Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Codeine phosphate hemihydrate 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Codeine phosphate hemihydrate Expharma 20 mg tablets
Each tablet contains 20 mg codeine phosphate hemihydrate equivalent to 14.73 mg codeine.
Excipient with known effect: each tablet contains 112.50 mg of lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Codeine phosphate hemihydrate Expharma 20 mg tablets
White or almost white, round, flat, bevelled-edge tablets of 8.5 mm diameter, engraved with '20' on one side and scored on the other side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine is indicated in adults and children older than 12 years of age for:

- treatment of acute moderate pain which is not relieved by other analgesics such as paracetamol or ibuprofen (alone)
- symptomatic relief of unproductive cough
- symptomatic relief of diarrhoea, after failure of loperamide.

4.2 Posology and method of administration

Posology

Analgesia
Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240 mg.

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.

The analgesic effect is not materially enhanced by increasing the dose to a level greater than recommended below.

Adults:
The recommended dose for adults is 30-60 mg every 6 hours up to a maximum dosage of 240 mg per day.

Paediatric population

Children aged 12 years to 18 years:
The recommended dose for children aged 12 years and older is 30- 60 mg every 6 hours up to a maximum dosage of 240 mg per day. The dose should be based on the body weight (0.5-1 mg/kg).

Children aged less than 12 years:
Codeine should not be used for the treatment of acute moderate pain 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).

Diarrhoea
Adults:
The recommended dose for adults is 15-60 mg three to four times daily.

Paediatric population

Children aged 12 years to 18 years:
The recommended dose is 15-60 mg three to four times daily.

Children aged less than 12 years:
Codeine should not be used for the treatment of diarrhoea 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).

Cough
Adults
The recommended dose for adults is 15-30 mg three to four times daily.

Paediatric population

Children aged 12 years to 18 years:
The recommended dose is 15-30 mg three to four times daily.

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

Children aged less than 12 years:
Codeine is contraindicated in children below the age of 12 years for the symptomatic treatment of cough (see section 4.3).

Special populations
Renal impairment
Impairment of renal function results in slower elimination of codeine and the active metabolite morphine which may lead to toxicity even at therapeutic doses.

Hepatic impairment
Data on the use of codeine in patients with mild or moderate hepatic impairment are lacking. Cautious selection of the appropriate therapeutic dose is advised in these patients.

Method of Administration
For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, other opioids or to any of the excipients listed in section 6.1.
- Respiratory depression
- Obstructive airways disease, e.g. emphysema
- Uncontrolled/partly controlled asthma
- Hepatic failure
- Acute alcoholism
- Codeine is also contraindicated in conditions where inhibition of peristalsis is to be avoided, where there is a risk of paralytic ileus, where abdominal distension develops, or in acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic associated colitis (e.g. pseudomembranous colitis) or diarrhoea caused by poisoning.
- Use should be avoided in patients with raised intracranial pressure or head injury (in addition to the risk of respiratory depression and increased intracranial pressure, may affect pupillary and other responses vital for neurological assessment)
- Codeine should not be given to comatose patients
- In children below the age of 12 years for the symptomatic treatment of cough due to an increased risk of developing serious and life-threatening adverse reactions

- 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 breastfeeding (see section 4.6)
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers
- Concomitant use of MAO inhibitors. Codeine can be administered 2 weeks after stopping treatment with MAO inhibitors.

4.4 Special warnings and precautions for use

Codeine phosphate should be used with caution in the following conditions:

- There is a possible risk of CNS excitation or depression with concomitant use of opioids with MAOIs and use is not recommended (see section 4.3 and 4.5)
- Convulsions - may be induced or exacerbated
- Toxic psychosis
- Shock
- Hypotension and shock
- Cardiovascular disorders. Vagolytic action of codeine should be taken into account for patients with supraventricular tachycardia in the anamnesis.
- Reduced respiratory function or history of asthma
- Inflammatory bowel disease - codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure, therefore should be used with caution in diverticulitis, acute colitis, diarrhoea associated with pseudomembranous colitis or after bowel surgery
- Gastro-intestinal surgery - use with caution after recent GI surgery as opioids may alter GI motility
- Acute abdominal disorders
- The use of codeine may lead to constipation. Therefore, concomitant use of a laxative is recommended, unless codeine phosphate is used to treat diarrhoea.
- Hepatic impairment - avoid if severe. Codeine may precipitate coma
- Gall bladder disease or gall stones - opioids may cause biliary contraction. Avoid in biliary disorders
- Renal impairment
- Urinary tract surgery - following recent surgery patients will be more prone to urinary retention caused directly by spasm of the urethral sphincter, and via constipation caused by codeine
- Prostatic hypertrophy
- Urethral stricture
- Phaeochromocytoma - opioids may stimulate catecholamine release by inducing the release of endogenous histamine
- Adrenocortical insufficiency, e.g. Addison's Disease
- Myasthenia gravis
- Hypothyroidism, untreated myxoedema
- Drug abuse or dependence (including alcoholism)
- Pregnancy (see section 4.6)
- Elderly patients may metabolise and eliminate opioid analgesics more slowly than younger patients (see section 4.2).
- The risk benefit of continued use should be assessed regularly by the prescriber.

<u>CYP2D6 metabolism</u>

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 they will not obtain adequate analgesic effects. 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 prescribe doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, nausea, vomiting, shallow breathing, small pupils, constipation, lack of appetite and somnolence. 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	6.0%
Hungarian	1.9%
Northern European	1%-2%

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Codeine phosphate tablets 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 phosphate tablets 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).

Paediatric population

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.

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.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated (see section 4.3):

MAOIs (and drugs with MAOI action such as linezolid, moclobemide and selegiline) due to the possible risk of excitation or depression. Avoid the concomitant use of MAOI. Codeine can be administered 2 weeks after discontinuation of therapy with MAOI.

Combinations to be used with caution:

Respiratory related

- Alcohol - enhanced sedative and hypotensive effect, increased risk of respiratory depression
- Sedative antihistamines - enhanced sedative and hypotensive effect and increased risk of respiratory depression
- Hypnotics, anxiolytics and other narcotic analgesics - enhanced sedative effect, increased risk of respiratory depression

Gastro intestinal related

- Anticholinergics (e.g. atropine) - risk of severe constipation which may lead to paralytic ileus, and/or urinary retention
- Metoclopramide and domperidone - antagonised effect on GI activity

- Antidiarrhoeal drugs (e.g. loperamide, kaolin) - increased risk of severe constipation.

CNS related

- Anaesthetics - enhanced sedative and hypotensive effect
- Tricyclic antidepressants - enhanced sedative effect
- Antipsychotics - enhanced sedative and hypotensive effect
- 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)
- Opioid antagonists e.g. buprenorphine, naltrexone, naloxone - may precipitate withdrawal symptom
- Quinidine - reduced analgesic effec
- Antihypertensive drugs - enhanced hypotensive effect
- Sodium oxybate - concomitant administration of codeine and sodium oxybate may cause increased CNS depression and/or respiratory depression and/or hypotension.

Pharmacokinetic interactions

- Ciprofloxacin when used as surgical prophylaxis - avoid premedication with opioids as they reduce plasma ciprofloxacin concentrations
- Ritonavir may increase plasma levels of opioid analgesics such as codeine
- Mexiletine - delayed absorption of mexiletine
- Cimetidine inhibits the metabolism of opioid analgesics causing increased plasma concentration of codeine.

Interference with laboratory tests

- Opioids may interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium ^{99m}Tc disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

4.6 Fertility, pregnancy and lactation

Pregnancy
Limited data on the use of codeine during human pregnancy do not show an increased incidence of congenital malformations. Opiates cross the placenta. When administering just prior to the partus codeine is expected to cause respiratory depression in the neonate. When opiates are being used chronically, this is expected to lead to physical dependence of the fetus, and withdrawal symptoms in the neonate. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. Codeine phosphate should only be used during pregnancy if strictly needed.
Gastric stasis and a risk of inhalation pneumonia could occur in the mother during labour. Administration should be avoided during the late stages of labour and during the delivery of a premature infant.

Breast-feeding
Codeine is contraindicated in women during breastfeeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolites 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.

If symptoms of opioid toxicity develop in either the mother or the infant, 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.

4.7 Effects on ability to drive and use machines

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Effects such as confusion, drowsiness, dizziness, hallucinations, blurred or double vision or convulsions may occur. The effects of alcohol are enhanced with this combination.

Patients should be advised, that if affected, they should not drive, operate machinery or take part in any activities where such impairment could put themselves or others at risk.

4.8 Undesirable effects

The following side effects may occur during the use of Codeine phosphate tablets. The side effects are listed below by system organ class and frequency.

The frequencies are defined as follows:
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)>

System Organ Class	**Adverse reactions**
Immune system disorders	
Rare	anaphylactoid reactions
Not known	symptoms which may be due to histamine release, i.e. rash, urticaria, pruritus, dyspnoea, hyperhidrosis, erythema or flushing, oedema
Psychiatric disorders	
Not known	mood altered (dysphoria, euphoric mood), depression, hallucination (seeing or hearing things that are not real), restlessness, agitation, nightmare, confusional state, disorientation, drug tolerance or dependence, libido decreased
Nervous system disorders	
Not known	confusional state, somnolence, malaise, vertigo, dizziness, seizure, headache, intracranial pressure increased, hypothermia.
Eye disorders	
Not known	miosis, vision blurred or diplopia
Cardiac disorders	
Not known	bradycardia, palpitations, tachycardia.
Vascular disorders	
Not known	syncope, hypotension, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Not known	respiratory depression with larger doses
Gastrointestinal disorders	
Rare	gastrointestinal hypermotility and megacolon (in chronic ulcerative colitis)
Not known	constipation (too constipating for long-term use), abdominal pain, pancreatitis, nausea, vomiting, dry mouth
Hepatobiliary disorders	
Not known	biliary colic
Musculoskeletal and connective tissue disorders	
Not known	muscle rigidity
Renal and urinary disorders	
Not known	ureteral spasm, antidiuretic effect, urinary retention
Reproductive system and breast disorders	
Not known	erectile dysfunction
Metabolism and nutrition disorders	
Not known	decreased appetite
General disorders and administration site conditions	
Not known	asthenia, fatigue

Withdrawal effects: abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration, and increase in heart rate, respiratory rate and blood pressure. NOTE - tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

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.

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

The effects of overdose will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. The lethal dose in adults is estimated at 0.5-1.0 grams of codeine (corresponding to 7-14 mg / kg body weight).

Symptoms
Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large.
The triad of coma, pinpoint pupils and respiratory depression is considered indicative of opioid overdose with dilation of the pupils occurring as hypoxia develops.
Nausea and vomiting are common Other opioid overdose symptoms include hypothermia, confusion, convulsions, severe dizziness, severe drowsiness, hypotension and tachycardia (possible but unlikely), nervousness or restlessness, excitement, hallucinations, bradycardia, circulatory failure, slow or troubled breathing, severe weakness, convulsions, especially in infants and children.
Rhabdomyolysis, progressing to renal failure, has been reported in overdose with opioids.

Management
Management 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 the 350 mg or a child more than 5 mg/kg. In acute overdose with respiratory depression or coma, the specific opioid antagonist naloxone is indicated using one of the recommended dose regimens- repeated doses may be required in a seriously poisoned patient as naloxone is a competitive antagonist with a short half-life. Patients should be observed closely for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opium alkaloids and derivatives, ATC code: R05D A04

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. It is also used in the treatment of cough and diarrhoea. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Codeine and its salts are readily absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one hour. Codeine is metabolised by O-and N-Demethylation in the liver to morphine and nor codeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half-life has been reported to be between 3 and 4 hours.

Absorption

Codeine is well absorbed from the gastrointestinal tract. After oral administration, peak plasma concentrations are reached after 1-2 hours.

Distribution
Codeine transfers across the placenta and excretes into breast milk. The extent of plasma protein binding of codeine is around 7-25%.

Biotransformation
Codeine is metabolised by CYP3A4 to norcodeine, which is further inactivated via glucuronidation. Approximately 10% of the absorbed codeine is demethylated into morphine by CYP2D6. Morphine is further converted to the active metabolite morphine-6-glucuronide.

Elimination
Codeine is metabolised in the liver and eliminates through the kidneys approximately 37% as glucuronide conjugates and 10% as unchanged codeine. The plasma elimination half-life is approximately 3-4 hours, which could be as high as 6 hours in case of hepatic impairment or after overdose.

Special patient groups (CYP2D6 polymorphism)
Due to genetic polymorphism, approximately 7% of the Caucasian population lacks functioning CYP2D6 enzyme. The analgesic effect of codeine can be decreased in such patients due to the lack of morphine formation. Further, 1-5% of the Caucasian population have an increased CYP2D6 activity. These patients may have elevated plasma morphine levels (see section 4.4 and 4.6) and especially in case of impaired renal function side effects of morphine may occur as the elimination of the active metabolite morphine-6-glucuronide is reduced. Increased CYP2D6 enzyme activity is more frequent in African and Mediterranean populations.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Cellactose 80 (lactose monohydrate, cellulose powder)
Silica, colloidal anhydrous
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PVdC//Alu blister: 3 years
HDPE container: 4 years
After first opening of the HDPE container: 12 months

6.4 Special precautions for storage

PVC/PVdC//Alu blister
Store below 25 °C. Keep the blister in the outer carton in order to protect from light.

HDPE container
This medicinal product does not require any special temperature storage conditions. Keep the container tightly closed in order to protect from light.

6.5 Nature and contents of container

Codeine phosphate hemihydrate Expharma 20 mg tablets
20, 30, 60, 90 or 100 tablets in clear, transparent PVC/PVdC//Alu blisters in a carton box with leaflet.
50, 100 or 250 tablets in white, opaque HDPE container with PP cap with desiccant and safety ring, in a carton box with leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Extractum Pharma zrt
Megyeri u. 64
Budapest IV
1044
Hungary

8 MARKETING AUTHORISATION NUMBER

PA25390/002/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th June 2025

10 DATE OF REVISION OF THE TEXT