zidovudine:* Increased risk of haematological toxicity when MYBULEN 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 MYBULEN SUSPENSION.
- *CYP2C9 Inhibitors:* Concomitant administration of MYBULEN SUSPENSION with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate), as in MYBULEN 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 MYBULEN SUSPENSION dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose MYBULEN SUSPENSION is administered with either voriconazole or fluconazole.
- *Herbal extracts:* Ginkgo biloba may potentiate the risk of bleeding with MYBULEN SUSPENSION.

4.6 Fertility, pregnancy and lactation

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

Pregnancy

Ibuprofen

First trimester

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.

Second and third trimester

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, such as ibuprofen as in MYBULEN SUSPENSION, may expose the foetus to:

• Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension).

• Renal dysfunction, which may progress to renal failure with oligohydramnios (see section 4.4).

At the end of pregnancy, the mother and the neonate may be exposed to:

• Possible prolongation of bleeding time.

• Inhibition of uterine contractions, which may result in delayed or prolonged labour (see section 4.4).

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

Breastfeeding

NSAIDs, such as ibuprofen as in MYBULEN SUSPENSION, can appear in the breast milk in very low concentrations. MYBULEN SUSPENSION is not recommended for use by breastfeeding women (see section 4.3).

Fertility

The use of MYBULEN 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

MYBULEN SUSPENSION has a minor influence on the ability to drive or use machines. Since adverse reactions such as drowsiness, dizziness and blurred vision, have been reported in patients receiving MYBULEN SUSPENSION, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain MYBULEN SUSPENSION does not adversely affect their ability to do so (see section 4.4).

4.8 Undesirable effects

a) *Summary of the safety profile*

Ibuprofen:

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI 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 MYBULEN SUSPENSION, administration. Less frequently, gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed.

b) Tabulated list of adverse reactions

Ibuprofen

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Rhinitis, aseptic meningitis	
Blood and the lymphatic system disorders		Agranulocytosis, thrombocytopenia, leucopenia, neutropenia, aplastic anaemia, haemolytic anaemia, pancytopenia	
Immune system disorders		Hypersensitivity reactions, anaphylactic reaction	
Psychiatric disorders		Insomnia, anxiety, depression, confusional state, nervousness.	
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		Heart failure which may be precipitated in compromised patients, angina pectoris, cardiac dysrhythmias, myocardial infarction, oedema	
Vascular disorders		Hypertension	
Respiratory, thoracic and mediastinal disorders		Asthma, bronchospasm, dyspnoea	

Gastrointestinal disorders	Dyspepsia, diarrhoea, nausea, vomiting, abdominal cramps and pain, flatulence, constipation, melaena, haematemesis, gastrointestinal haemorrhage	Peptic ulceration, bloating, decreased appetite, gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation, pancreatitis, ulcerative stomatitis	Exacerbation of Colitis and Crohn´s disease.
Hepatobiliary 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 eosinophilia and systemic symptoms (DRESS syndrome)/ Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE), Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders		Impaired renal function, acute reversible renal failure, nephrotoxicity in various 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 the lymphatic system disorders		Haematological reaction (including thrombocytopenia, leucopenia, pancytopenia, neutropenia, agranulocytosis)	
Immune system disorders		Hypersensitivity reactions resulting in reversible skin rash (which may be accompanied by fever and mucosal lesions) or blood disorders	

Metabolism and nutrition disorders			Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis
Hepatobiliary disorders		Hepatitis	
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)
Metabolism and nutrition disorders			Hypokalaemia
Nervous system disorders		Confusion, vertigo, restlessness, changes in mood, raised intracranial pressure, drowsiness	
Eye disorders		Myosis	
Cardiac disorders		Bradycardia, palpitations, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		Respiratory depression	
Gastrointestinal disorders		Nausea, vomiting, constipation, dry mouth	
Skin and subcutaneous tissue disorders		Sweating, facial flushing, urticaria, pruritus	
Renal and urinary disorders		Micturition difficulties, ureteric or biliary spasm	
General disorders and administrative site conditions		Hypothermia	

c) Description of selected adverse reactions

Ibuprofen

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

Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs, such as ibuprofen as in MYBULEN 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, e.g., 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 MYBULEN SUSPENSION. Clinical studies suggest that use of ibuprofen, as in MYBULEN 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 MYBULEN SUSPENSION, has been described. If signs of an infection occur or get worse during use of MYBULEN 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. 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.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

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

4.9 Overdose

Symptoms

(see section 4.8 and 4.4)

Paracetamol

Symptoms of paracetamol overdose 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 of paracetamol, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentrations and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported. Cerebral oedema and non-specific myocardial depression have occurred.

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.

Ibuprofen

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.

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).

Large overdoses are generally well tolerated when no other medicines are being taken.

Treatment

Treatment of overdosage is symptomatic and supportive.

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. A delay in starting treatment may mean that the antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 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.

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 as a 5 % solution may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

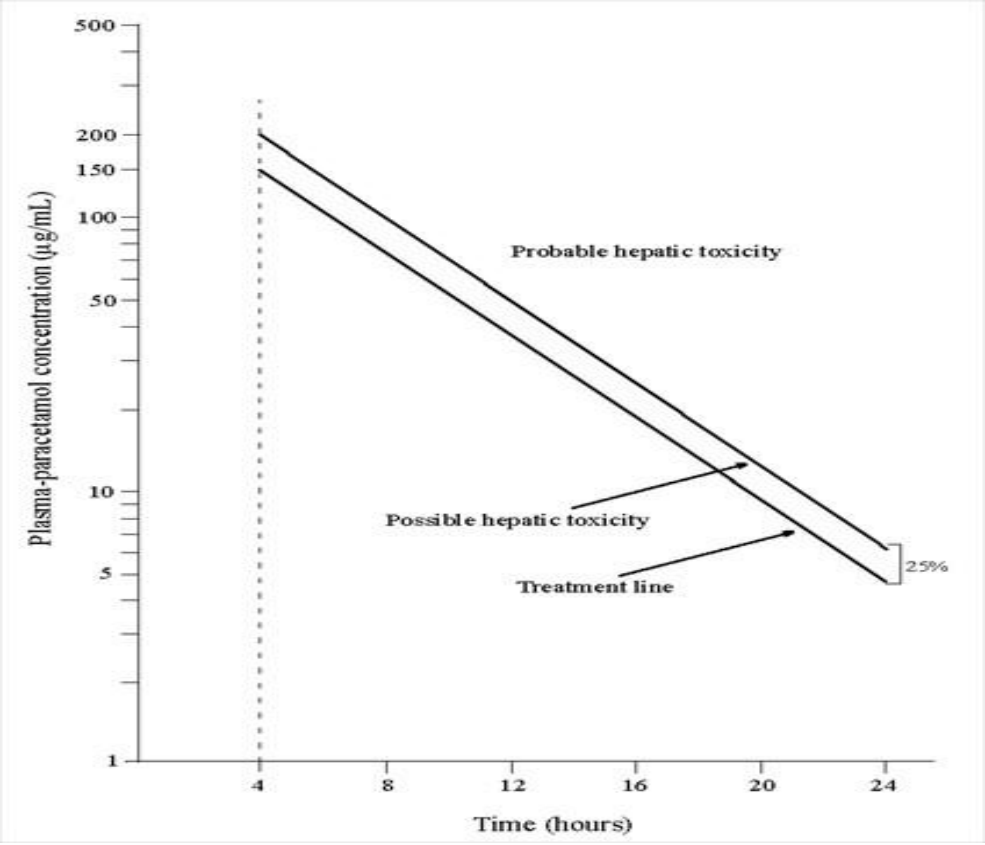
A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours, unless high, may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the treatment nomogram.

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.



Codeine phosphate

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.

Ibuprofen

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

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

MYBULEN 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

Carbomer, colour raspberry red (C.I.14720), flavour blackcurrant, flavour tutti-frutti, glycerol, polysorbate, purified water, saccharin sodium, sodium benzoate, sodium citrate (for pH adjustment), sodium cyclamate, sodium metabisulphite, sorbitol solution.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C in a well-closed container.

Protect from light.

6.5 Nature and contents of container

100 ml is packed into a round, amber glass bottle and sealed with a white, polypropylene child-proof screw cap with a low-density polyethylene liner. The bottle is placed in an outer cardboard carton with a leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

A39/2.8/0237

9. DATE OF FIRST AUTHORISATION

23 September 2005

10. DATE OF REVISION OF TEXT

18 November 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

Namibia: NS2 10/2.8/0562

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