1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

MYBULEN CAPSULES 200 mg/ 10 mg/ 250 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of MYBULEN CAPSULES contains 200 mg ibuprofen, 10 mg codeine phosphate, 250 mg paracetamol.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

MYBULEN CAPSULES is a white to off-white, compacted powder, encapsulated in a size “0” capsule with a blue cap and blue body.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MYBULEN CAPSULES are 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

DO NOT EXCEED THE RECOMMENDED DOSE.

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

Adults (over the age of 12 years)

Take one to two capsules 4 hourly.

Do not take more than 6 capsules in a 24 hour period.

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

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

Paediatric population

Not recommended for children 12 years of age and younger.

Method of administration

For oral administration.

4.3. Contraindications

MYBULEN CAPSULES are contraindicated in:

- Patients with hypersensitivity to ibuprofen, paracetamol, codeine, or to any excipients in MYBULEN CAPSULES (see section 6.1).
- Patients who are sensitive to aspirin or other NSAIDs.
- Patients with a history of gastrointestinal ulceration, bleeding or perforation (PUBs) related to previous NSAIDs, including MYBULEN CAPSULES.
- Patients with an active or a history of recurrent gastrointestinal ulcer, haemorrhage or perforations.
- Patients with impaired hepatic and renal function (see section 4.4).

- Patients with heart failure or cardiovascular disease.
- 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 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.
- 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

Ibuprofen

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

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 CAPSULES therapy (see section 4.3).

MYBULEN CAPSULES should only be administered under strict consideration of the benefit-risk ratio in the following conditions: Systemic Lupus Erythematosus (SLE) or mixed connective tissue diseases; congenital disturbance of porphyrin metabolism (e.g. acute intermittent porphyria).

Special care has to be taken in the following cases:

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

Elderly

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

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

Gastrointestinal bleeding, ulceration and perforation

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

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

Patients with a history of gastrointestinal toxicity, 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 anti-platelet medicines such as acetylsalicylic acid (see section 4.5).

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

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

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

Cardiovascular and cerebrovascular effects

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

In view of MYBULEN CAPSULES'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 CAPSULES after careful consideration.

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported (see section 4.8).

Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported.

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

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

Drug reaction with eosinophillia and systemic symptoms

Drug reaction with eosinophillia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs such as MYBULEN CAPSULES. 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 MYBULEN CAPSULES and evaluate the patient immediately.

Hepatic effects

Hepatic function impairment may increase the risk of hepatotoxicity (see sections 4.3 and 4.8).

Renal effects

Ibuprofen, as in MYBULEN CAPSULES, may cause the retention of sodium, potassium and fluid in patients who have not previously suffered from renal disorders because of its effect on renal perfusion. This may cause oedema or even lead to cardiac insufficiency or hypertension in predisposed patients.

MYBULEN CAPSULES are contraindicated in renal function impairment as renal failure may be provoked (see section 4.3).

There have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome. Cases of renal toxicity have also been observed in patients in whom prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of MYBULEN CAPSULES may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of suffering this reaction are those with renal dysfunction, heart failure, hepatic dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of MYBULEN CAPSULES is generally followed by recovery to the pre-treatment state.

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

Asthma

Asthma may be exacerbated (see section 4.3).

Masking of symptoms of underlying infections

The antipyretic, analgesic and anti-inflammatory action of MYBULEN CAPSULES may mask the signs and symptoms of the occurrence 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 CAPSULES are administered for fever or pain relief in relation to infection, monitoring of infection is advised. In nonhospital settings, the patient should consult a doctor if symptoms persist or worsen.

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Aseptic meningitis

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

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

Other precautions

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

Bronchospasm, urticaria or angioedema may be precipitated in patients suffering from or with a previous history of bronchial asthma, chronic rhinitis, sinusitis, nasal polyps, adenoids or allergic diseases. Ibuprofen, as in MYBULEN CAPSULES, may mask the signs or symptoms of an infection (fever, pain and swelling).

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

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

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

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

Foetal toxicity

Limit use of NSAIDs, including MYBULEN CAPSULES, between 20 and 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Avoid use of NSAIDs in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.3 and 4.6).

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 CAPSULES is necessary between 20 weeks and 30 weeks gestation, limit MYBULEN CAPSULES use to the lowest effective dose and shortest duration possible.

Healthcare professionals should consider ultrasound monitoring of amniotic fluid if MYBULEN CAPSULES treatment extends beyond 48 hours. Discontinue MYBULEN CAPSULES if oligohydramnios occurs and follow up according to clinical practice.

Paracetamol

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

General precautions

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

Alcohol

Alcohol should be avoided.

Increased risk of liver toxicity, especially in alcoholics using high doses of MYBULEN CAPSULES for a prolonged period of time.

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, patients should contact their doctor as additional treatment may be necessary.

Codeine phosphate

Dependency

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

General precautions

MYBULEN CAPSULES 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 CAPSULES 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.
- Drug abuse or dependence, as these patients are predisposed to drug abuse. Alcohol should be avoided (see section 4.5).
- Gallbladder disease or gallstones as these may cause biliary tract spasm.
- Recent gastrointestinal tract surgery.
- Hypothyroidism, as MYBULEN CAPSULES may increase the risk of respiratory depression and prolonged central nervous system depression.
- Adrenocortical insufficiency.
- Inflammatory or obstructive bowel disorders, as the risk of toxic megacolon may be increased.

- Prostatic hypertrophy, urethral obstruction, urethral stricture or recent urinary tract surgery as urinary retention may be precipitated by MYBULEN CAPSULES.

Elderly

In elderly or debilitated patients the dosage should be reduced.

Paediatric population

MYBULEN CAPSULES are not recommended for children under twelve years of age (see section 4.2).

4.5. Interaction with other medicines and other forms of interaction

Ibuprofen

Concomitant use of ibuprofen and the following medicines should be avoided

Acetylsalicylic acid

Concomitant administration of ibuprofen, as in MYBULEN CAPSULES, and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Data suggest that ibuprofen, as in MYBULEN CAPSULES, may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of MYBULEN CAPSULES may reduce the cardio protective effect of low-dose acetylsalicylic acid cannot be excluded.

Other NSAIDs including cyclooxygenase- 2 selective inhibitors

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

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

Anti-coagulants

MYBULEN CAPSULES may enhance the effects of anti-coagulants such as warfarin or heparin (see section 4.3 and 4.4).

Methotrexate

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

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

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

Corticosteroids

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

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

Increased risk of gastrointestinal bleeding and ulceration (see section 4.4).

Antihypertensives, beta blockers and diuretics

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

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

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

Diuretics can also increase the risk of nephrotoxicity of MYBULEN CAPSULES.

Captopril

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

Aminoglycosides

MYBULEN CAPSULES may decrease the excretion of aminoglycosides and increase their toxicity.

Antidiabetic medicines (eg. sulfonylureas)

The hypoglycaemic effects of these medicines may be increased.

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

Digoxin, phenytoin and lithium

MYBULEN CAPSULES may exacerbate cardiac failure and reduce glomerular filtration rate.

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

Ciclosporin

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

Tacrolimus

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

Colestyramine

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

Mifepristone

If NSAIDs, such ibuprofen as in MYBULEN CAPSULES, are used within 8 to 12 days after mifepristone administration they can reduce the effect of mifepristone. A decrease in the efficacy of mifepristone may occur due to the antiprostaglandin properties of MYBULEN CAPSULES.

Probenecid or sulfinpyrazone

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

Quinolone antibiotics

MYBULEN CAPSULES can increase the risk of convulsions associated with quinolone antibiotics. Patients taking MYBULEN CAPSULES and quinolones may have an increased risk of developing convulsions.

Zidovudine

Increased risk of haematological toxicity when MYBULEN CAPSULES are given with zidovudine. There is evidence of an increased risk of haemarthrosis and haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen, as in MYBULEN CAPSULES. Blood counts 1 to 2 weeks after starting use together are recommended.

Ritonavir

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

Moclobemide (MAOI)

The side effects of MYBULEN CAPSULES may be enhanced with moclobemide.

Bone marrow depressants

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

Alcohol, bisphosphonates and oxpentifylline

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

Baclofen

Elevated baclofen toxicity.

CYP2C9 Inhibitors

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

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

Herbal extracts

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

Paracetamol

Enzyme-inducing and hepatotoxic medicines

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

Metoclopramide

Absorption of paracetamol, as in MYBULEN CAPSULES, may be accelerated.

Colestyramine

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

Probenecid

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

Codeine phosphate

Monoamine oxidase inhibitors (MAOIs)

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

Alcohol or central nervous system depressants

The depressant effects of MYBULEN CAPSULES is enhanced.

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.

4.6. Fertility, pregnancy and lactation

MYBULEN CAPSULES are 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 the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-

implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Second and third trimester

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

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

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

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour (see section 4.4).

Because of these risks, the use of MYBULEN CAPSULES, 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).

Codeine phosphate

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

Paracetamol

Paracetamol as part of a combination medicine, as contained in MYBULEN CAPSULES, should not be taken. Frequent use of paracetamol in late pregnancy may be associated with an increased risk of persistent wheezing in the infant which may persist into childhood.

Breastfeeding

Ibuprofen

Ibuprofen, as in MYBULEN CAPSULES is excreted in the breast milk in very low concentrations.

With therapeutic doses during short term treatment the risk for influence on the infant seems unlikely. If, however, longer treatment is prescribed, early weaning should be considered.

MYBULEN CAPSULES should not be used during breastfeeding.

Codeine phosphate

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

Fertility

Ibuprofen

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

4.7. Effects on ability to drive and use machines

MYBULEN CAPSULES has a minor influence on the ability to drive or use machines.

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

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 gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

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

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

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

b) Tabulated list of adverse reactions

Ibuprofen

System organ class	Frequent	Less frequent	Frequency unknown

			(cannot be estimated from the available data)
Infections and infestations		Rhinitis, aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, nausea, vomiting, fever or disorientation	
Blood and the lymphatic system disorders		Haematopoietic disorders (leukopenia, pancytopenia, agranulocytosis, thrombocytopenia with or without purpura, aplastic anaemia, haemolytic anaemia, anaemia, neutropenia). The first symptoms or signs may include: fever, sore throat, surface mouth ulcers, flu-like symptoms, severe fatigue, nasal and skin bleeding, unexplained bleeding and bruising	
Immune system disorders		Hypersensitivity reactions such as urticaria, pruritus, purpura and exanthema as well as asthma attacks (sometimes with hypotension); severe hypersensitivity reactions. The symptoms may include: facial oedema, swelling of the tongue, internal laryngeal swelling with constriction of the airways, dyspnoea, tachycardia, fall of blood pressure to the point of life- threatening shock	Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea
Psychiatric disorders		Confusional state, nervousness, insomnia, depression, anxiety, hallucination	
Nervous system disorders	Dizziness	Drowsiness, headache, somnolence, fatigue, agitation, irritability	Paraesthesia
Eye disorders		Blurred vision, other ocular reactions, toxic amblyopia	Visual impairment, toxic optic neuropathy
Ear and labyrinth disorders		Tinnitus	Impaired hearing, vertigo

Cardiac disorders		Heart failure may be precipitated in compromised patients, angina pectoris, cardiac dysrhythmias palpitations, myocardial infarction, acute pulmonary oedema.	Oedema, hypertension
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Gastrointestinal disorders	Heartburn, dyspepsia, abdominal cramps and pain, nausea, vomiting, flatulence, diarrhoea, constipation, gastric irritation	Peptic ulceration, perforation or gastrointestinal bleeding sometimes fatal; gastrointestinal ulcers, sometimes with bleeding and perforation, occult blood loss which may lead to anaemia, melaena, haematemesis, ulcerative stomatitis; exacerbation of colitis, Crohn's disease and inflammatory bowel disease, complications of colonic diverticula (perforation, fistula), gastritis, bloating, decreased appetite, oesophagitis, pancreatitis, intestinal strictures	
Hepatobiliary disorders		Abnormalities of liver function tests, hepatitis, jaundice, liver dysfunction, liver damage, especially in long-term use, hepatic failure	
Skin and subcutaneous tissue disorders	Skin rash, pruritus	Photosensitivity reaction, severe forms of skin reactions (erythema multiforme, exfoliative dermatitis, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, alopecia, necrotising fasciitis	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders		Impairment of renal function, acute renal failure, renal papillary necrosis in long-term use; development of oedema especially in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis which can be associated with renal failure	
General disorders and administrative site conditions			Malaise

Investigations		Increase of blood urea nitrogen, serum transaminases and alkaline phosphatase, decrease in haemoglobin and haematocrit values, inhibition of platelet aggregation, prolonged bleeding time, decrease of serum calcium, increase in serum uric acid	

Paracetamol

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Haematological reaction (including agranulocytosis, thrombocytopenia, neutropenia, pancytopenia, leukopenia)	
Hepatobiliary disorders		Hepatitis	
Skin and subcutaneous tissue disorders		Hypersensitivity reactions resulting in reversible skin rash (which may be accompanied by fever and mucosal lesions) or blood disorders	
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		Confusion, drowsiness, restlessness, changes in mood, vertigo, raised intracranial pressure	
Eye disorders		Miosis	
Cardiac disorders		Bradycardia, palpitations, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		Respiratory depression	
Gastrointestinal disorders		Nausea, vomiting, constipation, dry mouth	

Hepatobiliary disorders		Biliary spasm	
Skin and subcutaneous tissue disorders		Sweating, facial flushing, urticaria, pruritus	
Renal and urinary disorders		Micturition difficulties, ureteric spasm	
General disorders and administrative site conditions		Hypothermia	

c) Description of selected adverse reactions

Ibuprofen

Acute reversible renal failure has been reported.

Hypersensitivity reactions have been reported following treatment with ibuprofen, as in MYBULEN CAPSULES. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The pathogenic mechanism of medicine-induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with medicine intake, and disappearance of symptoms after medicine discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen, in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

Codeine phosphate

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

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

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

d) Paediatric population

MYBULEN CAPSULES are not recommended for use for children under twelve years of age (see section 4.2).

e) Other special populations

The dosage should be reduced in elderly and debilitated patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

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

4.9. Overdose

Symptoms

The most frequently reported symptoms of overdose for the ingredients as contained in MYBULEN CAPSULES are mentioned below.

Ibuprofen

Most patients who have ingested significant amounts of ibuprofen, as in MYBULEN CAPSULES, will manifest symptoms within 4 to 6 hours.

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

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

In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, dizziness, drowsiness, occasionally excitation and loss of consciousness or coma. Children may also develop myoclonic cramps. In serious poisoning metabolic acidosis may occur, hypothermia and hyperkalaemia may also occur, and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Paracetamol

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 of paracetamol, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentrations and international normalised ratio (INR) (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

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

Treatment

The following treatment is indicated for the ingredients as contained in MYBULEN CAPSULES

Prompt treatment is essential as MYBULEN CAPSULES contains paracetamol.

Ibuprofen

Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Within one hour of ingestion of a potentially toxic amount, oral administration of activated charcoal should be considered.

Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

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

Frequent or prolonged convulsions should be treated with intravenous diazepam or lorazepam.

Other measures may be indicated by the patient's clinical condition.

If ibuprofen has already been absorbed, alkaline substances should be administered to promote the excretion of the acid ibuprofen in the urine.

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

Paracetamol

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.

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

paracetamol poisoning (see above). In patients who are stuperose or comatose, endotracheal intubation should precede gastric lavage in order to avoid aspiration.

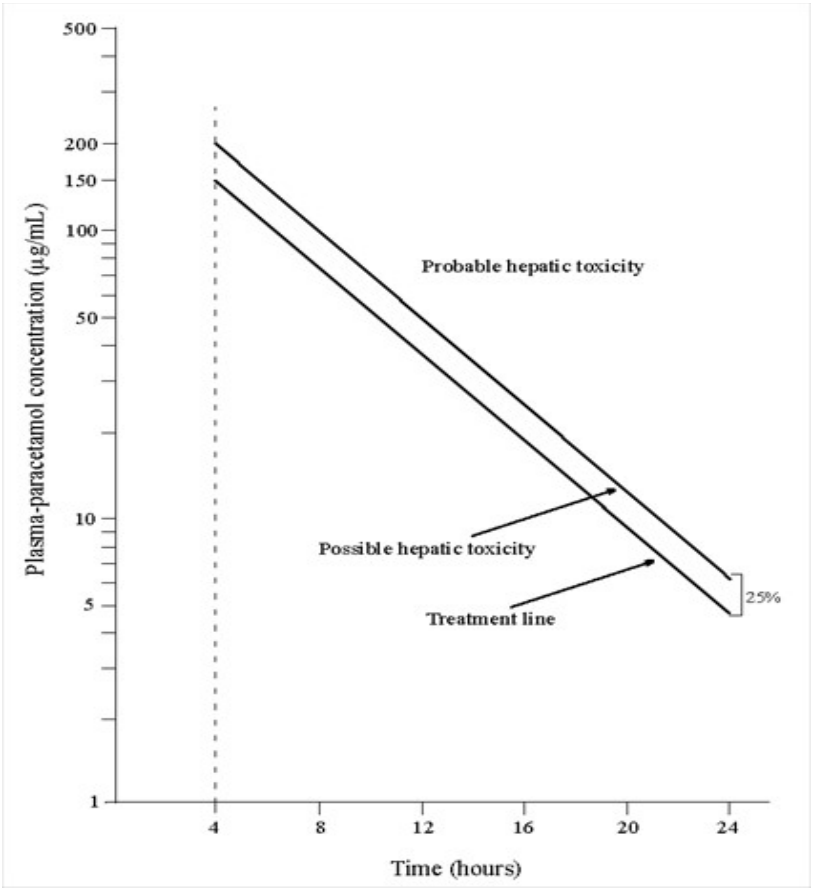
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

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

Although the oral 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 plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the treatment 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.

Codeine phosphate

Treatment of overdosage is symptomatic and supportive.

Treatment is based on clinical presentation.

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.

Consider pre-hospital administration of activated charcoal as 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.

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 Analgesic combinations.

Pharmacotherapeutic group: Codeine and other non-opioid analgesics

ATC code: N02AJ09

Mechanism of action

MYBULEN CAPSULES have an analgesic, anti-inflammatory and antipyretic action.

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.

Paracetamol has analgesic and antipyretic effects.

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

5.2 Pharmacokinetic properties

Absorption

Ibuprofen

Ibuprofen is rapidly absorbed from the gastrointestinal tract after oral administration.

Paracetamol

Absorption following oral administration is rapid and almost complete.

Codeine phosphate

Codeine is readily absorbed from the gastrointestinal tract

Distribution

Ibuprofen

The half-life of ibuprofen is about 2 hours.

Paracetamol

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

Codeine phosphate

Its half-life is 2,5 to 4 hours. The time to peak effect is 1 to 2 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 about 3 % of a dose may be excreted unchanged.

Codeine phosphate

Codeine is eliminated via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Brilliant blue (C.I. 42090), carmoisine (C.I. 14720), colloidal silicon dioxide, gelatin, magnesium stearate, quinoline yellow (C.I. 47005), sodium starch glycollate, titanium dioxide (C.I. 77891)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C in airtight containers.

Protect from moisture.

Keep in original packaging until required for use.

6.5. Nature and contents of container

10 capsules are packed in a clear polyvinylchloride, polyethylene, polyvinylidene chloride film sealed with an aluminium foil backing. The blister strips are packed into a unit cardboard carton together with a leaflet.

30 capsules are packed in a white polypropylene securitainer and sealed with a red or blue low-density polyethylene cap with a tamper evident seal together with a silica gel sachet or a white desiccant disc and a leaflet.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

8. REGISTRATION NUMBER

A38/2.8/0527

9. DATE OF FIRST AUTHORISATION

29 July 2005

10. DATE OF REVISION OF TEXT

23 December 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

Namibia: NS2 10/2.8/0548

ZA_MYBUCAP_2212_00