1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

MYBULEN is a blue, capsule-shaped, film-coated tablet with a break score on one side and debossed with C25 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSAGE.

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

Adults (over the age of 12 years):

Take one to two tablets six hourly if necessary.

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

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

Paediatric population

Not recommended for children 12 years of age and younger.

Method of administration

For oral administration.

4.3 Contraindications

MYBULEN is contraindicated in:

- Patients with hypersensitivity to ibuprofen, paracetamol, codeine or to any excipients in MYBULEN (see section 6.1).
- Patients with a history of gastrointestinal bleeding, ulceration or perforation (PUBs) related to previous NSAIDs, including MYBULEN.
- 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 who are sensitive to aspirin or other non-steroidal anti-inflammatory medicine (NSAIDs).
- Patients during an attack of bronchial asthma, uncontrolled asthma, acute 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).
- Safety in lactation has not been established.
- Women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

Ibuprofen as in MYBULEN

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 therapy (see section 4.3).

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

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

Gastrointestinal bleeding, ulceration and perforation

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

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

Patients with a history of gastrointestinal toxicity, particularly if 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, 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, treatment with MYBULEN should be stopped.

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

Cardiovascular and cerebrovascular effects

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 therapy.

The inherent potential of MYBULEN to cause fluid retention can precipitate heart failure 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 after careful consideration.

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 If a patient develops SCARs, treatment with MYBULEN 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 in the majority of cases within the first month of treatment.

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

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

Hepatic effects

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

Renal effects

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

There have been reports of acute interstitial nephritis with haematuria, proteinuria and occasionally nephrotic syndrome. Cases of renal toxicity have also been observed in patients in whom prostaglandins play a compensatory role in the maintenance of renal perfusion. In these patients, administration of MYBULEN 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 is generally followed by recovery to the pre-treatment state.

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 generalized 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 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, as in MYBULEN, 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.

Asthma

Asthma may be exacerbated (see section 4.3).

Masking of symptoms of underlying infections

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

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 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 (e.g., anaphylactic shock) are observed. At the first signs of hypersensitivity reaction after taking MYBULEN, therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Allergic conditions with a possibility of cross sensitivity with other NSAIDs, including aspirin (see section 4.3 and 4.5).

Bronchospasm, 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, may mask the signs or symptoms of an infection (fever, pain and swelling).

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

MYBULEN 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, especially if affecting the gastrointestinal tract or the central nervous system.
Patients on MYBULEN 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 the use of NSAIDs, including MYBULEN, 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 is necessary between 20 weeks and 30 weeks gestation, limit MYBULEN use to the lowest effective dose and shortest duration possible.
Healthcare professionals should consider ultrasound monitoring of amniotic fluid if MYBULEN treatment extends beyond 48 hours. Discontinue MYBULEN if oligohydramnios occurs and follow up according to clinical practice.

Paracetamol as in MYBULEN

MYBULEN 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.

High Anion gap metabolic acidosis (HAGMA)

Caution is advised if MYBULEN 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. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

General precautions

Dosages of MYBULEN 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 for a prolonged period of time.

Codeine phosphate as in MYBULEN

Dependency

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

Use in patients with a history of mental health disorders

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

General precautions

MYBULEN 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 may decrease respiratory drive and increase airway resistance in these patients (see section 4.3).
- Cardiac dysrhythmias, as this may be induced or exacerbated.
- Convulsions or history thereof, as this 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 this may cause biliary tract spasm.
- Recent gastrointestinal tract surgery.
- Hypothyroidism may increase risk of respiratory depression and prolonged central nervous system depression.
- Adrenocortical insufficiency.
- Inflammatory or obstructive bowel disorders, as risk of toxic megacolon may be increased.
- Prostatic hypertrophy, obstruction, urethral stricture or recent urinary tract surgery as urinary retention may be precipitated by MYBULEN.
- Risk of severe constipation if used with antidiarrhoeal medicines such as diphenoxylate (see section 4.5).
- Myasthenia gravis.

Consult your doctor if pain or fever persists or gets worse, if new symptoms occur or if redness and swelling is present, as these could be signs of a serious condition. Consult a doctor if no relief is obtained from the recommended dosage (see section 4.2).

Elderly

In elderly or debilitated patients, the dosage should be reduced.

Paediatric population

MYBULEN is not recommended for children 12 years of age and younger (see section 4.2)

4.5 Interaction with other medicines and other forms of interaction

Ibuprofen as in MYBULEN

Concomitant use of ibuprofen and the following medicines should be avoided

Acetylsalicylic acid

Concomitant administration of ibuprofen, as in MYBULEN, and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Data suggest that ibuprofen, as in MYBULEN, 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 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, 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 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.

NSAID, such as ibuprofen, as in MYBULEN, 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 and high doses of methotrexate should be avoided. Also, the potential risk of interactions in low dose treatment with methotrexate should be considered, especially in patients with impaired renal function. In combined treatment, renal function should be monitored.

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

Corticosteroids

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

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

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

Antihypertensives, beta blockers and diuretics

NSAIDs, such as ibuprofen, as in MYBULEN, 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 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.

Captopril

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

Aminoglycosides

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

Antidiabetic medicines (e.g. sulphonylureas)

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 may exacerbate cardiac failure, reduce glomerular filtration rate.

Co-administration of MYBULEN 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, either.

Tacrolimus

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

Colestyramine

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

Mifepristone

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

Probenecid or sulfinpyrazone

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

Quinolone antibiotics

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

Zidovudine

Increased risk of haematological toxicity when NSAIDs, such as ibuprofen, as in MYBULEN, 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. 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.

Alcohol, bisphosphonates and oxpentifylline

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

Baclofen

Elevated baclofen toxicity.

CYP2C9 Inhibitors

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

Paracetamol as in MYBULEN

Enzyme inducing and hepatotoxic medicines

Increased risk of hepatotoxicity. Possible decrease in therapeutic effects of paracetamol, as in MYBULEN. Hepatotoxicity at therapeutic doses of MYBULEN has been reported in patients receiving isoniazid.

The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing medicines such as carbamazepine, phenobarbital, phenytoin, primidone or rifampicin.

Metoclopramide, domperidone

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

Colestyramine

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

Probenecid

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

Flucloxacillin

Caution should be taken when MYBULEN 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).

Codeine phosphate as in MYBULEN

Monoamine oxidase inhibitors (MAOIs)

Sometimes fatal reactions may occur in patients taking MAOIs concomitantly and also within 14 days of stopping treatment with MAOIs (see section 4.3). Central nervous system (CNS) depression or excitation may occur.

Alcohol or central nervous system depressants

The depressant effects of codeine, as in MYBULEN, are enhanced.

Anticholinergics, antimuscarinics or medications 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.

Hypotension producing medicines

Hypotensive effects may be potentiated.

Hydroxyzine

Analgesia as well as increased CNS depressant and hypotensive effects may be increased.

Quinidine

The analgesic effect of MYBULEN may be inhibited.

Mexiletine

The absorption of mexiletine and thus reduce the antiarrhythmic effect.

Metoclopramide, cisapride, domperidone

MYBULEN may antagonise the gastrointestinal effects.

Cimetidine

The metabolism of MYBULEN is inhibited resulting in increased plasma concentrations.

Naloxone

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of MYBULEN.

Naltrexone also blocks the therapeutic effect of MYBULEN.

4.6 Fertility, pregnancy and lactation

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

Pregnancy

Ibuprofen as in MYBULEN

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, 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, 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 as in MYBULEN

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

Breastfeeding

Ibuprofen as in MYBULEN

Ibuprofen, as in MYBULEN, is excreted in the breast milk in low concentrations. With therapeutic doses during short term treatment the risk for influence on infant seems unlikely. If, however, longer treatment is prescribed, early weaning should be considered.

MYBULEN should not be used during breastfeeding.

Codeine phosphate as in MYBULEN

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

Fertility

Ibuprofen as in MYBULEN

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 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, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that MYBULEN does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

Ibuprofen as in MYBULEN

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. Gastritis has been observed, less frequently.

Clinical studies suggest that use of ibuprofen, as in MYBULEN, 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.

In view of the MYBULEN's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients (see section 4.3 and section 4.4).

b) Tabulated list of adverse reactions

Ibuprofen as in MYBULEN

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 (leucopenia, 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 fever, angioedema, 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, vertigo
Eye disorders		Blurred vision, other ocular reactions, toxic amblyopia.	Visual impairment, toxic optic neuropathy.
Ear and labyrinth disorders		Tinnitus.	Impaired hearing.
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.	Alveolitis, pulmonary eosinophilia.
Gastrointestinal disorders	Heartburn, dyspepsia, abdominal cramps and pain, nausea, vomiting, flatulence, diarrhoea, constipation.	Peptic ulceration, perforation or gastrointestinal bleeding, sometimes fatal; gastrointestinal ulcers, sometimes with bleeding and perforation, occult blood loss which may lead to anaemia, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, inflammatory bowel disease, complications of	

		colonic diverticula (perforation, fistula) , gastritis, oesophagitis, pancreatitis, intestinal strictures, bloating, decreased appetite.	
Hepatobiliary disorders		Abnormalities of liver function tests, hepatitis, jaundice, liver dysfunction, liver damage, especially in long-term use, hepatic failure.	Hepatotoxicity.
Skin and subcutaneous tissue disorders	Skin rash, pruritus.	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)/ Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE), Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders		Impairment of renal function, acute reversible renal failure, haematuria, renal papillary necrosis in long-term use, development of oedema especially in patients with arterial hypertension or renal insufficiency, nephritic syndrome, interstitial nephritis which can be associated with renal failure.	Renal tubular acidosis
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 as in MYBULEN

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, leucopenia).	
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, pancreatitis.	
Skin and subcutaneous tissue disorders		dermatitis, erythematous or urticarial rash accompanied by fever and mucosal lesions.	
Renal and urinary disorders		Renal colic, renal failure, sterile pyuria.	

Codeine phosphate as in MYBULEN

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Metabolism and nutrition disorders			Hypokalaemia
Psychiatric disorders		Euphoria.	
Nervous system disorders		Confusion, drowsiness, restlessness, changes in mood, vertigo, raised intracranial pressure.	
Eye disorders		Miosis, blurred or double vision.	
Cardiac disorders		Bradycardia, palpitations, orthostatic hypotension.	
Respiratory, thoracic and		Respiratory depression.	

mediastinal disorders			
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. 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 e.g., 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, 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 is not recommended for use in 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 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

Treatment is symptomatic and supportive (see section 4.4).

Ibuprofen as in MYBULEN

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

Symptoms

The most frequently reported symptoms of overdose include 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.

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.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Treatment

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.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

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

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

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

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

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

Paracetamol as in MYBULEN

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.

Symptoms

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, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and international normalised ratio (INR) (prolongation of the prothrombin time).

Liver damage may lead to encephalopathy, coma and death.

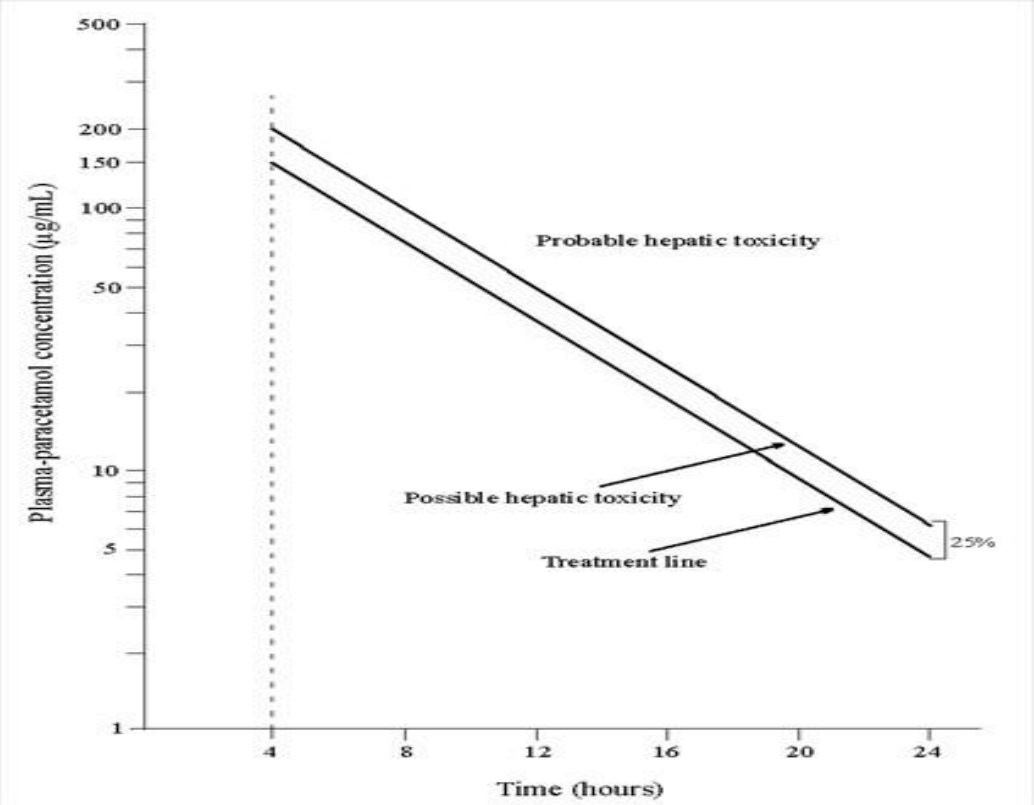
Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Treatment

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

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

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours, 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 as in MYBULEN

Symptoms

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

Treatment

Treatment of overdosage is symptomatic and supportive.

Immediate attention should be given to maintaining adequate respiration. Naloxone should be given intravenously in a dose of 0,4 mg every 2 to 3 minutes until improvement occurs or to a maximum of 10 mg. Children may be given 0,01 mg/kg initially followed by a dose of 0,1 mg/kg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 2.8 Analgesic combinations.

Pharmacotherapeutic group: Codeine and other non-opioid analgesics

ATC code: N02AJ09

Mechanism of action

MYBULEN has an analgesic, anti-inflammatory and antipyretic action.

Ibuprofen is a non-steroidal anti-inflammatory agent (NSAID) and has analgesic, antipyretic and anti-inflammatory activities.

Ibuprofen exerts its anti-inflammatory action peripherally in inflamed tissue by reducing prostaglandin activity and by inhibiting synthesis and/or actions of other local mediators of the inflammatory response.

Paracetamol has analgesic and antipyretic effects.

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

5.2 Pharmacokinetic properties

Absorption

Ibuprofen

Absorbed from the gastrointestinal tract after oral administration.

Paracetamol

Absorption following oral administration is rapid and almost complete.

Codeine phosphate

Codeine is readily absorbed from the gastrointestinal tract.

Distribution

Ibuprofen

The half-life of ibuprofen is about 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 FCF (C.I. 42090), hypromellose, magnesium stearate, microcrystalline cellulose, pregelatinised starch, povidone, talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

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

Protect from light.

Keep in original packaging until required for use.

6.5 Nature and contents of container

30 tablets are packed into a white polypropylene securitainer together with a desiccant disc or silica gel sachet, rayon and a leaflet, and sealed with a dark blue low density polyethylene cap.

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

30/2.8/0138

9. DATE OF FIRST AUTHORISATION

30 June 1999

10. DATE OF REVISION OF TEXT

18 November 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

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Botswana: BOT1001619 S3

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