Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tylex 30 mg / 500 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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:
The usual dose is one or two capsules up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose should not exceed 240 mg of codeine phosphate hemihydrate (i.e. not more than eight capsules per 24 hours should be taken).

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 yearsbecause 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.

4.3 Contraindications

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

For 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

The risk-benefit of continued use should be assessed regularly by the prescriber.
The duration of treatment with Tylex should be limited to 3 days.

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

Concomitant use of Tylex and sedative medicines such as benzodiazepine 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 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.

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 malnutrition and 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 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.

These 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 and prostatic hypertrophy or urethral stricture, myasthenia gravis, reduced blood volume, seizures, shock, inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated.

Opioid analgesics should be avoided in patients with pancreatobiliary tract disorders.
Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is 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 positively identified with aspirin-induced asthma or those 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. Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

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. 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 can produce drug dependence of the morphine type, and therefore has the potential for being abused. Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped. Codeine may impair the mental/or physical abilities required for the performance of potentially hazardous tasks.

Abrupt withdrawal of opioids from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use.

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.

The long term use of high doses of combined codeine – paracetamol has been associated with the occurrence of deafness.

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 patients. 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 medicine such a 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 these 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 duration and dose of one or both agents should be reduced (see section 4.4).

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.

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).

Cases of serotonin syndrome, a potentially life-threatening condition, 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). Similar cases have also been reported with codeine. This may occur within the recommended dose.

Therefore, caution is advised when paracetamol/codeine is coadministered with medicinal products that affect the serotonergic neurotransmitter systems. Patients should be monitored for the sign and symptoms suggestive of serotonin syndrome in case of coadministration of these drugs. If serotonin syndrome is suspected, treatment with paracetamol/codeine should be discontinued.

Concurrent use of MAO 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.

Concurrent use of codeine with quinidine, fluoxetine, paroxetine or sertraline may result in inhibition of CYP2D6 which may cause opioid toxcity.

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

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

The anti-coagulant 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.

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.

Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance.

Concurrent use of codeine with fluoxetine, paroxetine, sertraline, neuroleptics, bupropion and methadone may result in inhibition of CYP2D6 which results 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
These capsules are not recommended during pregnancy since safety in pregnant women has not been established. The use of Tylex should be avoided during labour.

Studies in animals have shown reproductive toxicity.
Epidemiological studies have reported cases of various congenital malformations. However, due to the limitations of the published studies and contradictory conclusions from other epidemiological studies, the causal association cannot be confirmed.
Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Codeine has been shown to cross the placental barrier.Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.

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.

Codeine should not be used 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 are unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal. If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

4.7 Effects on ability to drive and use machines

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

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.

Codeine can produce common 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. Tolerance and dependence can occur, especially with prolonged high dosage of codeine.

- Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.
- Prolonged use of a painkiller for headaches can make them worse.

A tabulated list of adverse reactions are outlined below:

The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Immune system disorders	Rare	Hypersensitivity including skin rash may occur
	Not known	Anaphylactic shock, angioedema
Metabolism and nutritiondisorders	Not known	High anion gap metabolicacidosis
Blood and lymphatic system disorders	Rare	Agranulocytosis, thrombocytopenia
	Very Rare	Neutropenia, leucopenia
Psychiatric disorders	Common	Dysphoria, euphoria
	Unknown	Hallucination
Nervous system disorders	Common	Dizziness, light-headedness, sedation
Respiratory, thoracic and mediastinal disorders	Common	Shortness of breath, asthma
	Not known	Bronchospasm
Gastrointestinal disorders	Common	Nausea & vomiting, constipation, abdominal pain
	Rare	Pancreatitis
Skin and subcutaneous tissue disorders	Common	Pruritus, rash, urticaria
	Very rare	Very rare cases of serious 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.

In clinical use of paracetamol-containing products, blood dyscrasias (including thrombocytopenia and agranulocytosis) are reported rarely (<1/10000, >1/1000).

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

Deafness has been reported in patients after long term use of high doses of codeine – paracetamol.

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

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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Paracetamol
Paracetamol overdose can result in liver damage which may be fatal.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

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.

Some patients may be at increased risk of liver damage from paracetamol toxicity:
Risk factors include;

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias, pancreatitis and pancytopenia have also been reported.

Emergency Procedure:
Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.

Symptomatic treatment should be implemented.

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

Symptoms:
Serious overdose with codeine is characterised by respiratory depression, pin-point size pupils (miosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdose with codeine, apnoea, circulatory collapse, cardiac arrest and death may occur.

Management:
Primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway and the institution of controlled ventilation. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Opioid antagonists may be employed. Gastric lavage should be considered. Patients should remain under observation, as per hospital guidelines and on a case per case basis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N02A J06

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 microgram 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

Pregelatinised potato 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

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

PVC/foil blisters in strips containing 8, 10 or 20 capsules each, pack sizes: 8, 24 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

UCB (Pharma) Ireland Limited
United Drug House
Magna Drive, Magna Business Park
Citywest Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0891/014/001

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