Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

DAFALGAN CODEINE, scored effervescent tablet

2. Qualitative and quantitative composition

Paracetamol.....500 mg
codeine phosphate hemihydrate.....30 mg
For one scored effervescent tablet
Excipients with known effect: one tablet contains 30 mg aspartame (E951) (source of phenylalanine), 59 mg sodium benzoate (E211), 385 mg sodium, 300 mg sorbitol (E420) and in the flavouring, 0,5 mg ethanol 5 mg fructose, glucose, sucrose and sulphites.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Scored effervescent tablet.

4. Clinical particulars

4.1 Therapeutic indications

For the relief of severe pain.

DAFALGAN CODEINE, scored effervescent tablet is indicated for patients over the age of 12 years for the treatment of acute pain of moderate intensity which cannot be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with Co-codamol in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

The posology should be adjusted according to the intensity of the pain; the lowest effective dose should generally be used for the shortest possible duration. This dose can be taken up to 4 times a day, observing a 6-hour interval between each dose.

The duration of the treatment should not exceed 3 days, and if the pain is not relieved, it is recommended that patients/caregivers seek the advice of a doctor.

Always observe an interval of 6 hours between two doses.

The usual posology depends on the age and weight of the patient (see dosage table below):

Weight (age)	**Dose** per administration	**Minimum interval** between each administration	**Maximum daily dose**
31 to 50 kg (aged from around 12 to 15 years)	**1 tablet** i.e. 500 mg paracetamol + 30 mg codeine	**6 hours**	**4 tablets per day** i.e. 2 g paracetamol + 120 mg codeine
>50 kg (aged from around 15 to 18 years)	**1** (to 2) **tablet** i.e. 500 mg to 1 g paracetamol + 30 to 60 mg codeine	**6 hours**	**6 tablets per day** i.e. 3 g paracetamol + 180 mg codeine
Adult	**1** (to 2) **tablet** i.e. 500 mg to 1 g paracetamol + 30 to 60 mg codeine	**6 hours**	**6** (to 8) **tablets per day** i.e. 3 (to 4) g paracetamol + 180 (to 240) mg codeine

Adults
It is usually not necessary to take more than 6 tablets per day. However, in cases of more intense pain, this posology may be increased to 8tablets **per day (maximum posology**). The maximum daily total dose of paracetamol should not exceed 4 g per day; the maximum total daily dose of codeine should not exceed 240 mg.

Paediatric population
Children under the age of 12 years
Codeine should not be used in children under the age of 12 years due to the risk of opioid toxicity associated with the variable and non-predictive metabolisation of codeine to morphine (see sections 4.3 and 4.4).

Children aged from 12 to 18 years
It is essential to **observe the posologies defined according to the weight of the adolescent** and therefore choose an adjusted formulation.

The recommended daily dose is:

- around 60 mg/kg/day of **paracetamol** in 4 doses, i.e. around 15 mg/kg every 6 hours,
- around 3 mg/kg/day of **codeine** in 4 doses, i.e. around 0.5 to 1 mg/kg every 6 hours.

In adolescents weighing more than 50 kg: It is usually not necessary to take more than 1 tablet per administration. However, in cases of more intense pain, the dose can be increased to 2 tablets per administration, **without taking more than 6 effervescent tablets per day (maximum posology).**

Special populations

Elderly subjects

The initial dose should be halved in relation to the recommended adult dose, and this may be increased based on tolerance and needs.

Renal impairment

In the case of renal impairment, there is a risk of accumulation of codeine and paracetamol. As a result:

- the interval between two doses will be a minimum of 8 hours,
- a reduction of the dose should be considered,
- in children, close monitoring should be put in place.

Hepatic impairment

In patients with active or compensated chronic liver disease, particularly those with mild to moderate hepatocellular impairment or Gilbert syndrome (non-haemolytic familial jaundice), the dose of paracetamol should not exceed 3 g/day.

Other

The total daily maximum dose of paracetamol should not exceed 60 mg/kg/day (no more than 3 g/d) in the following situations:

- adults weighing less than 50 kg,
- chronic alcoholism,
- chronic malnutrition (low reserves of hepatic glutathione),
- dehydration.

Maximum recommended doses

Caution: take all medicinal products into account in order to prevent an overdose, including medicinal products obtained without a prescription (see section 4.4).

The total daily maximum dose of **codeine** should not exceed 240 mg.

The total daily maximum dose of **paracetamol** should not exceed (see section 4.9):

- 80 mg/kg/day in children weighing less than 37 kg,
- 3 g per day in children weighing between 38 kg and 50 kg,
- 4 g per day in adults and children weighing more than 50 kg.

Method of administration

Oral use.

The effervescent tablets must be dissolved in a glass of water before being administered.

Treatment goals and discontinuation

Before initiating treatment with Dafalgan Codeine, 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).

4.3 Contraindications

- Children under the age of 12 years.
- Hypersensitivity to any of the excipients listed in section 6.1.

Related to paracetamol:

- Hypersensitivity to paracetamol.
- Severe hepatocellular impairment.

Related to codeine:

- Hypersensitivity to codeine.
- Concomitant use with sodium oxybate (see section 4.5).
- In patients with asthma and respiratory impairment, whatever the degree of respiratory Impairment, due to the depressant effect of codeine on the respiratory centres.
- When breast-feeding (see section 4.6).
- In all patients under the age of 18 years after tonsillectomy and/or adenoidectomy in the context of

- Sleep-obstructive apnoea, due to an increased risk of life-threatening serious adverse events (see section 4.4).
- In patients known to be ultra-rapid CYP2D6 metabolisers (see section 4.4).
- Acute alcoholism,
- Head injuries,
- Raised intra-cranial pressure
- Following biliary tract surgery.

4.4 Special warnings and precautions for use

Special warnings

In order to prevent a risk of overdose:
verify the absence of codeine and paracetamol in the composition of other medicinal products,

- including medicinal products obtained without a prescription.
- observe the maximum recommended doses (see section 4.2).

Related to paracetamol:

In adults weighing more than 50 kg, THE TOTAL DOSE OF PARACETAMOL SHOULD NOT EXCEED 4 GRAMS PAR DAY (see section 4.9).

Paracetamol can cause serious cutaneous reactions such as acute generalised exanthematoupustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed of the early signs of these serious cutaneous reactions, and the onset of a rash or other signs of hypersensitivity necessitates discontinuation of the treatment.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin.. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring, is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Related to codeine:

Deafferentation pain (neurogenic pain) does not respond to the codeine-paracetamol combination.

Monitoring should include the child's alertness in particular: before taking this medicinal product, please make sure that the child does not have an excessive or abnormal tendency to drowsiness.

CYP2D6 metabolism:
Codeine is metabolised to morphine by the CYP2D6 hepatic enzyme, its active metabolite. In the case of deficit or absence of this enzyme, the expected analgesic effect will not be obtained.

It is estimated that up to 7% of the Caucasian population may have this deficit.

However, if the patient is a rapid or ultra-rapid metaboliser, there is an increased risk of developing adverse effects due to toxicity of the opioids, even at therapeutic doses. These patients transform codeine in morphine rapidly: as a result, their morphine level in serum is higher than expected.

General symptoms of opioid toxicity include confusion, drowsiness, superficial respiration, miosis, nausea, vomiting, constipation and loss of appetite. In severe cases, patients may present symptoms of respiratory and circulatory depression that are life-threatening and, in very rare cases, fatal.

The estimated prevalence of ultra-rapid metabolisers in the different populations are summarised 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% to 2%

Post-surgery in children

Some cases published in literature have shown that codeine, used post-surgery in children after tonsillectomy and/or adenoidectomy in the context of obstructive sleep apnoea syndrome, is associated with rare adverse effects that can be life-threatening, or even fatal (see section 4.3). All of these children had received codeine at the recommended doses; however, some evidence showed that these children were rapid or ultra-rapid metabolisers of codeine to morphine.

Children with impaired respiratory function

Codeine is not recommended in children with impaired respiratory function due to neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or pulmonary tract infections, multiple trauma or long surgical procedures. These factors may aggravate the symptoms of morphine toxicity.

Effects on the central nervous system

The effects of opioids on the central nervous system (CNS) can cause severe respiratory depression, which can be fatal.
The depressant effects of opioids on the CNS, including respiratory depression and sedation, should be considered in the case of known or suspected intracranial pathology, such as head trauma or other intracranial lesions. In addition, these effects on the CNS may complicate the neurological evaluation.

Opioids should be used with caution in epileptic patients, given their ability to reduce the crisis threshold.
Prolonged use of analgesics, including opioids, increases the risk of cephalalgia by medicinal product abuse.
Opioid treatment, especially in chronic use, may trigger hyperalgesia in some subjects.

Respiratory effects

Opioids cause respiratory depression by depressant effects on the CNS. The risk of respiratory depression may increase when used concomitantly with other medicinal products, and in the case of pharmacogenetic factors.

Gastrointestinal effects

Constipation, which may be refractory to laxative treatment, is an adverse effect of opioid treatment, and requires gastrointestinal transit monitoring.

Nausea and vomiting are also among the adverse effects of opioid treatment. In some subjects, the incidence of nausea and vomiting may decrease with development of a tolerance.

The administration of opioids may mask the symptoms of an acute abdominal disease.

Some opioids, including morphine, may increase the pressure on the sphincter of Oddi, suggesting that precautions should be taken in

cases of biliary tract diseases such as pancreatitis and cholelithiasis, even if a definitive effect has not been determined.

Dermatological effects

Pruritus is an adverse event of opioid treatment.

Hormonal effects

Opioids can lower hormone levels and should be used with caution in patients with hormonal disorders.

Immunological effects

Some opioids, including morphine, may inhibit immunological function. The clinical significance of this effect has not been determined.

Musculoskeletal effects

Opioid treatment can cause muscle rigidity and myoclonus.

Effects on urinary tracts

Opioids can cause urinary retention by decreasing the tone of the smooth muscles in the bladder and the perception of bladder distension by inhibition of the urinary reflex. Therefore, opioids should be used with caution in patients with urethral stricture or prostatic hypertrophy.

Cardiovascular and cerebrovascular effects

Patients with hypovolaemia or hypotension will be monitored for any eventual haemodynamic effects.

Tolerance

A reduction in analgesic efficacy or tolerance may occur with prolonged use of opioids. Cross- tolerance is not complete among opioids, and tolerance may develop at different rates for different opioids.

Dependence, abuse and misuse

DAFALGAN CODEINE, scored effervescent tablet contains codeine, the regular or prolonged use of which can lead to psychological and physical dependence. This medicine should be used with caution in patients with a history of abuse and/or dependence (including drugs and alcohol) or mental disorder (eg major depression). Abuse or

misuse may result in overdose and/or death (see section 4.9).

Precautions for use

Elderly subjects: the initial dose should be halved in relation to the recommended dose, and this may be increased based on tolerance and needs (see section 4.2).

Related to paracetamol:

Paracetamol should be used with caution in the case of:

- weight <50 kg (see section 4.2),
- renal impairment (see section 4.2),
- mild to moderate hepatocellular impairment (see section 4.2),
- Gilbert syndrome (non-haemolytic familial jaundice) (see section 4.2),
- Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency (which may lead to haemolytic anaemia),
- chronic alcoholism, excessive consumption of alcohol (3 or more alcoholic drinks every day), anorexia, bulimia or cachexia (see section 4.2),
- chronic malnutrition (low reserves of hepatic glutathione) (see section 4.2),
- dehydration, hypovolaemia (see section 4.2).

In the event of the discovery of acute viral hepatitis, treatment should be discontinued.

Related to codeine:

- The absorption of alcohol during treatment is not recommended due to the presence of codeine.
- In the case of intracranial hypertension, codeine may increase the extent of this hypertension.
- In the case of a productive cough, codeine may interfere with sputum.
- In cholecystectomised patients, codeine can cause acute abdominal pain syndrome of the biliary or pancreatic type, most often associated with biological abnormalities, suggestive of a spasm of the sphincter of Oddi.
- Elderly subjects may have an increased risk of adverse effects associated with opioids, such as respiratory depression and constipation. In addition, elderly subjects have a higher likelihood of concomitant use of medicinal products and this may increase the risk of medicinal product interactions.

Related to the presence of excipients with known effect:

This medicinal product contains sucrose. Patients with a fructose intolerance, glucose and galactose malabsorption syndrome, or a sucrase-isomaltase deficiency (rare hereditary diseases) should not take this medicinal product.

This medicinal product contains 300 mg sorbitol (E420) in each effervescent tablet. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

This medicine contains 59 mg sodium benzoate (E211) in each effervescent tablet.

This medicine contains 0,5 mg ethanol in each effervescent tablet. The small amount of alcohol in this medicine will not have any noticeable effects.
This medicine contains 5 mg fructose in each effervescent tablet. The additive effect of concomitantly administered products containing fructose (or sorbitol) and dietary intake of fructose (or sorbitol) should be taken into account.

This medicine contains glucose in each effervescent tablet. Patient with rare glucose-galactose malabsorption should not take this medicine.

This medicine contains 385 mg sodium in each effervescent tablet. This is equivalent to 19.25% of the maximum daily dietary intake of sodium recommended by the WHO. The maximum daily dose of this product (6 effervescent tablets) is equivalent to 115,5% of the maximum daily dietary intake of sodium recommended by the WHO. DAFALGAN CODEINE, scored effervescent tablet has a high sodium content; this should be taken into account in patients who follow a low salt (sodium) diet.

This medicine contains 30 mg aspartame (E951) in each effervescent tablet. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
This medicine contains “sulphites” and may, in rare cases, cause severe hypersensitivity reactions and bronchospasms.

4.5 Interaction with other medicinal products and other forms of interaction

RELATED TO PARACETAMOL

+ Vitamin K antagonists

Risk of increase of the Vitamin K antagonist effect and of the risk of haemorrhage in the event that paracetamol is taken at maximum doses (4 g/day) for at least 4 days.

More frequent control of the INR. Potential adjustment of the Vitamin K antagonist dosage during treatment with paracetamol and after its discontinuation.

+ Flucloxacillin

Caution is advised when paracetamol is administered concomitantly with flucloxacillin due to the increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with a risk factor for glutathione deficiency, such as severe renal impairment, sepsis, malnutrition, or chronic alcoholism. Close monitoring is recommended in order to detect the onset of HAGMA, via the testing for urinary 5-oxoproline.

Interactions with paraclinical testing

Administration of paracetamol can cause errors in blood glucose tests using the glucose oxidase- peroxidase method in the case of abnormally high concentrations.

Administration of paracetamol can cause errors in blood uric acid assays using the phosphotungstic acid method.

RELATED TO CODEINE

Combinations contraindicated

+ Sodium oxybate

Increased risk of respiratory depression which may be fatal in case of overdose.

Combinations not recommended

+ Alcohol (drink or excipient)

The sedative effect of codeine is increased by alcohol.
Impaired alertness may make driving vehicles and using machines dangerous. Avoid consuming alcoholic beverages or medicinal products containing alcohol.

+ Bupropion, Cinacalcet, Duloxetine, Terbinafine

Risk of ineffectiveness of the opioid by inhibition of its metabolism by the inhibitor.

+ Fluoxetine, Paroxetine, Quinidine

Decreased efficacy of the opioid by inhibition of its metabolism by the inhibitor.

+Morphine-derived agonist-antagonist drugs

Reduced analgesic effect by competitive blocking of the receptors, with the risk of onset of withdrawal syndrome.

+ Partial morphine-derived antagonist drugs

Risk of reduction in analgesic effect.

Combinations to be taken into account

+ Pure morphine analgesics, morphine-like antitussives, pure morphine antitussives, others morphin analgesics, Methadone

Increased risk of respiratory depression which may be fatal in case of overdose.

+ Other sedative drugs

Increased central depression.

Impaired alertness may make driving and using machines dangerous.

+ Barbiturates, benzodiazepines and related drugs

Increased risk of sedation and respiratory depression which may lead to coma and death, especially in the elderly. The dose and duration of concomitant use should be limited as much as possible.

+ Atropinic drugs

Significant risk of colic akinesia, with severe constipation.

4.6 Pregnancy and Lactation

Pregnancy

Related to 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.

Related to codeine:

Clinically, although some case-control studies indicate an increased risk of the occurrence of cardiac malformations, most of the epidemiological studies rule out a malformative risk.
Animal studies have shown a teratogenic effect.
Consequently, if clinically needed, occasional use of DAFALGAN CODEINE, scored effervescent tablet can be considered during pregnancy; however, it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.
In case of administration at the end of pregnancy, take into account the morphine-mimetic properties of this medicinal product (theoretical risk of respiratory depression in the newborn after high doses before delivery, risk of withdrawal syndrome in the case of chronic administration at the end of pregnancy).

Breast-feeding

This medicinal product is contraindicated during breast-feeding (see section 4.3):

Paracetamol and codeine are excreted in human milk.

Treatment during breast-feeding is conditioned by the presence of codeine.

At normal therapeutic doses, codeine and its active metabolite may be present in human milk at very low doses and are unlikely to cause adverse effects in the breastfed child. However, if the patient is an ultra-rapid CYP2D6 metaboliser, a significant amount of the active metabolite, morphine, may be present in the maternal blood as well as the human milk. In very rare cases, these high levels may lead to symptoms of opioid toxicity in children (drowsiness, difficulty sucking, respiratory pauses or even depressions, and hypotonia) which can be fatal.

Fertility

Related to paracetamol:

Due to the potential mechanism of action on cyclooxygenase and prostaglandin synthesis, paracetamol may alter fertility in women, with an effect on ovulation reversible upon discontinuation of treatment.
Some effects on male fertility have been observed in an animal study. The relevance of these effects in humans is not known.

Related to codeine:

There are no animal data on male and female fertility.

4.7 Effects on ability to drive and use machines

Caution is drawn, particularly among vehicle drivers and machine users, to the risk of drowsiness due to the presence of codeine.

4.8 Undesirable effects

RELATED TO PARACETAMOL

• Some rare cases of hypersensitivity reactions, such as anaphylactic shock (hypotension (as an anaphylaxis symptom)), angioedema (Quincke's oedema), erythema, urticaria, skin rash) have been reported. Their occurrence requires the definitive discontinuation of this medicinal product and related medicinal products.
• Very rare cases of serious cutaneous reactions (acute generalised exanthematous pustulosis, toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported and require the discontinuation of treatment.
• Exceptionally rare cases of thrombocytopenia, leukopenia and neutropenia have been reported.
• Some cases of diarrhoea, abdominal pain, increase of liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase), increased or decreased INR, have been reported.

RELATED TO CODEINE

At therapeutic doses, the adverse effects of codeine are comparable to those of other opiates but are rarer and more moderate.Possibility of:

- sedation, euphoria, dysphoria, hallucination,
- miosis, myoclonus, rhabdomyolysis paresthesias, syncope, tremors, urinary retention, renal impairment,
- hypersensitivity reactions (pruritus, urticaria and rash),

- constipation, nausea and vomiting,
- drowsiness, dizzy spells,
- bronchospasm, respiratory depression (see section 4.3),
- acute abdominal pain syndrome of the biliary or pancreatic type, suggestive of a sphincter of Oddi spasm, occurring particularly in cholecystectomised patients.
- abuse. Prolonged use leads to a risk of drug dependence (see section 4.4).
- There is a risk of withdrawal syndrome following an abrupt stop of the treatment, which can be observed in the user and in the newborn child of a mother intoxicated with codeine during the pregnancy (see section 4.6).

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. There is no known specific antidote for bortezomib overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: PERIPHERAL ANALGESIC/ OPIOID ANALGESIC, ATC code: N02BE51.

N: Central nervous system.

Mechanism of action

• Paracetamol: analgesic - antipyretic.
• Codeine phosphate: central analgesic.

The combination of paracetamol and codeine phosphate has significantly greater analgesic activity than its individual components, with a more prolonged effect over time.

Codeine is an analgesic with weak central action. It exercises its effect thanks to its action on the μ- opioid receptors, although its affinity for these receptors is low. Its analgesic effect is due to its conversion to morphine. Codeine, particularly when combined with other analgesics such as paracetamol, has been shown to be effective in the treatment of nociceptive pain.

5.2 Pharmacokinetic properties

Paracetamol and codeine have superposable absorption and kinetics that are not altered when combined.

PARACETAMOL

Absorption

The absorption of paracetamol for oral use is complete and fast. Maximum plasma concentrations are reached 30 to 60 minutes after ingestion.

Distribution

Paracetamol is distributed rapidly throughout all tissues. The concentrations are comparable in the blood, saliva and plasma. The binding to plasma proteins is weak.

Metabolism

Paracetamol is metabolised primarily by the liver. The two major metabolic routes are conjugation with glucuronic acid and sulphate. The latter route can be rapidly saturated at posologies that exceed the therapeutic doses. A minor route, catalysed by the P450 cytochrome, is the formation of a reactive intermediate (N-acetyl benzoquinoneimine), which, under normal conditions of use, is rapidly detoxified by the reduced glutathione and eliminated in the urine after conjugation with cysteine and mercaptopurine acid. However, during massive intoxication, the quantity of this toxic metabolite is increased.

Elimination

Elimination is primarily urinary. 90% of the ingested dose is excreted by the kidney in 24 hours, mainly in the form of glucuronide (60 to 80%) and sulphate (20 to 30%) conjugates. Less than 5% is eliminated unchanged. The elimination half-life is approximately 2 hours.
Pathophysiological variations
• Renal impairment: in the case of renal impairment (see section 4.2), the elimination of paracetamol and its metabolites is

delayed.
• Elderly patients: the conjugating ability is unchanged (see section 4.2).

CODEINE

After oral ingestion, codeine is well absorbed and its relative bioavailability is 40 to 70% relative to the intramuscular route. Plasma concentrations peak within 1 hour and then decrease with a half-life of 2 to 4 hours. Codeine is metabolised to give codeine-6-glucuronide, morphine and norcodeine.

The elimination of codeine and its metabolites occurs almost entirely via renal excretion (85 to 90%), essentially in the form of glucuronide conjugates; the elimination is considered complete after 48 hours. The percentages of the administered dose (free product + conjugate) found in the urine are as follows: about 10% in the form of morphine, 10% of norcodeine, 50 to 70% of codeine. Approximately 25 to 30% of the codeine administered binds to plasma proteins.

5.3 Preclinical safety data

Animal studies are not available relative to paracetamol and codeine combination.

Related to paracetamol:

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

Conventional preclinical studies of safety pharmacology, genotoxicity, repeated dose toxicity and carcinogenic potential did not reveal any special risk for humans at therapeutic doses.

In hepatotoxic doses, paracetamol has shown a genotoxic and carcinogenic potential (tumours in the liver and bladder) in mice and rats. However, this genotoxic and carcinogenic activity is considered as related to the modifications in the metabolism of paracetamol during the administration of elevated doses or concentrations and does not present a risk for clinical use.

In rats, effects on male fertility (oligospermia, abnormal sperm motility and decrease in the fertilising potential of sperm) at high doses (500 and 1000 mg/kg of body weight per day) have been observed.

Related to codeine:

Preclinical studies of genotoxicity, repeated dose toxicity, reproductive toxicity and carcinogenesis have not shown a particular risk to humans at therapeutic doses.

At maternotoxic doses, fetotoxicity was observed in animals. Animal studies have shown a teratogenic effect.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium bicarbonate, anhydrous sodium carbonate, anhydrous citric acid, sorbitol (E420), sodium docusate, sodium benzoate (E211), povidone, aspartame (E951), natural grapefruit flavouring (including traces amount of ethanol, fructose, glucose, sucrose, and sulphites).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

3 years

6.4 Special Precautions for storage

Store in the original package in order to protect from moisture.

Tube: Close the tube tightly immediately after use.

6.5 Nature and Content of container

16 tablets in tube (polypropylene).

40 tablets in blister strip (aluminium polyethylene).

100 tablets in blister strip (aluminium polyethylene). Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder

LABOREX KENYA

8. Marketing Authorization Number

CTD10577

9. Date of first authorization/renewal of the authorization

23/04/2024

10. Date of revision of the text

12/05/2015