SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol/Codeïne Eurogenerics 500 mg/30 mg tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Each tablet contains 17.1 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to almost white, capsule-shaped, flat tablet with bevelled edge. There is 'PC2' debossed on one side and a score line on the other side of the tablet. Approximate dimension of the capsule-shaped tablets are 17,5 mm length and 7 mm width.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol/Codeïne EG is indicated for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).
Paracetamol/Codeïne EG is indicated in patients older than 12 years of age.

4.2 Posology and method of administration

Paracetamol/Codeïne EG should be used at the lowest effective dose and the duration of treatment should be kept as short as possible and limited to three days.

Posology

Adults with body weight > 50 kg
1 to 2 tablets per intake, depending on the severity of the pain and the patient's response. This dose may be taken up to 3 times per day, with an interval of not less than 6 hours. If needed, this dose may be increased to 8 tablets per 24 hours. The maximum dose of 8 tablets per 24 hours should not be exceeded. The maximum daily dose should not exceed 4 g paracetamol and 240 mg codeine per 24 hours.

Adults with body weight < 50kg
The maximum daily dose is based on the body weight: the maximum daily dose should not exceed 60 mg/kg of paracetamol per 24 hours.

Paediatric population:

Adolescents >50kg
1 to 2 tablets per intake, depending on the severity of the pain and the patient's response. This dose may be taken up to 3 times per day, with an interval of not less than 6 hours. The maximum dose of 6 tablets (3 g paracetamol and 180 mg codeine) per 24 hours should not be exceeded.

Children and adolescents aged 12 – 18 years with body weight 33 kg – 50 kg
The dose is based on body weight and is 0.5 – 1 mg/kg codeine and 15 mg/kg paracetamol per intake. The recommended dose for children from 12 years of age is 1 tablet per intake. This dose may be taken up to 3 times a day, according to the severity of the pain and the patient's response, with an interval of not less than 6 hours.
The maximum daily dose should not exceed 60 mg/kg of paracetamol and 240 mg of codeine per 24 hours.

Children aged less than 12 years or adolescents with body weight < 33 kg:
Codeine should not be used in children or adolescents with body weight < 33 kg. Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see section 4.3 and 4.4).
Paracetamol/Codeïne EG 500 mg/30 mg tablets are not suitable for children weighing less than 33 kg.

Special populations:

Elderly:
Elderly patients may have an increased sensitivity to opioid analgesics and therefore an increased risk of opioid-related side effects. In elderly patients, an initial dose should be used that is lower than the usual adult dose and adjusted according to tolerance and individual needs of the patient.
In addition, it should be taken into account that renal and hepatic impairment are more common in elderly patients (see section 4.4).

Renal impairment:
Renal insufficiency increases the risk of accumulation of paracetamol and codeine. In patients with moderate or severe renal insufficiency, the minimum interval between each administration should be adjusted according to the following schedule.

Creatinine clearance	Dose interval
CrCl 10 to > 50 ml/min	6 hours
CrCl < 10 ml/min	8 Hours

Hepatic insufficiency:
Hepatic insufficiency increases the risk of accumulation of paracetamol and codeine.
In patients with hepatic insufficiency, the dose should be reduced, or the dose interval extended. The maximum daily dose of paracetamol should not exceed 60 mg/kg/day (with a maximum of 2 g/day) in the following cases:
- adults with a body weight of less than 50 kg;
- patients with active chronic or compensated liver disease, and in particular with mild to moderate hepatic insufficiency;
- Gilbert's syndrome (familial hyperbilirubinemia);
- chronic alcoholism;
- chronic malnutrition (low hepatic glutathione reserves);
- dehydration.

Codeine dose reduction should be considered in patients with hepatic insufficiency.

Method of administration
Take the tablets unchewed with a sufficient amount of water.

4.3 Contraindications
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or phenacetin.
- Renal insufficiency or severe hepatocellular insufficiency.
- Respiratory insufficiency or obstructive respiratory disorders (e.g. emphysema).
- Acute asthma.
- Acute alcohol intoxication
- The repeated administration of paracetamol is contra-indicated in patients with anaemia, heart, lung, kidney or liver diseases.
- 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 who are breastfeeding (see section 4.6).
- In patients for whom it is known, they are CYP2D6 ultra-rapid metabolisers.
- Concomitant use of MAO inhibitors (see section 4.5)
- Children under 12 years of age
- Head injuries, raised intra-cranial pressure.

4.4 Special warnings and precautions for use

The consumption of alcoholic beverages during treatment is formally discouraged.

Due to the presence of paracetamol:
- As with any analgesic, treatment should be kept as short as possible and the duration should be strictly limited to the duration of symptoms, as it has not been completely ruled out that paracetamol plays a role in the development of analgesic nephropathy.
- Long-term or frequent use is not recommended. Prolonged use, except under medical supervision, may be harmful to health.
- The maximum dose must not be exceeded under any circumstances. To avoid the risk of overdose avoid, no other products containing paracetamol should be taken simultaneously.
- Ingestion of a multiple of the daily dose at one time can cause severe liver damage; there is not always loss of consciousness. However, it is necessary to seek medical attention immediately consult medical attention due to the risk of irreversible liver damage (see section 4.9).
- Paracetamol should be used with caution in the presence of the following risk factors which may lower the threshold for hepatic toxicity. The dosage should be adjusted and the maximum daily dose must absolutely not be exceeded in these patients (see section 4.2):
    - Mild to moderate hepatic insufficiency;
    - Moderate to severe renal insufficiency (creatinine clearance ≤ 50 ml/min). Administration of paracetamol to patients with moderate to severe renal impairment may lead to accumulation of conjugated compounds;
    - Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency) (may lead to haemolytic anaemia);
    - Chronic alcoholism, the excessive consumption of alcohol (3 or more alcoholic drinks per day);
    - Anorexia, bulimia or cachexia, chronic malnutrition (low liver glutathione reserves);
    - Dehydration, hypovolaemia;

    - Concomitant treatment with drugs affecting liver function. The risk of hepatotoxicity may be greater in patients taking enzyme inducers such as barbiturates and antiepileptic drugs (see section 4.5). In these cases, accumulation of toxic metabolites of paracetamol may exacerbate or cause liver disease.
- Paracetamol can cause severe skin reactions, such as acute generalised exanthematous pustulosis (AGEP), stevens-johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be made aware of the warning signs of these serious skin reactions and use of the drug should be discontinued if rashes or other signs of hypersensitivity occur.
- In children and adolescents treated with 60 mg/kg paracetamol daily, the combination with another antipyretic is not justified unless the drug is ineffective.
- In case of acute fever or signs of secondary infection or persistent symptoms, a doctor should be consulted.

Due to the presence of codeine phosphate:
- Long-term administration or supratherapeutic doses of codeine may lead to physical and psychological dependence and withdrawal syndrome if treatment is abruptly discontinued. Therefore, long-term use of <Poduct name> is not recommended. In patients with a current or previous opioid dependence, <Poduct name> should be used with caution and alternative treatments should be considered. Especially in patients with chronic respiratory insufficiency, attention should be paid to possible worsening of respiratory depression (which can be fatal).
- Caution is recommended in case of intracranial hypertension.
- Opioids should be used with caution in patients with epilepsy because they can lower the epileptogenic threshold may decrease.
- In case of a productive cough, the codeine may interfere with coughing up.
- Patients who no longer have a gallbladder may experience acute abdominal pain, generally associated with laboratory test abnormalities suggesting sphincter of oddi spasm.
- Prolonged use of pain medication, including opiates, increases the risk of headaches due to excessive use of the medication.
- Treatment with opiates, especially with chronic use, can cause hyperalgesia in some people
- Administration of opioids can mask symptoms of acute abdominal distress.
- The administration of opioids can lead to decreased hormone levels and should therefore be used with caution in patients with hormonal disorders.
- Some opioids, including morphine, may have an inhibitory effect on immune function. The clinical significance of that effect remains to be established.
- <Product name> should be used with caution in patients with asthma. Opiates, especially morphine and its derivatives, may cause the release of histamine.
- Opiates can cause urinary retention by reducing the tonus of the smooth bladder muscles and awareness of bladder swelling and inhibit the mictiereflex. Therefore, opioids should be used with caution in patients with urethral stricture or prostatic hypertrophy.
- Persons with hypovolaemia or hypotension receiving opiates should be monitored for possible haemodynamic effects.
- To avoid the risk of overdose or serious side effects, check whether other medicines being administered (prescription or non-prescription) do not contain opiates or other suppressors of the central nervous system (see section 4.9).
- Caution is recommended in patients with a current or previous opioid or alcohol dependency
- Caution is recommended in patients with renal impairment (see section 4.2), fever, inflammatory bowel disease and recent abdominal or renal surgery
- Caution is also recommended in patients with hypothyroidism, untreated myxedema, cardiovascular disease, toxic psychosis, shock, acute bowel disease, adrenal insufficiency, gallbladder disease or gallstones and prostate hyperplasia or prostate obstruction.

Risk of concomitant use of sedatives such as benzodiazepines or related medicinal products:
- Concomitant use of Paracetamol/Codeïne EG and sedatives such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death;
- In light of these risks, these sedatives should only be prescribed concomitantly in patients with no treatment alternatives;
- If it is decided to prescribe Paracetamol/Codeïne EG concomitantly with sedatives, the lowest effective dose should be used, and the duration of treatment should be as short as possible;
- Patients should be monitored closely for signs and symptoms of respiratory depression and sedation. In this regard, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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.

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. However, side effects may occur. 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 (see section 4.9).

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.

In mothers with ultra-fast CYP2D6 metabolism who are still breastfeeding their infants and receiving treatment with codeine, there is a high risk of neonatal overdose and death due to high serum concentrations of morphine (see section 4.6).
Although, if accurate tests are available, CYP2D6 genotyping before initiation of treatment with analgesics is ideal, careful monitoring for signs of opioid toxicity is crucial. At known ultra-fast CYP2D6 metabolisers, alternative treatment is recommended.

Estimates of prevalence of ultra-rapid metabolisers in 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 % - 2 %

Paediatric patients:
Paediatric patients should be closely monitored for signs of progressive depression of the central nervous system due to codeine, such as extreme drowsiness or slower respiratory rhythm. Pharmacogenetic differences in the metabolism of codeine may increase the risk of side effects or reduce response to treatment.

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.

Elderly patients
Elderly patients may have an increased sensitivity to opioid analgesics and therefore an increased risk of opioid-related side effects such as respiratory depression and constipation. In elderly patients, an initial dose should be used that is lower than the usual dose for adults adults and adjusted according to the patient's tolerance and individual needs (see section 4.2). Elderly patients are also more likely to be taking other medicines concomitantly, which may increase the risk of drug interactions.
In elderly patients, liver and kidney tests should be performed to detect any liver or renal insufficiency beforehand.

Flucloxacillin
Caution should be exercised when co-administering paracetamol and flucloxacillin because of an increased risk of metabolic acidosis with increased anion gap (HAGMA), especially in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), and in patients taking maximum daily doses of paracetamol. Close monitoring, including measurement of 5-oxoproline in urine, is recommended.

Excipient with known effect
[Product name] contains 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

Strong enzyme inducers:
Paracetamol is completely metabolised in the liver. Some metabolites of paracetamol are hepatotoxic and co-administration with strong enzyme inducers (rifampicin, certain antiepileptics, etc.) may therefore lead to hepatotoxic reactions, especially when high doses of paracetamol are used.

Codeine phosphate, alcohol or drugs that can have a depressant effect on the central nervous system:
The concomitant use of codeine phosphate with alcohol or central nervous system depressants such as anxiolytics, antidepressants, MAO inhibitors, other narcotic analgesics, barbiturates, antihistamines H1, clonidine and related products, hypnotics and neuroleptics should be avoided because of enhancement of the depressing effect. More specifically, the use of Paracetamol/Codeïne EG should be avoided for up to 14 days after discontinuation of the MAO inhibitors.

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines 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).
Barbiturates, benzodiazepines, morphine derivatives (analgesics, antitussives, substitution treatment) may increase the risk of respiratory depression. The dose and duration of concomitant use should be limited (see section 4.4).

Opiate agonists / partial antagonists and agonists:
Use with opiate agonists / partial antagonists and agonists (buprenorphine, butorphanol, nalbufine, nalorphin, pentazocine) may lead to a decrease in analgesic effect and opiate withdrawal symptoms. The dose and duration of concomitant use should be limited (see section 4.4).

Other drugs that may cause drowsiness:
Other drugs that are metabolized by CYP2D6 or that inhibit CYP2D6, such as SSRIs (paroxetine, fluoxetine, bupropion and sertraline), neuroleptics (chlorpromazine, haloperidol, levomepromazine, thioridazine), tricyclic antidepressants (imipramine, clomipramine, amitriptyline, nortriptyline), celecoxib, quinidine, dexamethasone and rifampicin may reduce the analgesic effect of codeine. The dose and duration of concomitant use should be limited (see section 4.4).

Anticholinergics:
Anticholinergics co-administered with opiates, such as codeine, may increase the inhibition of intestinal function and increase the risk of intestinal stasis. The dose and duration of use should be limited.

Non-steroidal anti-inflammatory drugs:
Because Paracetamol/Codeïne EG does not irritate the gastric mucosa, it can be administered to ulcerated patients or can be combined with nonsteroidal anti-inflammatory drugs for a limited period of time.

Anticoagulants:
Due to its low level of binding to plasma proteins, it may be combined with anticoagulants. However, long-term treatment with more than 2 g of paracetamol per day may increase the risk of bleeding and requires regular monitoring of the International Normalised Ratio (INR). The duration of concomitant use with Paracetamol/Codeïne EG should be limited.

Alcohol, barbiturates, phenytoin, carbamazepine and isoniazid:
In case of an overdose, alcohol, barbiturates, phenytoin, carbamazepine and isoniazid may increase the risk for the liver (see sections 4.4 and 4.9).

Diflunisal:
Concomitant administration of diflunisal and paracetamol increases plasma levels of paracetamol by approximately 50 %. The dose and duration of concomitant use should be limited.

Chloramphenicol:
Concurrent use of chloramphenicol may extend the elimination half-time of chloramphenicol by 2 to 3 hours.

Metoclopramide, colestyramine and activated charcoal:
The absorption of paracetamol may be increased when associated with metoclopramide, and reduced when associated with cholestyramine or activated charcoal.

Colestyramine:
If co-administration of paracetamol and colestyramine is necessary, the paracetamol should be taken at least 1 hour before or 4 hours after the administration of colestyramine.

Oral contraceptives:
Oral contraceptives may increase the elimination time of paracetamol.

Phenytoin:
Concomitant administration of phenytoin may reduce the efficacy of paracetamol and lead to an increased risk of hepatotoxicity. Patients treated with phenytoin should avoid high and/or chronic doses of paracetamol. Patients should be monitored for signs of hepatotoxicity (see section 4.4).

Probenecid:
Probenecid blocks the binding of paracetamol to glucuronic acid, reducing the clearance of paracetamol is reduced by about a factor of 2. A reduction in the dose of paracetamol should be considered when co-administered with probenecid.

Salicylamide:
Salicylamide may prolong the half-life (t ½) of paracetamol.

Enzyme-inducing substances and alcohol:
Caution should be exercised when paracetamol is taken simultaneously with enzyme-inducing substances. Those substances include but are not limited to barbiturates, isoniazid, carbamazepine, rifampicin. The maximum daily dose must absolutely not be exceeded in those patients (see sections 4.2, 4.4 and 4.9).
During the duration of treatment, alcohol abuse is strongly discouraged (see section 4.4).

Zidovudine:
Concomitant administration of paracetamol and zidovudine may lead to neutropenia and hepatotoxicity. Chronic/frequent use of paracetamol should be avoided in patients treated with zidovudine. If chronic use of paracetamol and zidovudine is necessary, white blood cells and liver function should be monitored, especially in malnourished patients.

Vitamin K antagonists:
The effect of vitamin K antagonists may be enhanced, especially if high doses of paracetamol are taken. In this case, regular monitoring of the International Normalized Ratio (INR) is recommended.

Lamotrigine:
Reduced bioavailability of lamotrigine, with possible reduction of the therapeutic effect, due to

possible induction of hepatic metabolism. The dose and duration of concomitant use should be limited.

Metoclopramide and domperidone:
Accelerated resorption of paracetamol in the small intestine due to accelerated gastric emptying. The dose and duration of concomitant use should be limited.

Flucloxacillin:
Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

Interference with laboratory tests
Use of paracetamol can interfere with blood glucose level assessment by glucose oxidase peroxidase. Paracetamol may influence uric acid evaluation by phosphorus wolfram acid (false increase).

4.6 Fertility, pregnancy and lactation

Pregnancy

Codeine:
There are limited data on the use of codeine during pregnancy in human. Opiates pass the placenta. Its regular use during pregnancy can cause physical dependence in the foetus, leading to withdrawal symptoms in the newborn. Exposure to codeine during pregnancy and just before delivery could give rise to respiratory depression in the newborn. Administration of codeine just before delivery can cause delayed gastric emptying and a risk of pneumonia in the mother during delivery. Use of codeine by the mother at any stage of pregnancy may be associated with planned caesarean section. Its use in the third trimester may be associated with an increased risk of acute unplanned caesarean section and postpartum hemorrhages. Administration of codeine should be avoided during the late stages of delivery and during delivery of a premature neonate.

Paracetamol:
A large amount of data on pregnant women indicate neither malformative nor feto/neonatal toxicity by paracetamol. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Due to the presence of codeine, Paracetamol/Codeïne EG should not be used during pregnancy, unless the clinical situation justifies treatment with the combination of paracetamol and codeine.

Breast-feeding
Paracetamol/Codeïne EG is contraindicated 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.
The mother should be informed of the risks and signs of opioid toxicity, and both child and mother should be closely monitored.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data suggest that a negative effect on the breastfed child is unlikely.

Fertility
There are no data on the effects of paracetamol/codeine on fertility in humans.

4.7 Effects on ability to drive and use machines
The codeine contained in this medicine can, even when used as intended, alter alertness to such an extent as to impair the ability to actively participate in road traffic, operate machines, or perform dangerous work.

Paracetamol/Codeïne EG has major influence on the ability to drive and use machines

4.8 Undesirable effects

Paracetamol can lead to rare allergy-like undesirable effects on the skin (rash, erythema, urticaria), as well as other allergic reactions such as laryngeal oedema and anaphylactic reactions. If these occur, treatment must be discontinued. There is no allergic cross-reactivity with salicyl derivatives.

Biological signs of hepatotoxicity manifested by elevated transaminases have been reported following high dose treatment. This hepatotoxicity is potentiated by alcohol and hepatic microsomal enzyme inducers (see section 4.5).

In this section, frequencies of undesirable effects 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 Drug Reaction**		
	Frequency		
	Rare	**Very rare**	**Not known a**
Blood and lymphatic system disorders		thrombocytopenia, leukopenia, pancytopenia, neutropenia, haemolytic anaemia, agranulocytosis	anaemia
Immune system disorders	Allergic reactions	allergic reactions that require discontinuation of the treatment	anaphylactic reactions
Nervous system disorders	Headache		
Gastrointestinal disorders	abdominal pain, diarrhoea, nausea, vomiting, constipation		
Hepatobiliary disorders	hepatic impairment, hepatic insufficiency,	hepatotoxicity	hepatitis

	hepatic necrosis, jaundice		
Skin and subcutaneous tissue disorders	pruritus, rash, sweating, angioedema, urticaria	Very rare cases of severe skin reactions were reported. Acute generalized exanthematous pustulosis, toxic epidermal necrolysis, stevens-johnsons syndrome	
Renal and urinary disorders		sterile pyuria (cloudy urine)	nephropathy (interstitial nephritis, Tubular necrosis) after Prolonged use of high doses
General disorders and administration site conditions	dizziness, malaise		
Injury, poisoning and procedural complications	Overdose and intoxication		

The following adverse reactions have been reported after marketing.

System Organ Class	**Adverse Drug Reaction**			
	Frequency			
	common	**uncommon**	**Very rare**	**Not Known**
Blood and lymphatic system disorders		thrombocytopenia		
Immune system disorders		Anaphylactic shock, hypersensitivity, increased transaminase levels, increased aspartate aminotransferase levels, elevated levels of alkaline phosphatase in the blood, increased levels of amylase in the blood, increased gamma glutamyl levels, slow coagulation (elevated INR)		
Metabolism and nutrition disorders				High anion gap metabolic acidosis
Psychiatric disorders		Drug abuse, drug addiction, hallucination	Confusion	

Nervous system disorders	sleepiness	Dizziness, myoclonus, paraesthesia, Syncope, tremors		
Ear and labyrinth disorders		vertigo		
Vascular disorders		hypotension		
Respiratory, thoracic and mediastinal disorders		Congestion, respiratory depression		
Gastrointestinal disorders	Diarrhoea, constipation, nausea, vomiting, abdominal pain	Pancreatitis		
Hepatobiliary disorders		Bile colic, hepatitis		
Skin and subcutaneous tissue disorders		Quincke edema, erythema, pruritus, rash, urticaria		
Musculoskeletal and connective tissue disorders		Rabdomyolysis		
Renal and urinary disorders		Renal insufficiency, ischuria		
General disorders and administration site conditions		Asthenia, malaise, edema		

Very rare cases of severe skin reactions have been reported.

Description of selected adverse reactions: High anion gap metabolic acidosis: Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of overdose, there is a risk of acute liver toxicity, especially in elderly people, young children, in case of hepatic or renal insufficiency, chronic alcoholism, chronic malnutrition, when using enzyme inducers and in very lean adults (< 50 kg).

Hepatotoxicity often occurs only 24 to 48 hours after ingestion. Overdose can be fatal. In case

of overdose, a doctor should be consulted immediately, even in the absence of symptoms.

Symptoms

The maximum dose of opioids depends on interindividual differences. Codeine overdose is characterised in an initial phase characterised by nausea and vomiting. Acute depression of the respiratory centres may cause cyanosis, delayed breathing, drowsiness, rash, itching, ataxia and, in rarer cases, pulmonary oedema.

In severe cases, slowing of respiratory rate, respiratory pauses, miosis, convulsions, signs of histamine release: facial swelling, urticarial eruption, collapses, urinary retention.

In children, the toxic threshold is 2 mg/kg in a single intake; and in adults the lethal dose is estimated to be 0.5 to 1.0 g codeine (± 7 to 14 mg/kg).

Codeine overdose is treated with artificial respiration and the administration of naloxone by parenteral route.

In adults, a single intake of 8 to 10 g of paracetamol can lead to hepatic necrosis or jaundice. In children, the toxic dose is 120 mg/kg/day.

The toxic dose is lower in patients with hepatic insufficiency and chronic alcoholism, in chronically malnourished patients and in patients receiving enzyme inducers.

Paracetamol overdose (acute exposure due to ingestion of 7.5 g or more of paracetamol in an adult or 140 mg/kg bodyweight in children) in conjunction with glutathione depletion by more than 70% leads to the formation of increased quantities of hepatotoxic metabolite which, as it cannot be detoxified, gives rise to hepatocytolysis and possible complete and irreversible necrosis.

The early symptoms, which may appear as little as 12 to 24 hours after taking a potentially toxic dose, include: nausea, vomiting, anorexia, abdominal pain and sweats.

Liver damage, increased bilirubin or transaminase levels, decreased prothrombin levels, glucose metabolism abnormalities, decreased alkaline reserve, and often fatal coma occur between 12 and 48 hours after ingestion. Necrosis and hepatic insufficiency do not occur until 3 days after overdose.

Treatment

Consequently, if paracetamol overdose is suspected, the patient should be immediately hospitalised, and serum concentrations should be determined as soon as possible from 4 hours after ingestion.
Values greater than 200 µg/mL at 4 hours or greater than 50 µg/mL at 12 hours may indicate a high risk of hepatic necrosis. The usual liver function tests should be performed early and repeated at regular intervals (24 hours). In most cases, liver transaminase levels return to normal after 1 to 2 weeks, with full recovery of liver function. However, in very severe cases, liver transplantation may be required. However, in very severe cases, liver transplantation may be required.
To avoid the risk of overdose, check that other medicines administered (prescription or non-prescription) do not contain paracetamol.
Administration of paracetamol in higher doses than recommended carries a risk of very serious liver damage. The first clinical symptoms of liver damage are usually observed 1 or 2 days after paracetamol overdose. Maximum symptoms of liver damage are usually observed after

3 to 4 days. An antidote should be administered as soon as possible.
To avoid the risk of overdose or serious side effects, check whether other medicines administered (prescription or non-prescription) do not contain opiates or other suppressors of the central nervous system.

In case of overdose, the stomach should be emptied as soon as possible, i.e. within the first 10 hours, by gastric lavage or induction of vomiting. Treatment can start with the administration of activated charcoal, but the main therapeutic measure is administration of N-acetylcysteine (NAC).
There are two validated protocols for the use of NAC in paracetamol overdose, one by intravenous route, the other by oral route.

With oral administration, activated charcoal cannot be given, as it may interfere with NAC.
- Loading dose: 140 mg/kg NAC (in a 5% solution in water or fruit juice);
- Maintenance dose: 70 mg/kg every 4 hours, repeated 17 times (i.e. over 68 hours).

Early regular monitoring (every 24 hours) of liver function is strongly recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Analgesics
ATC code: N02BE51

Paracetamol/Codeïne EG is a fast-acting analgesic. It associates the complementary actions of paracetamol and codeine phosphate.

The analgesic effect of paracetamol is thought to be due to inhibition of prostaglandin synthesis in the central and peripheral nervous system.

Codeine is a centrally acting weak analgesic. Codeine exerts its effects 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 association of paracetamol and codeine phosphate has a considerably higher analgesic effect than the compounds alone, with a clearly longer effect.

5.2 Pharmacokinetic properties

Paracetamol and codeine and its salts have cumulative absorption and kinetics that do not change when associated.

Paracetamol
Fast and almost complete absorption in the intestine.
Rapid and uniform distribution in most tissues.
Low level of binding to plasma proteins (20 to 50%).
Plasma peak value reached after 30 to 60 minutes.
Plasma half-life of 2 to 3 hours in adults.

Hepatic metabolism: paracetamol follows two major metabolic pathways. It is eliminated in the urine as a conjugate with glucuronide (60 to 80%) and as a conjugate with sulphate (20 to 30%) and less than 5% is eliminated in unchanged form. A small fraction (less than 4%) is converted by cytochrome P450 to a oxidative metabolite that is believed to be hepatotoxic; this metabolite, which is usually eliminated at therapeutic doses by conjugation with glutathione, occurs in greater amounts during massive poisoning.
The half-life of paracetamol is longer in elderly patients and in patients with severe hepatic insufficiency. However, no accumulation of paracetamol in plasma due to impaired metabolism has been reported.

Codeine
Codeine is absorbed quickly at the intestinal level, and the maximum concentration is reached in 60 minutes. The plasma half-life is 2 to 3 hours in adults. There is little binding to plasma proteins (approximately 25%).
Codeine and its salts are metabolised in the liver and excreted in the urine in an inactive form composed mainly of glucuronide-conjugated derivatives. They have little affinity for opioid receptors.
Codeine and its salts cross the placental barrier, and codeine is also found in breast milk.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch,
Lactose monohydrate,
Talc (E553b),
Cellulose powdered (E460),
Povidone K30 (E1201),
Magnesium stearate (E572),
Stearic acid (E570).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/Aluminium blister

Pack sizes: 16, 16x1, 30 and 30x1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

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

7. MARKETING AUTHORISATION HOLDER

EG N.V.
Heizel Esplanade B22
1020 Brussel
België

8. MARKETING AUTHORISATION NUMBER(S)

RVG 131517

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 7 april 2025

10. DATE OF REVISION OF THE TEXT