

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Maxilief Effervescent Tablets Paracetamol 500mg Codeine Phosphate Hemihydrate 8mg Caffeine 30mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500mg, Codeine Phosphate 8mg and Caffeine 30mg.

Excipients with known effect:

Sorbitol (E420) 50mg and Sodium 388mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablets

Flat, white, bevelled-edge tablets, scored on one side and plain on reverse.

The scoreline is only to facilitate breaking and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of symptoms of headache, including migraine, musculoskeletal pain, toothache, backache, common cold, influenza and menstrual pain.

Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

For oral administration only.

Adults (including the elderly)

Two tablets dissolved in a glass of water three to four times in a 24 hour period as required. The dose should not be repeated more frequently than every 6 hours.

A maximum of 8 tablets in 24 hours should not be exceeded.

Paediatric population:

Maxilief is contraindicated in children below the age of 12 years for the symptomatic treatment of cold (see section 4.3).

Children aged 16 to 18 years:

One to two tablets dissolved in a glass of water every 6 hours when necessary up to a maximum of 8 tablets in 24 hours.

Children aged 12 to 15 years:

One tablet dissolved in a glass of water every 6 hours when necessary up to a maximum of four tablets in 24 hours.

Children aged less than 12 years:

Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Children aged 12 years to 18 years with compromised respiratory function:

Maxilief is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cold (see section 4.4).

Codeine should be used at the lowest effective dose for the shortest period of time. The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Renal impairment:

It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:

Adults:

Glomerular filtration rate	Dose
10-50 ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

Hepatic impairment:

In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged. The daily dose should not exceed 2g/day unless directed by a physician.

The elderly:

A reduced dose may be required (see section 4.4). Experience has indicated that normal adult dosage of paracetamol is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate. The maximum daily dose of paracetamol should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following situations, unless directed by a physician:

- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Acute asthma, respiratory depression.
- In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).
- In women during breast-feeding (see section 4.6).
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
- In children below the age of 12 years for the symptomatic treatment of cold due to an increased risk of developing serious and life-threatening adverse reactions.

4.4 Special warnings and precautions for use

Care is advised in the administration of paracetamol or codeine to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Care should be observed in administering the product to any patients whose condition may be exacerbated by opioids, particularly the elderly, who are especially sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostrate hypertrophy and those with inflammatory or obstructive bowel disorders or acute abdominal conditions (such as appendicitis). Patients with a history of cholecystectomy or recent biliary tree surgery should consult a doctor before using this product as it may cause acute pancreatitis in some patients.

Codeine is a narcotic analgesic and no more than the stated dose should be taken in any 24-hour period. Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability, once the drug is stopped. It is important that patients consult their doctor if a need to use codeine-containing products all the time is experienced.

Excessive intake of tea or coffee should be avoided with taking Maxilief. This product should only be used when clearly necessary. Prolonged use without medical supervision may be harmful. Do not exceed the stated dose. Do not take for more than 3 days without consulting a doctor.

If symptoms persist, consult your doctor. Immediate medical advice should be sought in the event of overdose because of the risk of irreversible liver damage. Keep out of the reach and sight of children.

CONTAINS PARACETAMOL.

Do not take with other paracetamol or codeine containing medicines.

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Hepatic impairment
- Chronic alcoholism
- Renal impairment ($GFR \leq 50 \text{ml/min}$)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

The product should be used with caution in patients with hypertension, oedema or renal insufficiency because of the sodium content.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of 'medication overuse headache' should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

CYP2D6 metabolism

Codeine 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. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. 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.

Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.00%
Hungarian	1.90%
Northern European	1% to 2%

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of Maxilief and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Maxilief concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Children with compromised respiratory function

Codeine 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.

4.5 Interaction with other medicinal products and other forms of interactions

The speed of absorption of paracetamol 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 daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Opioid analgesics should be given with care to patients receiving tricyclic antidepressants and monoamine oxidase inhibitors. The effect of CNS depressants (including alcohol) may be potentiated by codeine; these interactions are unlikely to be significant at the dosage involved.

Sedative medicines such as benzodiazepines or related drugs:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence for the safety of codeine in human pregnancy. If symptoms of opioid toxicity develop then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

Use of Maxilief Effervescent Tablets during pregnancy should be avoided, unless advised by a physician. This includes maternal use during labour because of the potential for respiratory depression in the neonate.

The safety of paracetamol-caffeine-codeine during pregnancy has not been established relative to the possible adverse effects on foetal development and should be avoided during pregnancy due to the possible increased risk of spontaneous abortion associated with caffeine consumption.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol and caffeine used in the recommended dosage.

Patients should follow the advice of their doctor regarding the use of Maxilief Effervescent Tablets.

Lactation

Maxilief is contraindicated in women during breast-feeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Paracetamol and caffeine are excreted in breast milk but not in a clinically significant amount.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by drowsiness.

4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data).

Adverse event frequencies have been estimated from spontaneous reports received through post marketing data and are considered to be very rare.

Paracetamol

Body System	Undesirable Effect
Blood and lymphatic system disorders	Haematopoietic disorders such as thrombocytopenia, leucopenia, agranulocytosis, and pancytopenia.
Immune system disorder	Anaphylaxis Cutaneous hypersensitivity reactions, including skin rashes, angioedema and Stevens Johnson syndrome
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs
Hepatobiliary disorders	Hepatic dysfunction
Skin and subcutaneous tissue disorder	Very rare cases of serious skin reactions have been reported.

Caffeine

Body System	Undesirable Effect
Central nervous system disorders	Nervousness Dizziness

When the recommended paracetamol-caffeine-codeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

Codeine

Adverse reactions identified during post-marketing use are listed below by organ system class. The frequency of these reactions is not known.

Body System	Undesirable Effect
Psychiatric disorders	Drug dependency can occur after prolonged use of codeine at high doses
Gastrointestinal disorder	Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy
Nervous system disorder	Dizziness, worsening of headache with prolonged use, drowsiness
Skin and subcutaneous tissue disorder	Pruritis, sweating

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Paracetamol

Paracetamol overdose can result in liver damage which may be fatal.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors include;

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Emergency Procedure:

Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.

Symptomatic treatment should be implemented.

Codeine

Effects of overdose due to codeine would be subsumed by serious liver toxicity caused by paracetamol overdose. Immediate medical management is required in the event of overdosage, even if symptoms of overdose are not present.

Symptoms and Signs

An overdose of codeine is characterized, in the first phase, by nausea and vomiting. An acute depression of the respiratory centre can cause cyanosis, slower breathing, drowsiness, ataxia and, more rarely, pulmonary oedema. Respiratory pauses, miosis, convulsion, collapse and urine retention. Signs of histamine release have been observed as well.

Treatment

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg of codeine or a child more than 5mg/kg of codeine. Give naloxone if coma or respiratory depression is present. Observe for at least four hours after ingestion or eight hours for a sustained release formulation.

Caffeine

Symptoms and Signs

Overdose of caffeine may produce nervousness, restlessness, insomnia, excitement, epigastric pain, vomiting, diuresis, facial flushing, muscle twitching, GI disturbance, tachycardia or cardiac arrhythmia, "rambling" flow of thought and speech, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions). psychomotor agitation or periods of inexhaustibility. It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Treatment

No specific antidote is available, but supportive measures such as beta adrenoreceptor antagonists to reverse the cardiotoxic effects may be used.

Sodium bicarbonate

High doses of sodium bicarbonate would be expected to induce gastrointestinal symptoms including belching and nausea. In addition, high doses of sodium bicarbonate may cause hypernatraemia, electrolytes should be monitored and patients managed accordingly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

<u>Product</u>	<u>Pharmacodynamic group</u>	<u>ATC Code</u>
Paracetamol	Analides	N02BE01
Codeine Phosphate	Opium alkaloids and derivatives	R05DA04
Caffeine	Xanthine derivatives	N06BC01

Paracetamol is an analgesic and antipyretic.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect 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.

Caffeine is a potent stimulator of the CNS.

5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract. It is relatively uniformly distributed throughout most body fluids and exhibits variable protein binding. Excretion is almost completely renal, in the form of conjugated metabolites.

Caffeine is absorbed readily after oral administration, maximal plasma concentrations are achieved within one hour and the plasma half-life is about 3.5 hours. 65-80 % of administered caffeine is excreted in the urine as 1-methyluric and 1-methylxanthine.

Codeine phosphate is well absorbed after oral administration and is widely distributed. About 86 % is excreted in the urine in 24 hours; 40-70 % is free of conjugated codeine, 5-15 % is free of conjugated morphine and 10-20 % is free of conjugated norcodeine.

5.3 Preclinical safety data

No further information is provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Saccharin Sodium (E954)
Sodium Hydrogen Carbonate
Povidone
Sodium Laurilsulfate
Citric Acid Anhydrous
Sodium Carbonate
Dimeticone

6.2 Incompatibilities

None.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

Laminate strip of paper/polyethylene/aluminium foil/polyethylene sachets contained in a carton.

Or

Laminate Strip of paper/polyethylene/aluminium foil/Surlyn Sachets contained in a carton

Pack sizes: 12 and 24 tablets.

60 tablets (dispensing pack).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
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8 MARKETING AUTHORISATION NUMBER

PA0126/113/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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