1.3.1.1.2 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

MYBULEN FORTE 400 mg/10 mg/500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of MYBULEN FORTE contains 400 mg ibuprofen, 10 mg codeine phosphate hemihydrate, 500 mg paracetamol. Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

MYBULEN FORTE is a white to off-white capsule shaped film-coated tablet debossed with “E19” on one side and breakline on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MYBULEN FORTE is indicated for the management of mild to moderate pain or fever of inflammatory origin for a maximum treatment period of 5 days.

4.2. Posology and method of administration

Medical supervision

Do not use continuously for more than 5 days without consulting your doctor. 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 (see section 4.4). Consult a doctor if no relief is obtained from the recommended dosage. Use the lowest effective dose for the shortest possible duration of treatment.

Posology

Adults (over the age of 12 years)

Take one tablet three times a day if necessary.

Do not take more than 3 (three) tablets in a 24 hour period.

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

Paediatric population

Not recommended for children under 12 years of age. Caution is required in adolescents (12 to 18 years) (see section 4.3 and 4.4).

Special populations

Hepatic and renal impairment

Patients suffering from hepatic and renal disease should take MYBULEN FORTE under medical supervision (see section 4.3).

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

DO NOT EXCEED THE RECOMMENDED DOSE (see section 4.4).

Method of administration

For oral administration.

4.3. Contraindications

MYBULEN FORTE is contraindicated in:

- Patients with hypersensitivity to paracetamol, ibuprofen, codeine or to any excipients in MYBULEN FORTE (see section 6.1).
- Patients with impaired hepatic and renal function (see section 4.2).
- Patients with a history of peptic ulcer disease or gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), including MYBULEN FORTE.
- Patients with diarrhoea associated with pseudomembranous colitis.
- Patients receiving coumarin anti-coagulants (see section 4.5).
- Patients with an active or a history of recurrent perforations, ulceration or bleeding (PUB).
- Patients who are hypersensitive to aspirin or other NSAIDs. Because of the possibility of cross-sensitivity due to structural relationships, which exists among NSAIDs, acute allergic reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds.
- Patients with heart failure or cardiovascular disease.
- Patients with acute 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 during an attack of bronchial asthma, uncontrolled asthma or bronchospasm or in heart failure secondary to chronic lung disease.
- Patients with nasal polyps associated with aspirin-induced bronchospasm.
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping such treatment (see section 4.5).
- Paediatric patients (0 to 18 years of age) who have undergone a tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see sections 4.2, 4.4 and 4.8).
- Women who are breastfeeding their infants and women in the third trimester of pregnancy (see section 4.4 and 4.6).
- Patients for whom it is known they are CYP2D6 ultra-rapid metabolisers (see section 4.5).
- Children younger than 12 years old (see section 4.2).
- Patients who have chronic constipation.

4.4. Special warnings and precautions for use

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

Paracetamol

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

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

Concurrent paracetamol products use

Patients should be advised not to exceed the recommended dose and not take other paracetamol-containing products concurrently (see section 4.2 and 4.5).

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 reaction 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 FORTE must immediately be discontinued and appropriate treatment instituted.

High Anion gap metabolic acidosis (HAGMA)

Caution is advised if MYBULEN FORTE 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 FORTE. Close monitoring, including measurement of urinary 5-oxoproline, is recommended (see section 4.5).

Ibuprofen

Masking of symptoms of underlying infection

Ibuprofen as contained in MYBULEN FORTE may mask the signs and symptoms of infection, such as fever and inflammation, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection.

Concomitant medicines

The use of MYBULEN FORTE with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding (see section 4.3 and 4.5).

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, including MYBULEN FORTE, especially gastrointestinal bleeding, ulceration and perforation, 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.

Paediatric population

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

Gastrointestinal (GI) perforation, ulceration or bleeding (PUBs)

GI bleeding or perforation, which can be fatal, has been reported with ibuprofen, as contained in MYBULEN FORTE, during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI PUBs is higher with increasing ibuprofen doses, in patients with a history of ulcers, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other medicines likely to increase GI risk. Patients with a history of GI disease, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment (see section 4.3).

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet medicines such as aspirin (see section 4.5). When GI bleeding or ulceration occurs in patients receiving MYBULEN FORTE, the treatment should be stopped. MYBULEN FORTE should be

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

Respiratory disorders

Caution is required if MYBULEN FORTE is administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs such as ibuprofen have been reported to precipitate bronchospasm in these patients (see section 4.3).

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema can occur in association with MYBULEN FORTE therapy. The use of ibuprofen, as contained in MYBULEN FORTE, particularly at a high dose (2400 mg/ daily) and in long term treatment, may be associated with an increased risk of arterial thrombotic events such as myocardial infarction or stroke.

Low dose ibuprofen (e.g. ≤ 1200mg daily), as contained in MYBULEN FORTE, is not associated with an increased risk of arterial thrombotic events, particularly myocardial infarction. Use of MYBULEN FORTE is contraindicated in heart failure (see section 4.3). Patients with uncontrolled hypertension, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with MYBULEN FORTE after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Renal effects

Ibuprofen, as in MYBULEN FORTE, 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 FORTE 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.

Caution should be used when initiating treatment with MYBULEN FORTE in patients with considerable dehydration. Long-term administration of ibuprofen, as contained in MYBULEN FORTE, has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of MYBULEN FORTE 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 this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly (see section 4.3). Discontinuation of MYBULEN FORTE is usually 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 in MYBULEN FORTE, as patients may become dependent on the codeine component (see warning on Opioid use disorder in sec). 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.

Hepatic effects

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

Asthma

Asthma may be exacerbated in patients suffering from or with a previous history of bronchial asthma or allergic disease. MYBULEN FORTE may decrease respiratory drive and increase airway resistance in these patients (see section 4.3).

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

Aseptic meningitis can occur in patients on MYBULEN FORTE therapy. Although it is probably more likely to occur in patients with SLE and related connective tissue diseases, it can occur in patients who do not have an underlying chronic disease.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS)

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

Haematological effects

Ibuprofen, as contained in MYBULEN FORTE, like other NSAIDs, can interfere with platelet aggregation and has been shown to prolong bleeding time.

Allergic conditions

There is a possibility of cross sensitivity.

Anaemia

May be exacerbated.

Surgery

Possible enhanced bleeding if surgery is required.

Impaired female fertility

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

Foetal toxicity

MYBULEN FORTE is contraindicated for use in pregnancy (see section 4.3.) Regular use of NSAIDs, as contained in MYBULEN FORTE during the third trimester of pregnancy, may result in oligohydramnios/foetal renal dysfunction or premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased (see sections 4.3 and 4.6).

Codeine phosphate

Concomitant disease states

Care should be observed in administering MYBULEN FORTE to any patient, whose condition may be exacerbated by opioids, as contained in MYBULEN FORTE, including the elderly, who may be sensitive to their central and GI effects, those on concurrent CNS depressant medicines, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders, Addison's disease or myasthenia gravis. Care should also be observed if prolonged therapy is contemplated.

Risks from concomitant use of opioids and benzodiazepines

Concomitant use of opioids, including codeine, with benzodiazepines may result in sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate. If a decision is made to prescribe codeine, as contained in MYBULEN FORTE, concomitantly with benzodiazepines, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of sedation and respiratory depression (see sections 4.3 and 4.5).

Risks from concomitant use of opioids and alcohol

Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended.

CYP2D6 metabolism

Codeine, as contained in MYBULEN FORTE, is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this

may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal (see section 4.3).

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, as contained in MYBULEN FORTE. Abuse or intentional misuse of MYBULEN FORTE 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 contained in MYBULEN FORTE, 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.

Use in patients with a history of mental health disorders

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

Opioid-Induced Hyperalgesia or Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain (hyperalgesia), or an increase in sensitivity to pain (allodynia).

This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect.

Symptoms of OIH include increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). The pain experienced may be at the same location of the underlying pain or can be more generalised or widespread in nature. These symptoms may suggest the occurrence of OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety).

MYBULEN FORTE should be used with caution in the following:

- Acute abdominal conditions: Diagnosis or clinical course may be obscured.
- Cardiac dysrhythmias: May be induced or exacerbated.
- Convulsions or history thereof: May be induced or exacerbated.
- Gallbladder disease or gallstones: May cause biliary tract spasm (see section 4.3).
- Recent gastrointestinal tract surgery.
- Hypothyroidism: Increase risk of respiratory depression and prolonged central nervous system depression.
- Risk of severe constipation if used with antidiarrhoeal medicines such as diphenoxylate (see sections 4.3 and 4.5)

Paediatric population

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

Post-operative use in children

There have been reports in the published literature that codeine, as contained in MYBULEN FORTE, given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine (see section 4.3).

Children with compromised respiratory function

Codeine, as contained in MYBULEN FORTE, is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity (see section 4.3).

4.5. Interaction with other medicines and other forms of interaction

Paracetamol

Isoniazid

Isoniazid may increase the risk of hepatotoxicity with therapeutic doses of paracetamol, as contained in MYBULEN FORTE.

Antiepileptic medicines

Antiepileptics, such as carbamazepine, phenobarbital, phenytoin and primidone can reduce the effects of paracetamol, as contained in MYBULEN FORTE, and increase the risk of hepatotoxicity.

Chloramphenicol

Paracetamol, as contained in MYBULEN FORTE, may increase the elimination half-life of chloramphenicol.

Oral contraceptives

Oral contraceptives may increase its rate of clearance.

Metoclopramide, domperidone, cholestyramine

The rate of absorption of paracetamol, as contained in MYBULEN FORTE, may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. Concomitant use of agents which slow the gastric emptying, may delay absorption and onset of action of paracetamol.

Warfarin and other anticoagulant medicines

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol, as contained in MYBULEN FORTE with increased risk of bleeding; occasional doses have no significant effect. Paracetamol as contained in MYBULEN FORTE, is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution is needed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon) and isolated reports have found an

increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in international normalised ratio (INR) has also been reported in controlled studies of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol, as contained in MYBULEN FORTE, regularly.

Enzyme inducing and hepatotoxic medicines

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

Probenecid

Excretion of paracetamol, as contained in MYBULEN FORTE, may be affected, and plasma concentrations altered. Pre-treatment with probenecid can decrease paracetamol, as contained in MYBULEN FORTE, clearance and increase its plasma half-life. Although urinary excretion of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

Salicylates

Prolonged concurrent use of MYBULEN FORTE with salicylates increases the risk of adverse renal effects.

Antibacterial medicines

The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme inducing medicines such as rifampicin. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has

been reported in patients receiving isoniazid, alone or with other medicines for tuberculosis.

Caution should be taken when MYBULEN FORTE 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).

Antiviral medicines

Severe hepatotoxicity has occurred after use of paracetamol, as contained in MYBULEN FORTE, in a patient taking zidovudine and co-trimoxazole. However, neither short-term nor long-term studies (the latter also in an individual patient) have shown any alteration of zidovudine elimination in patients taking zidovudine and paracetamol, as contained in MYBULEN FORTE.

Interferon alfa

Paracetamol, as contained in MYBULEN FORTE, has also been found to enhance the antiviral effect of interferon alfa.

Ibuprofen

Care should be taken in patients treated with any of the following medicines as interactions can occur.

Antihypertensives, beta-blockers and diuretics

MYBULEN FORTE may reduce the effect of antihypertensives, such as ACE inhibitors, beta-blockers 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.

Potassium-sparing diuretics and ACE inhibitors can also increase the risk of nephrotoxicity of MYBULEN FORTE and increase the risk of hyperkalaemia. Careful monitoring of potassium levels is necessary.

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

Cardiac glycosides

MYBULEN FORTE may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma cardiac glycoside levels.

Cholestyramine

The concomitant administration of ibuprofen, as contained in MYBULEN FORTE and cholestyramine may reduce the absorption of ibuprofen, as contained in MYBULEN FORTE, in the gastrointestinal tract. However, the clinical significance is unknown.

Digoxin, phenytoin, lithium

Co-administration of MYBULEN FORTE 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).

Methotrexate

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

NSAIDs, such as ibuprofen, as contained in MYBULEN FORTE may inhibit 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 FORTE 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.

Ciclosporin

Increased risk of nephrotoxicity.

Mifepristone

A decrease in the efficacy of the medicinal product can theoretically occur due to the anti-prostaglandin properties of MYBULEN FORTE. Limited evidence suggests that coadministration of MYBULEN FORTE on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

Probenecid or sulfinpyrazone

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

Other analgesics and cyclooxygenase-2 (COX-2) selective inhibitors

Avoid concomitant use of two or more NSAIDs, including COX-2 inhibitors, as this may increase the risk of adverse effects (see section 4.4).

Aspirin

Concomitant administration of ibuprofen, as contained in MYBULEN FORTE, and aspirin is not generally recommended because of the potential of increased adverse effects. Ibuprofen, as contained in MYBULEN FORTE, may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, no firm conclusions can be made for regular ibuprofen, as contained in MYBULEN FORTE, use, and no clinically relevant effect is considered to be likely for occasional use.

Corticosteroids

Increased risk of gastrointestinal PUBs with MYBULEN FORTE (see section 4.4).

Anticoagulants

MYBULEN FORTE may enhance the anticoagulant effects of anticoagulants, such as warfarin and heparin and it may increase the possibility of gastrointestinal ulceration or bleeding (see section 4.4).

Quinolone antibiotics

MYBULEN FORTE can increase the risk of convulsions associated with quinolone

antibiotics. Patients taking MYBULEN FORTE and quinolones may have an increased risk of developing convulsions.

Sulfonylureas

MYBULEN FORTE may potentiate the effects of sulfonylurea medications. There have been reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen, as contained in MYBULEN FORTE. In the case of simultaneous treatment, monitoring of blood glucose levels is recommended.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)-Increased risk of gastrointestinal bleeding and ulceration with MYBULEN FORTE (see section 4.4).

Tacrolimus

Increased risk of nephrotoxicity when MYBULEN FORTE are given with tacrolimus.

Zidovudine

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

Ritonavir

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

Alcohol, bisphosphonates and oxpentifylline

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

Baclofen

Elevated baclofen toxicity.

Captopril

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

Aminoglycosides

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

Herbal extracts

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

CYP2C9 Inhibitors

Concomitant administration of ibuprofen, as contained in MYBULEN FORTE, with CYP2C9 inhibitors may increase the exposure to ibuprofen, as contained in MYBULEN FORTE, (CYP2C9 substrate). With voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen, as contained in MYBULEN FORTE, exposure by approximately 80 to 100 % can occur. Reduction of the ibuprofen, as contained in MYBULEN FORTE, dose should be considered when potent CYP2C9 inhibitors are administered

concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

Bone marrow depressants

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

Codeine Phosphate

MAOIs

Concurrent use of MAOIs or tricyclic antidepressants with codeine, as contained in MYBULEN FORTE, may increase the effect of either the antidepressant or codeine (see section 4.3).

Alcohol or central nervous system (CNS) depressants

Alcohol and opioids increase the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see section 4.4).

Benzodiazepines and opioids increase the risk of sedation, respiratory depression, coma and death, because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see section 4.4).

The effects of CNS depressants (including other opioid analgesics, tranquilisers, sedative hypnotics and alcohol) may be potentiated by codeine, as contained in MYBULEN FORTE. When such therapy is contemplated, the dose of one or both agents should be reduced.

Anticholinergics

Concurrent use of anticholinergics and codeine, as contained in MYBULEN FORTE, may produce paralytic ileus.

Antidiarrhoeals and antiperistaltic agents

Concurrent use of codeine with antidiarrhoeal and antiperistaltic agents such as loperamide and kaolin may increase the risk of severe constipation.

Antimuscarinics or medications with muscarinic action

Concomitant use of antimuscarinics or medications with muscarinic action, e.g. atropine and some antidepressants may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.

Hypotension-producing medications

Hypotensive effects may be potentiated

Cimetidine

Cimetidine and other medicines which are known to influence the hepatic metabolism may enhance the effect of MYBULEN FORTE.

Antihistamines and antihypertensive

Concomitant administration of MYBULEN FORTE and antihistamines and antihypertensives may enhance the sedative and respiratory depressant effect.

Neuromuscular blocking agents

The respiratory depressant effect caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.

Quinidine

Analgesic effect of codeine, as contained in MYBULEN FORTE, can be inhibited.

Mexiletine

Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

Metoclopramide, cisapride and domperidone

Codeine, as contained in MYBULEN FORTE, may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.

Naloxone and naltrexone

Naloxone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids, as contained in MYBULEN FORTE.

Laboratory tests and gastric emptying studies

Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

4.6. Fertility, pregnancy and lactation

The use of MYBULEN FORTE is contraindicated in the third trimester of pregnancy and while breastfeeding (see section 4.3).

Pregnancy

Ibuprofen

MYBULEN FORTE is contraindicated in the third trimester of pregnancy (see sections 4.3 and 4.4).

Regular use of non-steroidal inflammatory drugs may result in:

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 %. 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, may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus

and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligohydroamniosis.

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.

Because of these risks, the use of MYBUCOD 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 section 4.3 and 4.4).

Codeine phosphate

MYBULEN FORTE 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.

An association between abnormalities of the respiratory tract and the use of codeine during the first three months of pregnancy was found in humans. Evidence for other malformations was also found in epidemiological studies with narcotic analgesics, including codeine. Codeine may therefore only be used during pregnancy, especially during the first three months, if clearly indicated and after a careful benefit-risk assessment.

In case of imminent birth or preterm birth, the use of codeine is contraindicated since codeine crosses the placental barrier and can cause neonatal respiratory depression.

Paracetamol

A large amount of data on pregnant women indicates neither malformative, nor foeto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy, however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breastfeeding

MYBULEN FORTE is contraindicated in breastfeeding (see section 4.3).

Codeine

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

Ibuprofen

In limited studies, ibuprofen as contained in MYBULEN FORTE, appears in the breast milk in very low concentration and is unlikely to affect the breastfed infant adversely. 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.

Fertility

The use of MYBULEN FORTE may impair female fertility and is not recommended in women attempting to conceive (see section 4.4).

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

4.8. Undesirable effects

Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.
Prolonged use of a painkiller for headaches can make them worse.

a) Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature.

b) Tabulated list of adverse reactions

Paracetamol

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Blood dyscrasias including* thrombocytopenia*, leucopenia,	

		pancytopenia, neutropenia, agranulocytosis*, anaemia	
Immune system disorders			Anaphylactic shock, angioedema, allergic reactions (hypersensitivity) including skin rash*
Metabolism and nutrition disorders			Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis
Hepato-biliary disorders			Hepatitis which may lead to acute hepatic failure, pancreatitis
Skin and subcutaneous tissue disorders		Skin rashes and other allergic reactions may occur. The rash is usually erythematous or urticaria but sometimes more serious and accompanied by fever and mucosal lesions, dermatitis	Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE)
Renal and urinary disorders		Renal colic, renal failure, sterile pyuria	

Ibuprofen

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation.	

Blood and the lymphatic system disorders	Leucopenia, thrombocytopenia, neutropenia, pancytopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia		
Immune system disorders		Anaphylactic reaction, hypersensitivity reactions including fever and angioedema	Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Psychiatric disorders	Nervousness, insomnia, depression	Anxiety, confusional state, hallucination.	
Nervous system disorders	Headache, Dizziness, drowsiness	Optic neuritis, paraesthesia, somnolence	
Eye disorders		Visual impairment, toxic optic neuropathy	
Ear and labyrinth disorders	Vertigo, tinnitus	Impaired hearing	
Cardiac disorders	Oedema, cardiac failure (see section 4.4)	Angina pectoris, cardiac dysrhythmias, oedema, hypertension,	
Vascular disorders		Hypertension	
Respiratory, thoracic and mediastinal disorders		Asthma, bronchospasm, dyspnoea	Alveolitis, pulmonary eosinophilia
Gastrointestinal disorders	Dyspepsia, gastritis, peptic ulcers, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, mouth ulcer, haematemesis, gastrointestinal haemorrhage (sometimes fatal), gastrointestinal perforation, exacerbation of colitis and Crohn´s disease	Pancreatitis	
Hepato-biliary disorders		Abnormal liver function, hepatic	Hepatotoxicity

		failure, hepatitis, jaundice	
Skin and subcutaneous tissue disorders	Rash	Pruritus, urticaria, purpura, photosensitivity reaction	Severe cutaneous adverse reactions (e.g. Erythema multiforme, bullous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders		Impaired renal function and toxic nephropathy in various forms, including interstitial nephritis, nephrotic syndrome and renal failure	Haematuria, fluid retention
General disorders and administrative site conditions	Fatigue		
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	

Codeine Phosphate

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Psychiatric disorders		Confusion, restlessness, change of mood, euphoria	
Nervous system disorders	Drowsiness	Vertigo, raised intracranial pressure	Dizziness, light-headedness, confusion*
Eye disorders		Changes in miosis, blurred or double vision	
Ear and labyrinth disorders			Vertigo, ototoxicity leading to sensorineural hearing loss*
Cardiac disorders		Bradycardia, palpitations, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		Respiratory depression, cough suppression	
Gastrointestinal disorders	Constipation	Nausea, vomiting, dry mouth	
Hepato-biliary disorders		Biliary spasm	
Skin and subcutaneous tissue disorders		Urticaria, pruritus	
Renal and urinary disorders		Micturition difficulties, ureteric, antidiuretic effect, urinary retention*	
General disorders and administrative site conditions		Sweating, facial flushing, hypothermia	

*Reported for combined paracetamol and codeine phosphate treatment

Paracetamol (Post-Marketing Experience)

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Skin and subcutaneous tissue disorders			Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE)

Ibuprofen (Post-Marketing Experience)

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Metabolism and nutrition disorders			Hypokalaemia
Renal and urinary disorders			Renal tubular acidosis

Codeine Phosphate (Post-Marketing Experience)

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Gastrointestinal disorders		Abdominal pain, including pancreatitis	

c) *Description of selected adverse reactionsIbuprofen*

Acute reversible renal failure has been reported.

Hypersensitivity reactions have been reported following treatment with ibuprofen, as in MYBULEN FORTE.

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

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Ibuprofen

Symptoms

The most likely symptoms of overdosage are gastrointestinal such as abdominal pain, epigastric pain, nausea, vomiting or more rarely diarrhoea. A syndrome of coma, hyperkalaemia, with cardiac dysrhythmias, metabolic acidosis, pyrexia and respiratory and renal failure has been reported. Institute symptomatic and other supportive treatments, which may be necessary. Monitor and support vital functions.

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).

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. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount.

If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam.

Give bronchodilators for asthma.

Paracetamol

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours, are 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, increase serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

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

Treatment

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 drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazapine.

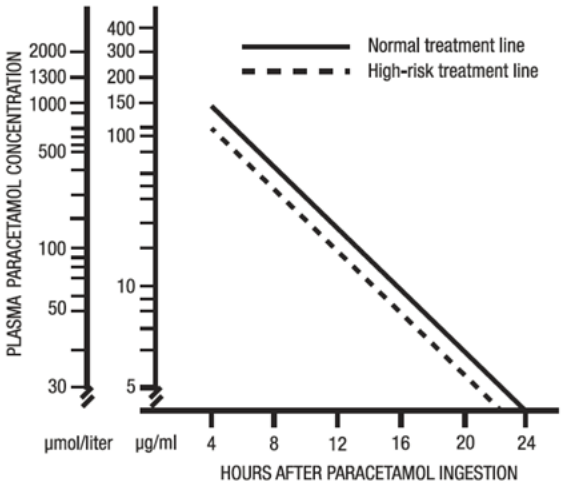
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within 8 hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

IV: An initial dose of 150 mg/kg N-acetylcysteine in 200 ml glucose injection given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 ml of glucose injection over the next 4 hours, and then 100 mg/kg in 1 000 ml glucose injection over the next 16 hours. The volume of intravenous fluids should be modified for children.

Orally (not the treatment of choice): 140 mg/kg as a 5 % solution initially, followed by a 70 mg/kg solution every 4 hours for 17 doses. N-acetylcysteine is more likely to be effective if administered within 8 hours of overdosage.

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 of N-acetylcysteine, can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against the time since ingestion in the nomogram below.



Those, whose plasma paracetamol levels are above the “Normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg 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.

If N-acetylcysteine is not available, methionine 2,5 g may be given immediately, followed by 2,5 g every four hours for three doses. Patients should however preferably be transferred to a facility where N-acetylcysteine can be given. Monitor all patients with significant ingestions for at least 96 hours.

Codeine Phosphate

Symptoms

Respiratory depression is the most important feature of overdosage and occurs with circulatory failure and deepening coma. Pin-point pupils, hypotension, hypoxia, shock, gastric hypomotility with ileus, hypothermia, excitement and convulsions, (especially in children) and non-cardiogenic pulmonary oedema occur. The opiate intoxication syndrome is described as a triad of depressed level of consciousness, miotic pupils, and decreased respiration.

Treatment

Treatment is based more on clinical presentation than on specific laboratory data, except when complications have occurred.

Immediate attention should be given to maintaining adequate respiration.

Consider pre-hospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway. Activated charcoal is most effective when administered within one hour of ingestion.

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 mg to 2 mg given as an intravenous bolus in both children and adults. This dose can also be given subcutaneously in the absence of intravenous access or intrathecally.

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

Paracetamol

Paracetamol is the active metabolite of phenacetin. Paracetamol has analgesic and antipyretic effects. However, it has weak anti-inflammatory effects, and has been thought to have a generally poor ability to inhibit cyclooxygenase (COX) in the presence of high concentrations of peroxides, as are found at sites of inflammation. COX inhibition might be disproportionately pronounced in the brain, explaining its antipyretic efficacy.

Ibuprofen

Ibuprofen is a propionic acid derivative with analgesic, anti- inflammatory and anti-pyretic activity. The medicine's therapeutic effects as an NSAID are thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis.

Codeine Phosphate

Codeine phosphate is a centrally acting weak analgesic. Codeine exerts its effects through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2. Pharmacokinetic properties

Paracetamol

Absorption

Paracetamol has excellent bioavailability. Peak plasma concentrations occur within 30 to 60 minutes, and the half-life in plasma is ~ 2 hours after therapeutic doses.

Distribution

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of paracetamol to plasma proteins is variable.

Biotransformation

Paracetamol primarily undergoes hepatic conjugation with glucuronic acid (~ 60 %), sulphuric acid (~ 35 %) or cysteine (~ 3 %). Small amounts of the hydroxylated and deacetylated metabolites have also been detected. A small proportion of paracetamol undergoes CYP-mediated N – hydroxylation to form NAPQI, a highly reactive intermediate. This metabolite normally reacts with sulphydryl groups in glutathione (GSH) and thereby is rendered harmless.

Elimination

Some 90 to 100 % of paracetamol may be recovered in the urine within the first day of therapeutic dosing.

Ibuprofen

Absorptio

Ibuprofen is rapidly absorbed from the gastrointestinal tract, peak serum concentrations occurring 1 to 2 hours after administration. The elimination half-life is approximately 2 hours.

Distribution

Ibuprofen is extensively bound to plasma proteins.

Ibuprofen's plasma protein binding is often concentration dependent and saturable at high concentrations. Ibuprofen is distributed widely throughout the body and readily penetrates arthritic joints, yielding synovial fluid concentrations in the range of half the plasma concentration.

Biotransformation

Ibuprofen is metabolised in the liver to two inactive metabolites (90 % is metabolised to hydroxylate or carboxylate derivatives) and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates.

Elimination

Hepatic biotransformation and renal excretion are the principal route of elimination for ibuprofen.

Codeine Phosphate

Absorption

Codeine phosphate is well absorbed after oral administration and is widely distributed.

Metabolism

Once absorbed codeine is metabolised by the liver. A small fraction (~ 10 %) of administered codeine is O-demethylated to morphine. The half-life of codeine in plasma is 2 to 4 hours. CYP2D6 catalyses the conversion of codeine to morphine.

Elimination

About 86 % is excreted in the urine in 24 hours; 40 to 70 % if free or conjugated morphine, 5 to 15% is free or conjugated norcodeine.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hypromellose (E464),macrogol, magnesium stearate, microcrystalline cellulose, povidone, pregelatinised starch, titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C.

6.5. Nature and contents of container

15 tablets are packed into a white round high density polyethylene (HDPE) bottle with polypropylene cap with induction seal wad. The bottle may be packed in an outer carton.

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

50/2.8/0490

9. DATE OF FIRST AUTHORISATION

23 January 2024

10. DATE OF REVISION OF TEXT

21 July 2025

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.