SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

PARACETAMOL CODEINE 500 mg / 30 mg, effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500mg and Codeine Phosphate hemihydrate 30mg.

Excipients with known effect: Each tablet also contains 487 mg of sorbitol and 413 mg of sodium.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet.

Bevelled, flat, round, white tablet with a scoreline on one face.

Although the tablets have a score line, they are not to be halved as they do not divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PARACETAMOL CODEINE 500 mg / 30 mg, effervescent tablets is indicated in the relief of severe pain in adults. Codeine is indicated in patients older than 16 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Posology:

Adults: The usual dose is one or two tablets every four hours as required. The total daily dose should not exceed 4 g paracetamol and 240 mg of codeine (8 tablets in a day).

Elderly: As for adults, however a reduced dose may be required (see section 4.4)

Paediatric population:
Adolescents 16-18 years old (body weight >35 kg)
The dose should primarily be calculated based on the codeine component and body weight. The recommended dose for codeine is 0.5-1 mg / kg body weight / dose with a maximum dose of codeine of 60 mg, every 6hours when necessary up to maximum dose of 240 mg daily. The maximum doses of 15 mg / kg body weight / dose (60 mg / kg body weight / day) of paracetamol and 1 mg / kg body weight / dose (4 mg / kg body weight / day) of codeine must not be exceeded. Do not take more than 8 tablets in a 24 hour period.

Children aged 12-15 years
This combination medicine is not suitable for children aged between 12-15 years. Doses depend on body weight and age; a single dose of paracetamol ranges from 10 to 15mg/kg body weight. For children aged between12-15 years, other formulations and dose strengths are more appropriate. Alternatively, the medicines can be prescribed separately.

Children aged less than 12 years:
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 sections 4.3 and 4.4).

Method of administration:
Oral use.
The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

Treatment goals and discontinuation
Before initiating treatment with PARACETAMOL 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).

Duration of treatment

The duration of treatment should be as short as possible 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.

4.3 Contraindications

Hypersensitivity to the active substances, or to any of the excipients listed in section 6.1.

Conditions where morphine and opioids are contraindicated e.g.:

- Acute asthma
- Respiratory depression
- Acute alcoholism
- Head injuries
- Raised intra-cranial pressure
- Following biliary tract surgery
- Breast-feeding (see Section 4.6)

Monoamine oxidase inhibitor therapy, concurrent or within 14 days.

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 patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
In the event of impending childbirth or in case of risk of premature birth (see section 4.6).

4.4 Special warnings and precautions for use

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR≤50ml/min)
- Gilbert's Syndrome (familial non haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose 6 phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

This medicine should be used after careful risk benefit assessment in case of:

- Opioid dependence
- Chronic constipation
- Impaired consciousness
- Compromised respiratory function and chronic obstructive airway disease

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 PARACETAMOL CODEINE. Repeated use of PARACETAMOL CODEINE 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 PARACETAMOL CODEINE 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 PARACETAMOL CODEINE and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2).

The patient should be made aware of the risks and signs of OUD as set out in the package leaflet. If these signs occur, patients should contact their physician.

For patients who experience signs and symptoms of OUD, and/or exhibit drug seeking behaviours, review of concomitant opioids and psycho-active drugs (like benzodiazepines) and consultation with an addiction specialist may be required.

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.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with codeine.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

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.

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.

Hepatobiliary disorders

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

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 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, 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.

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%

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.

This medicine should be administered with caution in certain patients, such as those with impaired cardiac, hepatic or renal function, hypotension, benign

prostatic hyperplasia, urethral stenosis, adrenal insufficiency (Addison's disease), hypothyroidism, multiple sclerosis, chronic colitis ulcerative, and diseases that present with reduced respiratory capacity such as emphysema, kyphoscoliosis and severe obesity.

This product should only be used with great care in any patient whose condition may be exacerbated by opioids such as those who are on concurrent CNS depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders.

Extensive use of analgesics to relieve headaches or migraines, especially at high doses, may induce headaches that must not be treated with increased doses of the drug. In such cases the analgesic should not continue to be taken without medical advice.
Use with caution in patients with convulsive disorders.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease. In patients with kidney failure (creatinine clearance lower than 10 ml/min): the interval between doses should be increased (minimum 8 hours). See section 4.2.

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre existing liver dysfunction (See Section 4.8).

Severe cutaneous adverse reactions (SCARs):
Very rare cases of serious skin reactions such as Stevens Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN) have been reported with the use of paracetamol.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop immediately this medicine treatment and seek medical advice.

Patients should be advised not to exceed the recommended dose and not take other paracetamol containing products concurrently.

Codeine has a primary potential for dependence. Tolerance, psychological and physical dependence (addiction) develop with prolonged use of high doses with withdrawal symptoms, such as restlessness and irritability, after sudden discontinuation of the drug. Cross tolerance with other opioids exists. Rapid relapses can be expected in patients with pre existing opiate dependence

(including those in remission). Administration must be discontinued gradually after prolonged treatments.

There have been reports of drug abuse with codeine, including cases in children and adolescents. Caution is particularly recommended for use in children, adolescents, young adults and in patients with a history of drug and/or alcohol abuse.

Risks from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of this medicine 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 this medicine 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).

Risks from concomitant use of opioids and alcohol:
Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma and death. Concomitant use with alcohol is not recommended (see section 4.5).

Care should be observed in administering the product to any patient whose condition may be exacerbated by opioids, particularly the elderly, who may be sensitive to their central and gastro-intestinal effects, those on concurrent CNS depressant drugs, those with prostatic hypertrophy and those with inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated.

This should be used upon medical advice in patients with:
Severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease.

Patients should be advised not to exceed the recommended dose and not to take other paracetamol containing products concurrently.

Patients should be advised to consult a doctor should symptoms persist and to keep the product out of the reach and sight of children.

Caution is advised in patients with underlying sensitivity to aspirin and/or to nonsteroidal anti-inflammatory drugs (NSAIDs).

The risk-benefit of continued use should be assessed regularly by the prescriber.

In patients who have had a cholecystectomy, codeine may induce acute biliary or pancreatic abdominal pain, which usually occurs with abnormal laboratory results, suggesting a spasm of the sphincter of Oddi. This medicine is contraindicated for use in these patients. Section 4.3.

If the patient has a productive cough, codeine may impede expectoration.

Elderly patients may be more sensitive to the effects of this medicinal product, especially respiratory depression; they are also more prone to suffering hypertrophy, prostatic obstruction and age related kidney impairment and they have a higher likelihood of undesirable effects due to opioid induced urinary retention.
Elderly patients: the initial dosage should be reduced to half the recommended dosage; this may be later increased based on patient tolerance and needs. See section 4.2.

In ultra rapid opiate/codeine metabolisers, there is an increased risk of developing opioid toxicity even at low doses.

Symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression.

The leaflet will state in a prominent position in the 'before taking' section:
Do not take for longer than directed by your prescriber.
Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets.

Taking a pain killer for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack (not boxed):
Do not take for longer than directed by your prescriber as taking codeine regularly for a long time can lead to addiction.

Important information regarding the ingredients of this medicine

Sodium: This medicinal product contains 413mg sodium per dose, equivalent to 20.65%of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to 162.5% of the WHO recommended maximum daily intake for sodium.

Paracetamol codeine is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Sorbitol: Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Paracetamol may increase the risk of bleeding in patients taking warfarin, antivitamin K and other coumarins. These patients should be monitored for appropriate coagulation and bleeding complications.

Co administration of flucloxacillin with paracetamol may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

Chelating resin can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.

Treatment with paracetamol may interfere with the assay of blood uric acid by the phosphotungstic acid method. Treatment with paracetamol may interfere with the assay of blood glucose when concentrations are abnormally high.

<u>Sedative medicines such as benzodiazepines or related drugs</u>
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4). Concomitant use of Paracetamol Codeine with gabapentinoids (gabapentin and

pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Alcohol and opioids
The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see section 4.4).

Mono Amine Oxidase Inhibitors (MAOI's)
Concomitant administration of MAOI can potentiate the central nervous effects and other side effects of unpredictable severity.

This medicine should not be used in patients currently receiving or within 14 days of stopping monoamine oxidase inhibitor therapy. See section 4.3.

CYP2D6 inhibitors
Codeine is metabolised by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine.
Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

CYP3A4 inducers
Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and rifampicin should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.
The hypotensive effects of antihypertensive agents, including diuretics, may be potentiated by codeine.

The CNS depressant action of this product may be enhanced by coadministration with any other drug which has a CNS depressant effect (e.g. anxiolytics, hypnotics, antidepressants, antipsychotics and alcohol). Concomitant use of any drug with a CNS depressant action should be avoided. If combined therapy is necessary, the dose of one or both agents should be reduced.

Tricyclic antidepressants
Concomitant administration of this product and MAOIs or tricyclic antidepressants may increase the effect of either the antidepressant or codeine.

Concomitant administration of codeine and anticholinergics may cause paralytic ileus.

Antiperistaltic anti diarrhoeal drugs
Concomitant administration of codeine with an anti-diarrhoeal agent increases the risk of severe constipation and CNS depression, and co-administration with an antimuscarinic drug may cause urinary retention.

Inadvisable combinations with codeine
Morphine agonists antagonists (buprenorphine, nalbuphine, pentazocine): Reduced analgesic effect due to competitive receptor blockade, with a risk of withdrawal syndrome.

Naltrexone: Risk of reduced analgesic effect. The doses of the morphine derivative should be increased if necessary.

The following combinations with PARACETAMOL CODEINE should be avoided: quinidine.

The following combinations with PARACETAMOL CODEINE may require dose adjustment: neuroleptics, antidepressants, warfarin, enzyme-inducing medications such as certain antiepileptics (phenytoin, phenobarbital, carbamazepine), rifampicin and St John's wort (*Hypericum perforatum*), probenecid, metoclopramide, cholestyramine and chloramphenicol.

Codeine
Codeine is probably active through the codeine being O-demethylated to morphine via the enzyme CYP2D6. This bioactivation is inhibited by certain medications, e.g. quinidine, terbinafine, certain antidepressants and neuroleptics, etc. These drugs therefore counter the effect of codeine. This interaction has been documented in studies on healthy trial subjects and/or pilot studies on patients.
Direct studies have been performed with quinidine, which is a very strong inhibitor of CYP2D6, and this combination should therefore be avoided. Neuroleptics and antidepressants also have an inhibiting effect on CYP2D6, which means that these combinations may require a dose adjustment. Enzyme-inducing medications such as rifampicin, barbiturates, several antiepileptics, St John's wort (Hypericum perforatum), etc. can produce reduced plasma concentrations of morphine (see also interaction with paracetamol).

Paracetamol
The hepatotoxicity of paracetamol may be increased in patients taking substances known to induce liver microsomal enzymes (e.g. barbiturates, tricyclic antidepressants and alcohol). Hepatotoxic substances may increase the possibility of paracetamol accumulation and overdose. This can increase the hepatotoxicity of paracetamol due to increased and more rapid formation of toxic metabolites. Isolated reports describe unexpected hepatotoxicity in patients taking phenobarbital, phenytoin, or carbamazepine after taking paracetamol. Therefore, caution should be taken in case of concomitant use of enzyme inducing substances.

Probenecid causes an almost 2-fold reduction clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.

- Salicylamide may prolong the elimination t1/2 of Paracetamol

- Metoclopramide and Domperidone: accelerate absorption of Paracetamol
- Cholestyramine: reduces absorption of Paracetamol
- Concomitant use of Paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
- Isoniazid: Reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver.
- Lamotrigine: Decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of its metabolism in the liver.

Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxydase-peroxydase.

Paracetamol may affect the pharmacokinetics of chloramphenicol. Therefore an analysis of chloramphenicol in plasma is recommended in the event of combination treatment with chloramphenicol for injection.

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).

4.6 Fertility, Pregnancy and lactation

***Pregnancy*:**
On the basis of published literature (Danish National Birth Cohort), paracetamol use during any time of pregnancy was associated with a small but statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months.
A large amount of data on the use of paracetamol in pregnant women indicate neither malformative, nor feto/neonatal toxicity.

Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

As a precautionary measure, use of this medicine should be avoided during the third trimester of pregnancy and during labour.

Careful consideration should be given before prescribing the product for pregnant patients. Regular use during pregnancy may cause dependence in the foetus, leading to withdrawal symptoms in the neonate.
Use of codeine during pregnancy may lead to withdrawal symptoms in neonates, and use during labour may cause neonatal respiratory depression. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

***Breast-feeding*:**
Codeine must not be used during breastfeeding (see section 4.3). At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an 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.

Paracetamol is excreted in breast milk but not in a clinically significant amount.

Administration to nursing women is not recommended as codeine may be secreted in breast milk and may cause respiratory depression in the infant. 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.

Fertility
There is no information available concerning the effect of this medicinal product on fertility.

4.7 Effects on ability to drive and use machines

Patients should be advised not to operate machinery if this product causes dizziness or sedation. Codeine may cause visual disturbances. This medicine may cause drowsiness, disturbances of visuomotor co-ordination and visual acuity.
This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
- The medicine has been prescribed to treat a medical or dental problem and

- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely.

4.8 Undesirable effects

Reported adverse reactions seem more prominent in ambulatory than non-ambulatory patients and some of these effects may be alleviated if the patient lies down.
The frequency using the following convention: Very common (≥1/10); Common (≥1/100 to < 1/10); Uncommon (≥1/1000 to < 1/100); Rare (≥1/10000 to < 1/1000); Very rare (< 1/10000), including isolated reports; Not known: frequency cannot be estimated from the available data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Codeine:

System Organ Class	**Very Common (≥1/10)**	**Rare (≥1/10,000 to <1/1000)**	**Not known (frequency cannot be estimated from the available data)**
Immune sysytem disorders			Hypersensitivity
Psychiatric disorders			Confusional state, dysphoria, euphoria. Long term use also entails the risk of drug dependence
Nervous system disorders	Light-headedness		Dizziness, Sedation, Headache, Seizure, Somnolence, Confusion
Eye disorders			Miosis, visuomotor coordination and visual acuity may be adversely affected in a dose dependent manner at higher doses or in particularly sensitive patients.
Ear and labyrinth disorders			Tinnitus
Vascular disorders			Hypotension
Respiratory, thoracic and mediastinal disorders	Shortness of breath		Respiratory depression
Gastrointestinal disorders	Abdominal pain		Constipation, vomiting, nausea, dry mouth, pancreatitis.

Hepatobiliary disorders			Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Rash, Urticaria		Pruritus
Renal and urinary disorders			Urinary retention
General disorders and administration conditions			Fatigue

Paracetamol:

System Organ Class	**Uncommon (≥1/1000 to < 1/100);**	**Rare (≥1/10,000 to <1/1000)**	**Very Rare (< 1/10000)**	**Not known (frequency cannot be estimated from the available data)**
Blood and lymphatic system disorders		platelet disorders, stem cell disorders, blood dyscrasias	Thrombocytopenia Leukopenia Neutropenia	Anaemia, Anaphylactic shock, agranulocytosis, hemolytic anemia, particular in patients with underlying glucose 6 phosphate dehydrogenase deficiency.
Immune system disorders				Hypersensitivity such as Anaphylactic shock, angioedema
Metabolism and Nutrition disorders			Hypoglycaemia	Pyroglutamic acidosis, in patients with pre disposing factors for glutathione depletion, high anion gap metabolic acidosis
Psychiatric disorders		Depression NOS, confusion, hallucinations		drug dependence (see section 4.4).
Nervous system disorders		Tremor NOS, headache NOS		Vertigo
Eye disorders		Abnormal vision		
Cardiac		Oedema		

disorders				
Vascular disorders				hypotension (with high doses).
Respiratory, thoracic and mediastinal disorders				Edema of the larynx Bronchospasm (more likely in asthmatics sensitive to aspirin or other NSAIDs)
Gastrointestinal disorders		Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting		Gastrointestinal effects
Hepato-biliary disorders		Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.	Hepatotoxicity	Cytolytic hepatitis, which may lead to acute hepatic failure
Skin and subcutaneous tissue disorders		Sweating, purpura, angioedema	Very rare cases of serious skin reactions have been reported, erythema, urticaria, rash	Toxic epidermal necrolysis (TEN), Stevens Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption
Renal and urinary disorders			Sterile pyuria (cloudy urine) and renal side effects	
General disorders and administration site conditions	Drug withdrawal syndrome	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.	Hypersensitivity reaction (requiring discontinuation of treatment), occurrence of pancreatitis.	
Injury, poisoning and procedural complications		Overdose and poisoning		

Codeine can cause respiratory depression particularly in overdosage and in patients with compromised respiratory function (see Section 4.9).

Liver damage in association with therapeutic use of paracetamol has been documented; most cases have occurred in conjunction with chronic alcohol abuse.
Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

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.

Drug dependence

Repeated use of Paracetamol Codeine 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).

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate help if they occur.

Codeine

The effects of Codeine over-dosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

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 pupils may be pin-point in size; nausea and vomiting are common. Hypotension, rash, pruritis, ataxia, pulmonary edema (more rare) and tachycardia are possible but unlikely.

The ingestion of very high doses can cause initial excitation, anxiety, insomnia followed by drowsiness in certain cases, areflexia progressing to stupor or coma, headache, miosis, alterations in blood pressure, arrhythmias, dry mouth, hypersensitivity reactions, cold clammy skin, bradycardia, tachycardia, convulsions, gastrointestinal disorders, nausea, vomiting and respiratory depression.
Severe intoxication can lead to apnoea, circulatory collapse, cardiac arrest and death.

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 than 350 mg or a child more than 5 mg/kg.
Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least 4 hours after ingestion, or 8 hours if a sustained release preparation has been taken.

Paracetamol
Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors:

If the patient
a. Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
or
b. Regularly consumes ethanol in excess of recommended amounts.
or
c. Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.
or
d. Patients with liver disease.
ore. Elderly patients
or
f. young children

Symptoms
Symptoms of paracetamol over-dosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain, or patients may be asymptomatic. Liver damage may become apparent 12 to 48 hours after ingestion. Increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin may occur and the INR may increase. Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.
Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding, disseminated intravascular coagulation and death.
Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage.
Cardiac arrhythmias, pancreatitis and pancytopenia have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol; however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, Anilides.

Paracetamol, combinations excl. psycholeptics

ATC Code: N02BE51

Mechanism of action

Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Paracetamol is a weak, reversible, isoform-nonspecific cyclooxygenase inhibitor at dosages of 1 g daily. The inhibitory effect of paracetamol on cyclooxygenase-1 is limited, and the drug does not inhibit platelet function. Animal studies have indicated that paracetamol strongly inhibits prostaglandin synthetase in the brain (which may account for its antipyretic and analgesic effects) but that it has little effect on peripheral tissue prostaglandins (which are involved in inflammatory reactions).

Clinical efficacy and safety

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

The conversion of codeine to morphine is effected by the CYP2D6. Well-characterised genetic polymorphism in CYP2D6 lead to the inability to covert codeine to morphine, thus making codeine ineffective as an analgesic for about 7% of the Caucasian population (see also section 4.4).

The fixed combination of paracetamol and codeine showed to be effective in nociceptive pain. However, data in chronic pain, cancer pain and neuropathic pain are lacking.

5.2 Pharmacokinetic properties

Paracetamol

Absorption

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Following oral administration of two effervescent tablets (i.e., a dose of paracetamol 1000mg and codeine 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 20.4μg/ml and 218.8ng/ml respectively. The mean times to maximum plasma concentrations were 0.34 hours for paracetamol and 0.42 hours for codeine phosphate.

The mean AUC for the 10 hours following administration was 50.0μg/ml per hour for paracetamol and 450.0ng/ml per hour for codeine.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low.

Biotransformation

Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulphuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-pbenzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cystein and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

The bioavailabilities of paracetamol and codeine phosphate when given as the combination are similar to those when they are given separately.

Codeine is mainly metabolized by glucuronidation to codeine-6-glucuronide. Minor routes of metabolism include O-demethylation leading to morphine, N-demethylation

to norcodeine and after both O- and N-demethylation formation of normorphine. Morphine and norcodeine are further transformed in glucuroconjugates. Unchanged codeine and its metabolites are mainly excreted by urinary route within 48h (84.4±15.9%).

The O-demethylation of codeine to morphine is catalyzed by the cytochrome P450 isozyme 2D6 (CYP2D6) which shows genetic polymorphism that may affect the efficacy and toxicity of codeine.

Genetic polymorphism in CYP2D6 leads to ultra-rapid, extensive and poor metaboliser phenotypes.

Elimination

Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.

Elimination half life is about 2 hours.

Physiopathological Variations

Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly Subjects. The capacity for conjugation is not modified.

Codeine

Codeine is absorbed rapidly following oral administration; peak plasma concentrations occur in about 1 h and the plasma half-life is about 3.5 h. The volume of distribution is approximately 3.6 l/kg. The total body clearance of codeine is approximately 0.85 l/min. Codeine crosses the placenta and is present in the milk of lactating mothers.

Biotransformation and elimination

Codeine is metabolised in the liver by *O*-demethylation to form morphine (codeine is in fact a pro-drug to morphine), and other metabolites. After an oral dose, about 86% is excreted in the urine in 24 h as free drug and metabolites, mostly in the form of metabolites. Some of a dose of codeine is excreted in the bile and trace amounts are found in the faeces. Unchanged drug accounts for 6-8% of the dose in urine in 24 h.

Due to genetic polymorphism in the liver enzyme CYP2D6 some patients have a deficiency to convert codeine to morphine leading to an inadequate analgesic effect. On the other hand there are patients who are extensive or ultra-rapid metabolisers. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. For further information see also section 4.4.

The bioavailabilities of paracetamol and codeine, when given as the combination, are similar to those when they are given separately.

5.3 Preclinical safety data

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

Paracetamol

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydrogen carbonate

Sodium carbonate anhydrous

Citric acid anhydrous

Sodium Docusate

Sorbitol (E420)

Saccharin Sodium

Dimeticone

Sodium Benzoate

Macrogol 6000

Natural grapefruit flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months for polypropylene tubes. Use within 2 years of first use.

12 months for foil strips

6.4 Special precautions for storage

For the foil strips:

This medicinal product does not require any special storage conditions.

For the polypropylene tubes:

Store in the original tubes. Keep the tubes tightly closed.

6.5 Nature and contents of container

Aluminium/polyethylene foils strips of 4, 8, 16, 32 and 100 effervescent tablets.

Polypropylene tubes of 8, 16, 32 and 96 effervescent tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The tablets should be placed in a glass of water and allowed to be dissolved completely. The resulting solution should be drunk immediately.

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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