Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Codeine phosphate hemihydrate 15 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Codeine phosphate hemihydrate 15 mg tablets
Each tablet contains 15 mg codeine phosphate hemihydrate equivalent to 11.05 mg codeine. Excipient with known effect: each tablet contains 84.375 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Codeine phosphate hemihydrate Expharma 15 mg tablets
White or almost white, round, flat-faced, bevelled-edge tablets of 7.5 mm diameter, engraved with '15' on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine phosphate hemihydrate 15 mg tabletsis 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

Codeine phosphate hemihydrate 15 mg tablets is indicated forsymptomatic relief of severe diarrhoea in adults, 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.

Paediatricpopulation

Childrenaged12yearsto18years:
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).

Childrenagedlessthan12years:
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).

Severe diarrhoea

The posology should be individualized to use the lowest effective dose for the shortest duration of time, taking into account the patient's general condition, age, weight and medical history (see sections 4.3 and 4.4).

Treatment should be initiated and supervised by a specialist, e.g. oncologist or gastroenterologist.

Particular caution should be exercised when prescribing this medicine due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4). The treatment period should be as short as possible.

Adults:
The recommended dose for adults is 15-60 mg three to four times daily up to a maximum of 240 mg per day.

Paediatricpopulation
Codeine should not be used for the treatment of severe diarrhoea in children and adolescents below the age of 18 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.

Paediatricpopulation

Childrenaged12yearsto18years:
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).

Childrenagedlessthan12years:
Codeine is contraindicated in children below the age of 12 years for the symptomatic treatment of cough (see section 4.3).

Specialpopulations

Elderly
Dosage should be reduced in the elderly where there is impairment of hepatic or renal function.

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

Hepaticimpairment
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.

Methodof Administration
For oral use.

Treatment goals and discontinuation
Before initiating treatment with Codeine phosphate hemihydrate 15 mg tablets, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
Codeine phosphate hemihydrate 15 mg tablets should not be used longer than necessary.

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 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 is used to treat severe diarrhoea.
- Hepatic impairment - avoid if severe. Codeine may precipitate coma
- 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.

Hepatobiliary disorders

Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

CYP2D6metabolism

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 prescribed 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%

Riskfromconcomitantuseofsedativemedicinessuchasbenzodiazepinesorrelateddrugs:

Concomitant use of Codeine phosphate hemihydrate 15 mg 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 hemihydrate 15 mg 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).

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Codeine phosphate hemihydrate 15 mg tablets. Repeated use of Codeine phosphate hemihydrate 15 mg tablets can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Codeine phosphate hemihydrate 15 mg tablets may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Codeine phosphate hemihydrate 15 mg tablets and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Paediatricpopulation

Post-operativeuseinchildren
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.

Childrenwithcompromisedrespiratoryfunction
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.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Combinationscontra-indicated(seesection4.3):

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.

Combinationstobeusedwithcaution:

Respiratoryrelated

- 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

Gastrointestinalrelated

- 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 i.e. gabapentinoids (gabapentin and pregabalin)
- The concomitant use of Codeine phosphate hemihydrate 15 mg tablets with sedative medicines such as benzodiazepines or related drugs, i.e. gabapentinoids (gabapentin and pregabalin) increases the risk of sedation, respiratory depression, hypotension, profound sedation, coma or 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 symptoms
- 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.

Pharmacokineticinteractions

- Ciprofloxacin when used as surgical prophylaxis - avoid premedication with opioids as they reduce plasma ciprofloxacin concentrations
- Mexiletine - delayed absorption of mexiletine
- CYP3A4 inhibitors: The concomitant use of codeine with CYP3A4 inhibitors (for example ritonavir as strong CYP3A4 inhibitor and cimetidine as moderate CYP3A4 inhibitor), may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome CYP2D6, resulting in higher morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of codeine is achieved. Consider dosage reduction of codeine until stable drug effects are achieved.

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower codeine levels, greater norcodeine levels, and less metabolism via CYP2D6 leading to lower morphine levels, resulting in decreased opioid efficacy or a

withdrawal syndrome in patients who had developed physical dependence to codeine. Consider increasing the codeine dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal.

1. CYP2D6 inhibitors: The effect of codeine is probably caused by its O-demethylation to morphine via the enzyme CYP2D6. Quinidine, a strong inhibitor of CYP2D6, reduces bioactivation of codeine, which decreases its effect. Concomitant use of codeine and strong CYP2D6 inhibitors should be avoided.Concomitant use with other CYP2D6 inhibitors, e.g. terbinafine, certain neuroleptics and antidepressants may require 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 and thus reduced analgetic effect. Dose adjustment should be considered. The enzyme-inducing effect may persist 2-3 weeks after discontinuation of the enzyme-inducing drug.
- Amitriptyline and clomipramine increase the analgetic effect of codeine, partly due to increased availability of morphine. Dose reduction should be considered to reduce the risk of side effects.

Interferencewithlaboratorytests

- 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
Risk benefit must be considered because opioid analgesics cross the placenta. Studies in animals have shown opioids to cause delayed ossification in mice and increased resorption in rats.

Codeine 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.

Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms in the neonate. During labour opioids enter the foetal circulation and may cause respiratory depression in the neonate. Respiratory malformation in neonates may be associated with exposure to codeine during pregnancy.

As with all medications caution should be exercised during pregnancy, especially in the first trimester. A possible association with respiratory and cardiac malformations has been reported following first trimester exposure to codeine.

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)>

SystemOrganClass	**Adversereactions**
Immunesystemdisorders	
Rare	anaphylactoid reactions
Notknown	symptoms which may be due to histamine release, i.e. rash, urticaria, pruritus, dyspnoea, hyperhidrosis, erythema or flushing, oedema
Psychiatricdisorders	
Notknown	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
Nervoussystemdisorders	
Notknown	confusional state, somnolence, malaise, vertigo, dizziness, seizure, headache, intracranial pressure increased, hypothermia.
Eyedisorders	
Notknown	miosis, vision blurred or diplopia
Cardiacdisorders	
Notknown	bradycardia, palpitations, tachycardia.
Vasculardisorders	
Notknown	syncope, hypotension, orthostatic hypotension
Respiratory,thoracicandmediastinaldisorders	
Notknown	respiratory depression with larger doses
Gastrointestinaldisorders	
Rare	gastrointestinal hypermotility and megacolon (in chronic ulcerative colitis)
Notknown	constipation (too constipating for long-term use), abdominal pain, pancreatitis, nausea, vomiting, dry mouth
Hepatobiliarydisorders	
Notknown	biliary colic, sphincter of Oddi dysfunction
Musculoskeletalandconnectivetissuedisorders	
Notknown	muscle rigidity
Renalandurinarydisorders	
Notknown	ureteral spasm, antidiuretic effect, urinary retention
Reproductivesystemandbreast disorders	
Notknown	erectile dysfunction
Metabolismandnutritiondisorders	
Notknown	decreased appetite
Generaldisordersandadministrationsiteconditions	
Notknown	asthenia, fatigue

Drug dependence

Repeated use of Codeine phosphate hemihydrate 15 mg tablets can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Reportingofsuspectedadversereactions
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: HPRA Pharmacovigilance, Website: www.hpra.ie.

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 severe 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.

Environmental risk assessment (ERA)
Environmental risk assessment studies have shown that codeine phosphate hemihydrate may cause endocrine disruption in the environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Lactose monohydrate
Cellulose powder
Silica, colloidal anhydrous
Sodium starch glycolate Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

*PVC/PVdC//Alublister:*3 years
*HDPEcontainer:*4 years
After first opening of the HDPE container: 1 year

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 15 mg tablets

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

This medicinal product may pose a risk to the environment. (See section 5.3)

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

PA25390/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th June 2025

10 DATE OF REVISION OF THE TEXT

May 2026