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 500 mg of paracetamol and 30 mg of codeine phosphate hemihydrate.

Excipients: sodium metabisulphite (E223), soya lecithin

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard.

Product imported from the UK:
Hard gelatin capsule with white body and red cap, both with “C30” printed in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the relief of moderate to severe pain.

4.2 Posology and method of administration

Adults: The capsules are given orally. The usual dose is one or two capsules every four hours as required. The total daily dose should not exceed 240 mg of codeine phosphate hemihydrate (i.e. not more than four doses per 24 hours should be taken).

Elderly: A reduced dose may be required.

Children: Use in children under 12 years of age is not recommended.

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.

4.3 Contraindications

Tylex Capsules should not be administered to patients who have previously exhibited hypersensitivity to either paracetamol or codeine, or to any of its excipients. Tylex contains soya lecithin. If you are allergic to peanut or soya, do not use this medicinal product.
Tylex Capsules are not recommended for children under the age of 12 years.

4.4 Special warnings and precautions for use

Because safety and effectiveness in the administration of paracetamol with codeine in children under 12 years of age have not been established, such use is not recommended.

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

These capsules should be used with caution in patients with head injuries, increased intracranial pressure, acute abdominal conditions, the elderly and debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture, myasthenia gravis, biliary tract disorders (including recent biliary tract surgery) , pre-existing respiratory depression or those with the potential to develop respiratory depression e.g. pulmonary emphysema, known ultra-rapid metabolisers of codeine, reduced blood volume, seizures, shock, ulcerative colitis.

The hazard of overdose is greater in those with non-cirrhotic 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.

Although paracetamol might logically be presumed to be the best alternative analgesic in patients with aspirin sensitivity, cross reactions have been reported.

Codeine is partially metabolised by CYP2D6. 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 ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at low doses. General 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. Estimates indicate that up to 1 to 2% of the caucasian population may be ultra-rapid metabolisers

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.

4.5 Interaction with other medicinal products and other forms of interaction

Patients receiving other central nervous system depressants (including other opioid analgesics, tranquillisers, sedative hypnotics and alcohol) concomitantly with Tylex may exhibit an additive depressant effect. When such therapy is contemplated, the dose of one or both agents should be reduced.

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.

Quinidine may reduce the concentration of morphine, the active metabolite of codeine, by >90% in patients who are known to have extensive metabolism via the cytochrome P452D6 pathway.

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.

Plasma-paracetamol concentrations, considered an indication for antidote treatment, should be halved in patients receiving enzyme-inducing drugs such as rifampicin, carbamazepine, henobarbital, phenytoin, or primidone.

4.6 Fertility, pregnancy and lactation

Tylex Capsules is not recommended during pregnancy since safety in pregnant women has not been established.

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 metabolites may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant.
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.

Use of codeine-containing medication during pregnancy may result in neonatal withdrawal symptoms.

Paracetamol is known to pass into breast milk.

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.

The most commonly (>1/100, <1/10) reported reactions are:

Central nervous system:	Dizziness
	Light-headedness
	Sedation
Gastro-Intestinal:	Nausea & vomiting
	Constipation
	Abdominal pain
Psychiatric:	Dysphoria
	Euphoria

Respiratory:	Shortness of breath Asthma
Skin:	Pruritus Rash Urticaria

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

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.

4.9 Overdose

Paracetamol

Acute hepatic necrosis is the most common complication of untreated paracetamol overdose and it usually occurs more than 2 days after ingestion. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. Toxicity is likely if more than 150 mg/kg of paracetamol is ingested.

The following groups are at risk of liver damage from paracetamol doses above recommended dose:

- patients on long-term treatment with drugs which induce liver enzymes (e.g. barbiturates, St John's Wort)
- people who drink excessive amounts of alcohol
- patients with depleted glutathione levels (e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia) Patients with pre-existing hepatitis C.

<u>Symptoms of paracetamol overdose include:</u>
Many patients may remain asymptomatic for the first 24 hours, or at most they may develop abdominal pain, nausea, vomiting, anorexia, diarrhoea and exhibit pallor. Abnormal liver function tests are not usually detectable until at least 18 hours after ingestion and maximum liver damage occurs 72 to 96 hours after ingestion. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage.

Other symptoms of paracetamol overdose include abnormalities of glucose metabolism and metabolic acidosis. Cardiac arrhythmias, pancreatitis and hypokalaemia have also been reported.In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death

<u>Management of overdose</u>
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.

Patients who have ingested more than 150 mg/kg should have gastric lavage performed if they present within an hour of ingestion. Activated charcoal may also be given. A plasma paracetamol level will indicate the likelihood of a patient developing high ALT/AST activities (i.e. > 1,000 i.u. /L) and must be measured at least 4 hours after ingestion. Plasma levels measured less than 4 hours post-ingestion cannot be interpreted. Patients with a plasma level above the treatment line require N-acetylcysteine (NAC). A paracetamol normogram should be employed to determine treatment levels.

Patients who present to an Accident and Emergency Department more than 8 hours after ingesting a paracetamol overdose are at greater risk of developing hepatic damage. In cases of severe poisoning, hepatic failure may progress to encephalopathy, coma and death.

Blood should be taken for a plasma level, but the NAC infusion should be started as soon as possible if more than 150 mg/kg was taken. The NAC infusion should not be delayed while awaiting the result of the plasma paracetamol level. Administration of the antidote should be stopped if the plasma level is subsequently found to be below the treatment line. General supportive measures must be available.

At the end of the NAC infusion, blood should be taken to check the INR and creatinine concentration. If the investigations are abnormal, a further infusion of NAC (at 16 hour dose), to be continued until recovery or death, should be considered.

Codeine
Symptoms of codeine overdose include:
Serious overdose with codeine is characterised by respiratory depression, 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 of overdose
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: NO2A A59 Codeine combinations; N20B E51 paracetamol combinations excluding psycholeptics.

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 an analgesic with uses similar to those of morphine but has only mild sedative effects. 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.

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 sulphate 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

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)
Pregelatinised starch
Calcium stearate
Aerosol OT-B (dioctyl sodium sulfosuccinate and sodium benzoate (E211))

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

Printing Ink:
Shellac
Soya lecithin
2-ethoxyethanol dimethylpolysiloxane
Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Store below 25°C.
Store in the original packaging and in a dry place to protect it from light and moisture.

6.5 Nature and contents of container

PVC/foil blisters in strips containing 10 capsules each, pack sizes: 100 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

LTT Pharma Limited
Unit 18, Oxleasow Road
East Moons Moat
Redditch
Worcestershire B98 0RE
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1562/088/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th September 2012

10 DATE OF REVISION OF THE TEXT