SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Altermol 500 mg/30 mg, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paracetamol 500 mg and codeine phosphate hemihydrate 30 mg.

Excipient with known effect: Each tablet contains 18 mg lactose monohydrate (see also section 4.4).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, to almost white, capsule shaped, flat beveled, uncoated tablet, 17.5 x 7 mm, embossed with “PC2” on one side and with score line 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

Opioid-sensitive pain when analgesics with only peripheral effect are not sufficient.

Codeine is indicated in adults, adolescents and children 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

Adults:
1-2 tablets 1-4 times in 24 hours. The maximum daily dose of codeine should not exceed 240 mg.

Paediatric population:
Adolescents from 12 years of age:
In the paediatric population 12-18 years the dose should primarily be based on the codeine component and body weight. Recommended single codeine dose is 0.5 - 1 mg codeine/kg, maximum 4 times daily.
The Altermol dose should be adjusted so that the paracetamol component does not exceed 15 mg/kg/dose (up to 60 mg/kg/day).

As the Altermol tablet cannot be split, children weighing less than 34 kg cannot be treated without exceeding the maximum recommended paracetamol dose.

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).

4.3 Contraindications

Altermol is contraindicated in:

- Bile duct spasm.
- Hypersensitivity to paracetamol, codeine or to any of the excipients, listed in section 6.1.
- 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 lifethreatening adverse reactions (see section 4.4)
- In women during breastfeeding (see section 4.6)
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

4.4 Special warnings and precautions for use

Caution in the event of acute bronchial asthma.

Risk of developing a dependency with high doses and prolonged usage. Altermol should not be prescribed for patients with addictive tendencies, as this patient group has an increased risk of taking excessive doses of centrally acting analgesics.
Should not be combined with other pain-relieving medication containing paracetamol. Doses higher than those recommended entail a risk of very serious liver damage. Clinical signs of liver damage generally appear after a couple of days and generally culminate after 4-6 days. An antidote should be given as soon as possible. See also section 4.9 Overdose.

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. It is even more important to take this into account if the patient also has impaired renal function (see section 5.2).
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	3.4-6.5 %
Asian	1.2-2 %
Caucasian	3.6-6.5 %
Greek	6.0 %
Hungarian	1.9 %
Northern European	1-2 %

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of codeine 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 codeine 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).

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 ultrarapid or extensive metabolisers in their ability to metabolise codeine to morphine.

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.

Altermol tablets contains lactose monohydrate. Should not be used in patients with hereditary galactose intolerance, a special form of hereditary lactase deficiency (Lapp Lactase deficiency) or glucose/galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with Altermol should be avoided: quinidine.

The following combinations with Altermol may require dose adjustment:
- Neuroleptics
- Antidepressants
- Warfarin
- Enzyme-inducing medications such as certain antiepileptics (phenytoin, phenobarbital, carbamazepine)
- Rifampicin and St John's wort (*Hypericum perforatum*)
- Probenecid
- Metoclopramide
- Cholestyramine
- Chloramphenicol

Simultaneous use of alcohol should be avoided.

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).

Codeine
Pharmacokinetic interactions:
The effect of codeine is probably caused by its O-demethylation to morphine via the enzyme CYP2D6. This bioactivation is inhibited by certain medications, e.g. quinidine, terbinafine, certain antidepressants and neuroleptics, etc. These drugs therefore counter the effect of codeine. This interaction has been documented in studies on healthy trial subjects and/or pilot studies on patients.
Direct studies have been performed with quinidine, which is a very strong inhibitor of CYP2D6, and this combination should therefore be avoided.
Neuroleptics and antidepressants also have an inhibiting effect on CYP2D6, which means that these combinations may require a dose adjustment.

Enzyme-inducing medications such as rifampicin, barbiturates, several antiepileptics, St John's wort (*Hypericum perforatum*), etc. can produce reduced plasma concentrations of morphine (see also interaction with paracetamol below).

Paracetamol
Pharmacodynamic interactions:
Studies have shown that the effect of *warfarin* may be enhanced during treatment with paracetamol. The effect seems to increase with increasing doses of paracetamol but it may appear even at doses of 1.5-2.0 g paracetamol per day for at least 5-7 days. Occasional normal doses of paracetamol are not considered to have any effect.

Pharmacokinetic interactions:
Enzyme-inducing substances, such as certain antiepileptics (*phenytoin, phenobarbital, carbamazepine*) have been shown in pharmacokinetic studies to produce a reduction to approximately 60% of the plasma AUC of paracetamol. Other substances with enzyme-inducing properties, e.g. *rifampicin* and *St John's wort* (*Hypericum perforatum*) are also suspected of producing reduced concentrations of paracetamol. In addition, these substances may increase the hepatotoxicity of paracetamol due to increased and more rapid formation of toxic metabolites. Therefore caution should be taken in case of concomitant use of enzyme inducing substances.

Probenecid nearly halves the clearance of paracetamol by inhibiting its conjugation with glucuronic acid. This probably means that the dose of paracetamol can be halved when being given at the same time as probenecid.

The rate of absorption of paracetamol can be increased by *metoclopramide*, but these substances can be given in combination. The absorption of paracetamol is reduced by *cholestyramine*. Cholestyramine should not be given within one hour if maximum analgesic effect is to be obtained.

Paracetamol may affect the pharmacokinetics of *chloramphenicol*. Therefore an analysis of chloramphenicol in plasma is recommended in the event of combination treatment with chloramphenicol for injection.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Paracetamol: A large amount of data on pregnant women indicate neither malformative, nor feto/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.

Codeine: Should be used with caution during the first trimester. In the event of prolonged treatment during pregnancy, the risk of neonatal abstinence syndrome should be taken into account.

Breastfeeding:
Codeine is contraindicated in women during breastfeeding (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.

4.7 Effects on ability to drive and use machines

Treatment with Altermol can impair the ability to react. This should be taken into account when full attention is required, for example, when driving.

4.8 Undesirable effects

Approximately 15% of people are estimated to experience undesirable effects, which can be mainly linked to the pharmacological effects of codeine. The undesirable effects are dose related.

In the below table all undesirable effects are classified according to system organ class and frequency.

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Frequency **System Organ Class**	**Common** (≥1/100 to 1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)
Immune system disorders			Allergic reaction Angioedema	
Gastrointestinal disorders:	Nausea Constipation			Pancreatitis
Hepatobiliary disorders		Biliary dyskinesia	Liver injury	
Skin and subcutaneous tissue disorders			Exanthema Urticaria	
General disorders and administration site conditions:	Tiredness			
Investigations			Creatinine increased	

Very rare cases of serious skin reactions have been reported.

Liver damage from use of paracetamol has occurred in connection with alcohol abuse.
With prolonged use the risk of renal damage cannot be completely excluded.

Dyskinesia of the bile duct can occur in predisposed patients.

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 the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose with this combination, the main risks are paracetamol's hepatotoxic effects and the respiratory depressant effect of codeine.

Toxicity: 2 Altermol tablets 500 mg/30 mg to a 5-year-old produced no symptoms following administration of charcoal. 20-30 Altermol tablets 500 mg/30 mg to adults produced severe intoxication.

Paracetamol

Overdose may saturate the conjugation ability of the liver, and subsequently a large proportion of the dose is metabolised oxidatively. If the glutathione deposits are depleted, irreversible binding of the reactive intermediary metabolite to the liver macromolecules takes place. It is therefore of the greatest importance that antidote treatment be initiated as soon as possible if there is to be any chance of preventing or limiting liver damage from toxic doses.

Initially following ingestion and for the first few days there may be abdominal pains, nausea and vomiting. Clinical symptoms of liver damage generally appear after a couple of days and generally culminate after 4-6 days. Kidney damage may occur. Pancreatitis and toxic myocardial damage with arrhythmia and heart failure have been reported.

Toxicity:

5 g during the course of 24 hours to a 3½-year-old, 15-20 g to adults, 10 g to an alcoholic produced lethal intoxication. A toxic dose for children and adults is generally >140 mg/kg. Starvation, dehydration, medication with enzyme-inducing substances such as certain antiepileptics (phenytoin, phenobarbital, carbamazepine), rifampicin and St John's wort (*Hypericum perforatum*) as well as chronic high alcohol consumption are risk factors and even a slight overdose can in those circumstances produce pronounced liver damage. Even subacute "therapeutic" overdose has led to severe intoxication with doses varying from 6 g/day for one week, 20 g for 2-3 days, etc.

Treatment:

Close monitoring of hepatic and renal function, coagulation status, fluid and electrolyte status. Acetylcysteine is the antidote, and treatment with acetylcysteine initiated within 8-10 hours provides complete protection from liver damage, after which the effect diminishes. However, acetylcysteine may provide some protection even after 10 hours, but in such cases prolonged treatment should be administered. Acetylcysteine also reduces mortality in the event of manifest paracetamol-induced liver damage. Liver and kidney failure therapy is often required in cases where the deadline for effective antidote treatment has passed and there are toxic concentrations present. Haemoperfusion may be indicated in special circumstances. In extreme cases a liver transplant may be required.

Codeine

The main symptoms are of the same type as for morphine intoxication: reduced consciousness, respiratory depression, miotic pupils.
In children in particular there may be convulsions, erythema and facial oedema. At higher doses, hypoxia, respiratory arrest, loss of consciousness, circulatory failure and pulmonary oedema may develop.

Toxicity:

Large individual variations. Tolerance development. Small children and the elderly are especially susceptible. A lethal dose for adults is estimated to be (0.5-)0.8-1 g. 20 mg in 24 hours to babies (3 kg) produced severe intoxication.
30 mg to an 11-month-old produced mild intoxication. At doses of > 5 mg/kg there is a risk of severe respiratory depression in children. 640 mg to an adult produced severe intoxication.

Treatment:

Treatment is symptomatic and aims to secure respiration. Naloxone is the antidote and corrects respiratory depression. However, naloxone cannot replace respirator treatment for severe intoxication.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: codeine and paracetamol, ATC code: N02AJ06.

Altermol is a combination analgesic containing paracetamol and codeine, which are two analgesic substances with different mechanisms of action. Paracetamol is an aniline derivative with analgesic effect.
The analgesic effect is probably linked to the fact that the paracetamol molecule can capture and neutralise free OH(-)- and O(-) radicals, which form in the event of tissue damage, for example. Paracetamol also inhibits the enzyme prostaglandin synthetase in CNS and thereby is believed to increase the pain threshold. Paracetamol weakly inhibits prostaglandin synthesis in peripheral tissues.

Unlike acetylsalicylic acid, paracetamol does not cause gastrointestinal irritation or an increased tendency to bleed.

Codeine has central analgesic properties that are probably due to its opiate receptor effect on the CNS.
The analgesic effect is obtained after ½-1 hour, with maximum effect within approximately two hours.

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.

5.2 Pharmacokinetic properties

Paracetamol and codeine are absorbed rapidly and almost completely, and maximum plasma concentrations are reached within one hour. Paracetamol and codeine are excreted via the kidneys. The half-life for paracetamol is approximately 2-2½ hours following a therapeutic dose, and the substance is metabolised through conjugation to glucuronide and sulphate. A small proportion is also metabolised oxidatively and bound to glutathione. It is excreted as cysteine and mercapturic acid conjugates. Codeine is primarily metabolised through glucuronidation. Codeine is O-demethylated to morphine via a minor metabolic route. This metabolic stage is catalysed by the enzyme CYP2D6.
Known slow metabolizers of the enzyme CYP2D6 may experience less of an effect due to the failure to form morphine.
The half-life for codeine is approximately 2-3 hours, and following metabolism, the substance is excreted in the urine primarily as codeine and norcodeine conjugates and also (approximately 20%) as a morphine conjugate and free codeine.

<u>Codeine</u>
Special patient groups:
Slow and ultra-fast metabolizers regarding CYP2D6
Codeine is metabolised primarily through glucuronidation, but via a minor metabolic route codeine is O-demethylated to morphine. This reaction is catalysed by the enzyme CYP2D6. Around 7% of the Caucasian population lack a functional CYP2D6 enzyme due to their set of genes and are called slow metabolizers. These individuals may experience less of an effect due to the failure to form morphine. Around 1% of the Caucasian population are ultra-fast metabolizers. Ultra-fast metabolizers have one or more duplications of their CYP2D6 coding genes and therefore have markedly increased CYP2D6 activity. These individuals will get increased plasma concentrations of morphine when given codeine and therefore run the risk of morphine-related undesirable effects (see also sections 4.4 and 4.6). It is even more important to take this into account if the patient also has impaired renal function, which can lead to increased concentration of the active metabolite morphine-6-glucuronide. The set of genes for CYP2D6 can be determined with genotyping.

5.3 Preclinical safety data

There is no preclinical safety data of relevance to the safety assessment other than that already observed in this summary of product characteristics.

Paracetamol
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, pregelatinized
Stearic acid
Povidone
Lactose monohydrate
Cellulose, microcrystalline (E460)
Talc (E553b)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister package of A1/clear PVC: 10, 20, 50 and 100 tablets.
HDPE container (white polyethylene bottle): 100 and 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Alternova A/S
Lodshusvej 11
4230 Skælskør
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

2019-07-30