## 1.3.1.1 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).

**Special populations**

*Hepatic and renal impairment*

Patients suffering from hepatic and renal disease should take MYBULEN FORTE under medical supervision.

**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).
- Severe hepatic impairment.
- Patients with a history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), including MYBULEN FORTE.
- Patients with impaired renal function (see section 4.2).
- Patients receiving coumarin anti-coagulants.
- Active or a history of recurrent perforations, ulceration of 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.
- Heart failure.
- Respiratory depression.
- Acute alcoholism.
- Acute asthma.
- Head injuries or raised intracranial pressure.
- Heart disease secondary to chronic lung disease.

- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping such treatment.
- 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).
- Pregnancy and lactation (see section 4.6).
- Patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
- Children younger than 12 years old (see section 4.2).

## 4.4. Special warnings and precautions for use

**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.

*Renal and hepatic impairment*

Care is advised in the administration of paracetamol as contained in MYBULEN FORTE to patients with severe renal or severe hepatic impairment (see section 4.3). The hazards of overdose are greater in those with alcoholic liver disease (see sections 4.2 and 4.3).

*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).

**Ibuprofen**

*Infection*

Ibuprofen as contained in MYBULEN FORTE may mask the signs of infection, such as fever and inflammation.

*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).

*Elderly*

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal.

*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 ulcer, 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 agents 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, renal and hepatic impairment*

The administration of an MYBULEN FORTE may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see section 4.3).

MYBULEN FORTE should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with ibuprofen, as contained in MYBULEN FORTE, administration.

*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) (see section 4.3).

*Renal effects*

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. Discontinuation of MYBULEN FORTE is usually followed by recovery to the pre-treatment state.

*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.

*Dermatological effects*

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, can occur with MYBULEN FORTE use. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. MYBULEN FORTE should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

*Haematological effects*

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

*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.

*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 4.3).

*Pregnancy*

Regular use of NSAIDs, as contained in MYBULEN FORTE during the third trimester of pregnancy, may result in 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 (see section 4.5).

*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.

*Drug reaction with eosinophillia and systemic symptoms*

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

**Paediatric population**

*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 may increase the risk of hepatotoxicity with therapeutic doses of paracetamol, as contained in MYBULEN FORTE.
- 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.
- Paracetamol, as contained in MYBULEN FORTE, may increase the elimination half-life of chloramphenicol.
- Oral contraceptives may increase its rate of clearance.
- The rate of absorption of paracetamol, as contained in MYBULEN FORTE, may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.
- 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.

**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 anti- hypertensives, such as ACE inhibitors, beta-blockers and diuretics.
- Diuretics and ACE inhibitors can also increase the risk of nephrotoxicity of MYBULEN FORTE and increase the risk of hyperkalaemia.
- 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.
- Lithium: Decreased elimination of lithium.
- Methotrexate: MYBULEN FORTE may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate.
- 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.
- 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 effects of anticoagulants, such as

warfarin (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.
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding 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 haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen, as contained in MYBULEN FORTE.
- Aminoglycosides: MYBULEN FORTE may decrease the excretion of aminoglycosides.
- Herbal extracts: Ginkgo biloba may potentiate the risk of bleeding with 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.

**Codeine Phosphate**

- 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.
- Concurrent use of MAOIs or tricyclic antidepressants with codeine, as contained in MYBULEN FORTE, may increase the effect of either the antidepressant or codeine.
- Concurrent use of anticholinergics and codeine, as contained in MYBULEN FORTE, may produce paralytic ileus.

## 4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established (see section 4.3).

**Pregnancy**

MYBULEN FORTE is contraindicated in 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.

**Breastfeeding**

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

**Fertility**

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

**4.7 Effects on ability to drive and use machines**

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) 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* |
| **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 | |
| **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, agranulocytosis, aplastic anaemia, haemolytic anaemia | | |
| **Immune system disorders** | | Anaphylactic reaction, hypersensitivity reactions including fever and angioedema | |
| **Psychiatric disorders** | Nervousness, insomnia, depression | Anxiety, confusional state. | |
| **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) | | |
| **Vascular disorders** | | Hypertension | |
| **Respiratory, thoracic and mediastinal disorders** | | Asthma, bronchospasm, dyspnoea | Alveolitis, pulmonary eosinophilia |
| **Gastrointestinal disorders** | Dyspepsia, gastritis, peptic ulcers, diarrhoea, nausea, vomiting, | Pancreatitis | |

| | | | |
|---|---|---|---|
| | abdominal pain, flatulence, constipation, melaena, mouth ulcer, haematemesis, gastrointestinal haemorrhage (sometimes fatal), gastrointestinal perforation, exacerbation of colitis and Crohn´s disease | | |
| **Hepato-biliary disorders** | | Abnormal liver function, hepatic failure, hepatitis, jaundice | Hepatotoxicity |
| **Skin and subcutaneous tissue disorders** | Rash | Pruritus, urticaria, purpura, photosensitivity reaction | Severe forms of skin reactions (e.g. Erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) 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 | | |

**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 | | Dizziness, light-headedness, confusion* |
| **Ear and labyrinth disorders** | | | Vertigo, ototoxicity leading to sensorineural hearing loss* |
| **Cardiac disorders** | | Bradycardia, palpitations, orthostatic hypotension | |
| **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

*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 “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org. za/Publications/Index/8

**Aspen Pharmacare:**

**E-mail:** Drugsafety@aspenpharma.com

**Tel:** 0800 118 088

## 4.9. Overdose

### Ibuprofen

The most likely symptoms of overdosage are gastrointestinal such as epigastric pain, nausea and vomiting. 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.

### Paracetamol

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

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of drugs that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazapine.
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 for Paracetamol overdosage:***

Prompt treatment is essential in the management of paracetamol overdosage. Any adult person who has ingested about 7,5 g or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding 4 hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube.

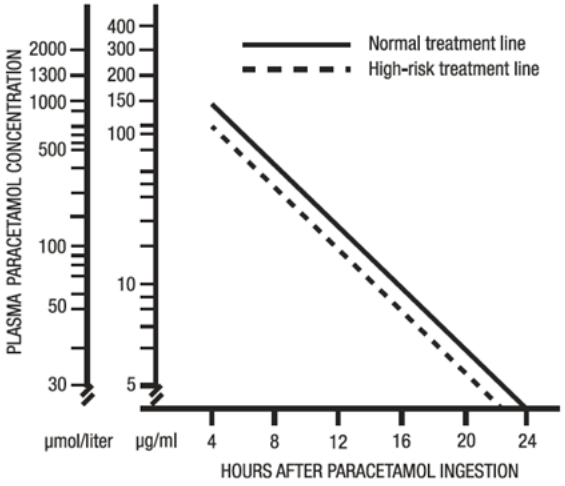
N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within 8 hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

**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**

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

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

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 t1/2 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**

Absorption

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 t1/2 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

High density polyethylene bottle which may be packed into a carton. Pack size of 15 tablets.

### 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

23 January 2024

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

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