SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Codalvonil 500 mg/30 mg, effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Effervescent tablets: Paracetamol 500 mg, codeine phosphate hemihydrate 30 mg.

Excipients with known effect:

Each effervescent tablet also contains 199 mg mannitol and 437 mg sodium (19 mmol). For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablets.

White, circular flat tablets, 25 mm diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults Effervescent tablets: 1-2 tablets 1-4 times a day.

Method of Administration

The effervescent tablets must be dissolved in approximately half a glass of water to produce a clear drink.

4.3 Contraindications

- Bile duct spasm.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- 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. Codalvonil 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.

Codeine

Ultra-fast metabolizers and morphine intoxication:

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.

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

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

Each Codalvonil effervescent tablet contains 19 mmol (or 437 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with Codalvonil should be avoided: quinidine. The following combinations with Codalvonil 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 and chloramphenicol.

Simultaneous use of alcohol should be avoided.

Codeine

Pharmacodynamic interactions:

Single case reports have indicated a possible interaction between codeine and serotonergic drugs like monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) resulting in serotonin syndrome.

Pharmacokinetic interactions:

Codeine is probably active through the codeine being O-demethylated 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 the dose of paracetamol but it may appear even at doses of 1.5-2.0 g paracetamol per day for at least 5-7 days. Individual doses of paracetamol at normal doses are not considered to have any effect.

Pharmacokinetic interactions:

Enzyme-inducing medications, 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, the risk of liver damage ought to be greater when giving the maximum recommended dose of paracetamol to patients who are already taking an enzyme-inducing medication.

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 speed of absorption of paracetamol can be raised with *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: No known risks associated with use during pregnancy. 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 should not be used 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 ultrarapid 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 Codalvonil 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.

Tabular listing of adverse events:

Frequencies are defined as Common ($\geq 1/100$ to <1/10), Uncommon ($\geq 1/1,000$ to <1/100), Rare ($\geq 1/10,000$ to <1/1,000) and Very rare (<1/10,000).

Immune system disorders	
Rare	Allergic reaction, angioedema, anaphylactic reaction
Gastrointestinal disorders:	
Common	Nausea, constipation
Very rare	Pancreatitis
Hepatobiliary disorders	
Uncommon	Biliary dyskinesia
Rare	Liver injury
Skin and subcutaneous disorders	
Rare	Exanthema, urticaria
Very rare	Serious skin reactions
General disorders and administration site conditions:	
Common	Tiredness
Investigations	
Rare	Creatinine increased

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

[To be completed nationally]

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.

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 Codalvonil tablets 500 mg/30 mg to a 5-year-old produced no symptoms following administration of charcoal. 20-30 Codalvonil 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 $3\frac{1}{2}$ -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, combinations, ATC code: N02AA59.

Codalvonil 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 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. The analgesic effect is obtained after $\frac{1}{2}$ -1 hour, with maximum effect within approximately two hours (*effervescent tablets*).

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.

Codeine

Special patient groups:

Slow and ultra-fast metabolizers of CYP2D6

Codeine is metabolised primarily through glucuronidation, but via a minor metabolic route codeine is O-demethylated to morphine. This metabolic stage is catalysed by the enzyme CYP2D6. Around 7% of the Caucasian population lack a functional CYP2D6 enzyme due to their genetic make-up. These people 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 coded genes and therefore have markedly increased CYP2D6 activity. These individuals have raised plasma concentrations of morphine 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 genetic make-up 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

One effervescent tablet contains: sodium hydrogen carbonate citric acid sodium dihydrogen citrate mannitol anhydrous sodium carbonate povidone sodium saccharin sodium citrate sodium chloride magnesium stearate sodium laurilsulfate flavourings (orange and lemon).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Effervescent tablets should be stored in the original package. Keep the tube tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Effervescent tablets: Tubes of 25, 50 (2 x 25) and 100 (4 x 25) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

To be completed nationally

8 MARKETING AUTHORISATION NUMBERS

To be completed nationally.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 15 Feb 2012

10 DATE OF REVISION OF THE TEXT

2016-04-15