SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tylex 30 mg / 500 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: Sodium metabisulfite (E223) 0.36 mg/capsule.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Hard gelatin capsule with white opaque body and red cap, both with ‘C30’ printed in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tylex Capsules is indicated for use in patients older than 12 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:
Tylex Capsules are given orally. The usual dose is one or two capsules every 4 to 6 hours when necessary to a maximum daily dose of 240 mg codeine and 4 g paracetamol (up to 8 capsules per day).

Duration of treatment:
Codeine should be used at the lowest effective dose for the shortest period of time.
The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects.

Elderly:
As for adults, however a reduced dose may be required. See warnings.

Paediatric population:
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).

Children aged 12 to 15 years:
One capsule every 6 hours when necessary to a maximum of 4 capsules in 24 hours.

Children aged 16 to 18 years:
One to two capsules every 6 hours when necessary up to a maximum of 8 capsules in 24 hours.

Method of administration

For oral administration.

Treatment goals and discontinuation
Before initiating treatment with Tylex, 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

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

In children under the age of 12 years.

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.

Conditions where morphine and opioids are contraindicated e.g:

- Acute asthma (see section 4.4. and 4.8)

- Respiratory depression (see section 4.8)
- Acute alcoholism (see section 4.4 and 4.5)
- Following biliary tract surgery
- Head injuries
- Raised intra-cranial pressure
- Breastfeeding (see section 4.6)

Monoamine oxidase inhibitor therapy, concurrent or within 14 days.

4.4 Special warnings and precautions for use

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs: Concomitant use of Tylex 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. 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.

If a decision is made to prescribe Tylex 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).

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.

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

Tylex capsules contain sodium metabisulfite, a sulfite that may cause allergic reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

Tylex capsules should be used with caution in patients sensitive to the effects of opioids, e.g. the elderly (who may be sensitive to their central and gastro-intestinal effects) and debilitated patients, patients with CNS depression, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, myasthenia gravis, inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated.

<u>Hepatobiliary disorders</u>

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

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.

Severe liver damage may occur if the maximal daily dose is exceeded, if Tylex is taken together with another paracetamol-containing product, or if Tylex is taken while consuming large amounts of alcohol.

Patients should be advised that immediate medical advice should be sought in the event of an overdose, because of the risk of delayed, serious liver damage. They should be advised not to exceed the recommended dose, not to take other paracetamol-containing products concurrently, to consult their doctor if symptoms persist and to keep the product out of the reach of children.

Administration of pethidine and possibly other opioid analgesics to patients taking a monoamine oxidase inhibitor (MAOI) has been associated with very severe and sometimes fatal reactions. If the use of codeine is considered essential, then great care should be taken in patients taking MAOIs or within 14 days of stopping MAOIs (see section 4.5).

Patients positively identified with aspirin induced asthma, or who have ever experienced an asthmatic reaction to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) or are at high risk of aspirin induced asthma should avoid all products that contain aspirin or NSAIDs indefinitely. In these patients paracetamol should be recommended in low or moderate dose (< 1000 mg in a single dose) unless contraindicated. Although paracetamol might logically be presumed to be the best alternative analgesic in patients with aspirin sensitivity, cross reactions have been reported.

CYP2D6 metabolism

When codeine is administered concurrently with inhibitors of the cytochrome P450 isoenzyme CYP2D6, there may be a reduction or loss of therapeutic effect of codeine (see section 4.5). 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. 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%

At high doses codeine has most of the disadvantages of morphine, including respiratory depression. Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks.

The duration of treatment with Tylex should be limited to 3 days.

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 Tylex. Repeated use of Tylex 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 Tylex 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 Tylex and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.
Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Paediatric population:

Tylex should be used with extreme caution in adolescents between 12 and 18 years. An alternative medicine should be considered if at all possible.

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 ultrarapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Adolescents between 12 and 18 years with compromised respiratory function
Codeine is not recommended for use in adolescents between 12 and 18 years 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 or obesity. These factors may worsen symptoms of morphine toxicity.

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicines such as benzodiazepines or related drugs:

Patients receiving other central nervous system depressants (including other opioid analgesics, tranquillisers, e.g. Benzodiazepines, sedative hypnotics and alcohol) concomitantly with Tylex capsules may exhibit an additive depressant effect as the effects of CNS depressants (including alcohol) may be potentiated by codeine. When such therapy is contemplated, the dose of one or both agents should be reduced (see section 4.4).

The concomitant use of opioids with gabapentinoids (gabapentin and pregabalin), sedative medicines such as benzodiazepines or related drugs may result in respiratory depression, hypotension, profound sedation, coma or death because of additive CNS depressant effect (see section 4.4).

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).

Concurrent use with centrally acting muscle relaxants may increase the risk of respiratory depression.

Concurrent use of MAOI inhibitors or tricyclic antidepressants with codeine may increase the effect of either the antidepressant or codeine. Concurrent use of anticholinergics and codeine may produce paralytic ileus.

MAOIs taken with pethidine have been associated with severe CNS excitation or depression (including hypertension or hypotension). Although this has not been documented with codeine, it is possible that a similar interaction may occur and therefore the use of codeine should be avoided while the patient is taking MAOIs and for 2 weeks after MAOI discontinuation.

Cases of serotonin syndrome, have been reported during concomitant use of opioids with serotonergic drugs (including selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors).

Therefore, caution is advised when paracetamol/codeine is coadministered with medicinal products that affect the serotonergic neurotransmitter systems. The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, treatment with paracetamol/codeine should be discontinued.

Enzyme-inducing medicines, such as some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine) have been shown in pharmacokinetic studies to reduce the plasma AUC of paracetamol to approximately 60 % Other substances with enzyme-inducing properties, e.g. rifampicin and St. John's wort (hypericum) are also suspected of causing lowered concentrations of paracetamol. In addition, the risk of liver damage during treatment with maximum recommended doses of paracetamol will be higher in patients being treated with enzyme-inducing agents.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

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.

Concurrent use of codeine with fluoxetine or paroxetine, bupropion and methadone may result in inhibition of CYP2D6 resulting in a decrease of the morphine concentration and therefore a reduction or loss of analgesic effect of codeine.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of Tylex Capsules are not recommended during pregnancy since safety in pregnant women has not been established.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Tylex Capsules should not be used during breastfeeding (see section 4.3).

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.

Also, 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.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.

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.

A tabulated list of adverse reactions are outlined below:

System Organ Class	Frequency	Adverse Effects
Blood and lymphatic system disorders	Not Known	Thrombocytopenia, agranulocytosis, neutropenia, leucopenia
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis
Immune system disorders	Not Known	Anaphylactic shock, hypersensitivity including skin rash may occur.
Psychiatric disorders	Not Known	Dysphoria, euphoria, hallucination, drug dependence (see section 4.4.)
Nervous system disorders	Not Known	Dizziness, sedation, headache
Ear and labyrinth disorders	Not Known	Deafness[1]
Respiratory thoracic and mediastinal disorders	Not Known	Bronchospasm, dyspnoea
Gastro-intestinal disorders	Not Known	Nausea, vomiting, constipation, abdominal pain, pancreatitis[2]
Hepatobiliary disorders	Not Known	Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Not Known	Pruritus, rash, urticaria Very rare cases of serious skin reactions have been reported.
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome

[1] Deafness has been reported in patients after long term use of high doses of codeine – paracetamol.
[2] Drug-induced pancreatitis associated with paracetamol has been reported in literature to be a rare reaction only occurring in patients taking in excess of the recommended doses. Literature reports have also associated cases of pancreatitis with codeine.

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.

There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

In clinical use of paracetamol containing products, there have been a few reports of blood dyscrasias including thrombocytopenia and agranulocytosis but these were not necessarily causally related to paracetamol.

Anaphylaxis, angioedema and toxic epidermal necrolysis have also been associated with the use of paracetamol.

Prolonged use of a painkiller for headaches can make them worse.

Codeine can produce typical opioid effects including constipation, nausea, vomiting, dizziness, light-headedness, confusion, drowsiness and urinary retention. The frequency and severity are determined by dosage, duration of treatment and individual sensitivity. Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is stopped.

Drug dependence
Repeated use of Tylex 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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose symptoms, emergency procedures, antidotes

Paracetamol
With overdose, there is a risk of severe liver toxicity, particularly in the elderly, young children, hepatic or renal insufficiency, chronic alcohol consumption, chronic malnutrition, when using enzyme inducing agents and in very lean adults (<50 kg).

Liver toxicity often does not occur until 24 to 48 hours after ingestion. Overdose can be fatal. In case of overdose, a doctor should be consulted immediately, even if there are no symptoms.

Symptoms: Nausea, vomiting, anorexia, pallor, abdominal pain usually occurs within the first 24 hours.

A strong overdose causes severe liver toxicity, with hepatic cytolysis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy, which can lead to coma

and death. At the same time, elevated levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin have been observed. Overdose may also result in disseminated intravascular coagulation.

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, phenobarbital, 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.

Symptoms
Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin may occur and the INR may increase. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, hypokalaemia, cerebral oedema, gastrointestinal bleeding 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.

Codeine
Simultaneous ingestion of alcohol and psychotropic drugs will potentiate the effects of overdosage.

Symptoms of codeine overdose may include:

- Central nervous system depression (including respiratory depression) but this is unlikely to be severe unless the overdose is large, or there is co-ingestion with other sedative agents or alcohol;
    - miosis;

- nausea and vomiting;
- hypotension and tachycardia are possible but unlikely.
- in severe overdose with codeine, apnoea, circulatory collapse, cardiac arrest and death may occur.

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 medical help if they occur.

Management
General symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within 1 hour after ingesting 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 with a short half-life, so large and repeated doses may be required in a seriously poisoned patient. Observe patients for at least 4 hours after ingestion.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: codeine and paracetamol
ATC Code: N02AJ06

Paracetamol has analgesic and antipyretic actions similar to those of aspirin with weak anti-inflammatory effects. Paracetamol is only a weak inhibitor of prostaglandin biosynthesis, although there is some evidence to suggest that it may be more effective against enzymes in the CNS than those in the periphery. This fact may partly account for its well documented ability to reduce fever and to induce analgesia, effects that involve actions on neural tissues. Single or repeated therapeutic doses of paracetamol have no effect on the cardiovascular and respiratory systems. Acid-based changes do not occur and gastric irritation, erosion or bleeding is not produced as may occur after salicylates. There is only a weak effect upon platelets and no effect on bleeding time or the excretion of uric acid.

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. The major effect is on the CNS and the bowel. The effects are remarkably diverse and include analgesia, drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting and alterations of the endocrine and autonomic nervous systems. The relief of pain is relatively selective, in that other sensory modalities, (touch, vibration, vision, hearing etc) are not obtunded. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentration occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

Codeine and its salts are absorbed from the gastro intestinal tract. Ingestion of codeine phosphate produces peak plasma codeine concentrations in about one hour. Codeine is metabolised by O- & N-demethylation in the liver to morphine and norcodeine. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half-life has been reported to be between 3 and 4 hours after administration by mouth or intravascular injection.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinized Starch
Calcium Stearate
Docusate sodium with sodium benzoate (E211)
Sodium metabisulfite (E223)

Capsule shell:
Gelatin
Titanium dioxide (E171)
Erythrosine (E127)
Indigo carmine (E132)

Printing ink:
Shellac
Propylene glycol
Ammonium hydroxide
Iron oxide black (E172)

6.2 Incompatibilities

None pertinent

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25°C. Keep container in the outer carton.

6.5 Nature and contents of container

Tamper-evident high density polyethylene bottles fitted with low density polyethylene caps, containing 24, 100 or 500 capsules.

PVC/aluminium foil blister strips containing 1x7, 2x7, 4x7, 1x8, 3x8, 50x6, 100x6, 5x20, 10x10 capsules.

Polypropylene securitainers containing 8, 16, 24, 32, 56 or 64 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

UCB Pharma Limited

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SL1 3WE

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8 MARKETING AUTHORISATION NUMBER(S)

PL 00039/0749

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