SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Terpin and Codeine Linctus

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Terpin hydrate 32.5mg/5ml
Codeine phosphate 16.0mg/5ml
Menthol 10.0mg/5ml

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Linctus

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Codeine is indicated in adults for symptomatic relief of troublesome coughs.

4.2 Posology and method of administration

Oral.

Adults:
5ml, diluted with water.

Elderly:
Use with caution, a reduced dose can be recommended by a doctor.

Paediatric population:
Codeine should not be used for the treatment of children under the age of 18 years.

Dosage schedule:
The dose may be repeated after 6 hours, but not more than 3 doses in any 24 hours.

If symptoms persist for more than 7 days consult your doctor.

4.3 Contraindications

Suspected opiate abuse, known hypersensitivity to codeine, terpin, menthol or to any of the other ingredients.
In cases of liver failure, respiratory depression, or patients at risk of paralytic ileus.
In patients with raised intracranial pressure or head injury.
In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.
During an acute asthmatic attack.
Children under 18 years of age.
In cases of acute colitis.
In women during breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use
Use with caution in patients with renal and hepatic impairment (but avoid if severe), patients suffering from asthma or other respiratory disorders, or patients with a history of asthma, hypotension, shock, myasthenia gravis, cardiac arrhythmias, acute abdomen, gallstones, prostatic hypertrophy, urethral stenosis, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders.

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).

Use with caution in the elderly as codeine may contribute to faecal impaction, producing incontinence, spurious diarrhoea, abdominal pain and rarely colonic obstruction. Prolonged use could aggravate irritable bowel syndrome.

A reduced dose is recommended in elderly or debilitated patients, in hepatic and renal impairment (but avoid if severe), in hypothyroidism, and in adrenocortical insufficiency. Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; although this is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence or in acute alcoholism.

Terpin and Codeine Linctus and other cough suppressants may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

If symptoms persist consult your doctor.

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 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 nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression.
Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>African/Ethiopian</td>
<td>29%</td>
</tr>
<tr>
<td>African/American</td>
<td>3.4% to 6.5%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.2% to 2%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3.6% to 6.5%</td>
</tr>
<tr>
<td>Greek</td>
<td>6.0%</td>
</tr>
<tr>
<td>Hungarian</td>
<td>1.9%</td>
</tr>
<tr>
<td>Northern European</td>
<td>1%-2%</td>
</tr>
</tbody>
</table>

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Precautions/warnings to be declared on labels:
- Take after food.
- Shake the bottle.
- Do not exceed the stated dose.
- Keep out of the sight and reach of children.
- Avoid alcoholic drinks.

This product contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

It contains 30 vol% ethanol (alcohol), i.e. up to 1180mg per dose, equivalent to 30ml beer or 13ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breastfeeding women, children and high risk groups such as patients with liver disease or epilepsy.

### 4.5 Interaction with other medicinal products and other forms of interaction

Antimuscarinics: codeine phosphate may increase the risk of antimuscarinic side effects such as dry mouth, urine retention and constipation (but this does not generally apply to antimuscarinics taken by inhalation).

Metabolism of codeine is accelerated by rifampicin leading to reduced effect.

As an opioid analgesic, codeine phosphate may potentiate the effects of tranquillisers such as barbiturates, general anaesthetics, anxiolytics and hypnotics, sedatives and alcohol.

Possible CNS excitation or depression (hypertension or hypotension) can occur when opioid analgesics are given with antidepressants such as moclobemide (a reversible MAO-A inhibitor). The sedative effects of codeine can possibly be increased when given with tricyclic antidepressants, with anxiolytics or hypnotics, or with sedating antihistamines. Antipsychotic medicines can enhance hypotensive and sedative effects when opioid analgesics are given with antipsychotics.

Monoamine oxidase inhibitors: 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, including MAO-B inhibitor selegiline. This may also apply to the antibacterial linezolid, which is a reversible, non-selective MAO Inhibitor.

Anti-emetics: The reduction in intestinal motility caused by codeine may delay the absorption or antagonise the gastrointestinal effects of other drugs e.g. metoclopramide and domperidone.

Metabolism of opioid analgesics is inhibited by cimetidine leading to increased plasma concentration.

Anti-arrhythmics: May delay the gastro-intestinal absorption of mexiletine or quinidine (which may also reduce the efficacy of codeine).

Opioid analgesics enhance the effects of sodium oxybate, used to treat symptoms of narcolepsy, and concomitant use should be avoided.

4.6 Fertility, pregnancy and lactation
There is no, or inadequate, evidence of safety in human pregnancy. The product should not be used during pregnancy unless considered necessary by the physician and should be avoided during the first trimester. Opioid administration in the third trimester may cause respiratory depression in the newborn, withdrawal effects in neonates of dependent mothers, gastric stasis and risk of inhalation pneumonia in the mother during labour.

Codeine should 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 codeine, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal. The infant itself may be a CYP2D6 ultra-rapid metaboliser. In either case on very rare occasions this may result in symptoms of opioid toxicity in the infant. (See also section 4.4).

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
Using the dose recommended, Terpin and Codeine Linctus is not considered to be a hazard, however the use of codeine phosphate at higher doses or in more sensitive individuals may cause sedation, dizziness and nausea. 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

The following undesirable effects have been reported following use of codeine phosphate or opioid analgesics and may arise following use of Terpin and Codeine Linctus. The frequency of adverse effects cannot be estimated from available data.

Psychiatric disorders: hallucinations, dysphoria, euphoria, mood changes, restlessness, confusion.

Nervous system disorders: dizziness, drowsiness, seizures, addiction, tolerance, dependence, headache, vertigo, malaise, sleep disturbances.

Eye disorders: miosis, visual disturbances.

Cardiac disorders: palpitations, bradycardia, tachycardia.

Vascular disorders: postural hypotension, hypothermia, facial flushing, oedema.

Respiratory, thoracic and mediastinal disorders: respiratory depression.

Gastrointestinal disorders: nausea, vomiting, constipation, abdominal pain, anorexia, pancreatitis, dry mouth.

Hepatobiliary disorders: biliary spasm.

Skin and subcutaneous tissue disorders: rashes, urticaria, pruritus, sweating.

Musculoskeletal and connective tissue disorders: muscle fasciculation or rigidity.

Renal and urinary disorders: difficulty with micturition, ureteric spasm or retention.

Reproductive system and breast disorders: decreased libido or potency.

The following undesirable effects have been reported following use of terpin hydrate:
Gastrointestinal disorders: nausea, vomiting, or abdominal pain may follow the ingestion of terpin hydrate on an empty stomach.

The following undesirable effects have been reported following use of codeine, terpin hydrate or menthol:

Immune system disorders: hypersensitivity reactions.

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.

4.9 Overdose

Codeine phosphate: The effects in overdosage with codeine 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 and tachycardia are possible but unlikely.

Management
This should include general symptomatic and supportive measures including clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adults presents within one hour of ingestion of more than 350mg or if more than 2.5mg/kg (adults and children) has been ingested.

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 four hours after ingestion, or eight hours if a sustained release presentation has been taken.

Menthol:

Symptoms
Ingestion of significant quantities of menthol is reported to cause symptoms similar to those seen after ingestion of camphor, including severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma.

Systemic features may be delayed up to 4 hours after ingestion and include ataxia, dizziness, headache, drowsiness, excitement, delirium, respiratory depression, convulsions and coma. Hypotension and tachycardia have been reported.

Management
As for management of camphor, supportive care, including anticonvulsant therapy, is appropriate for treatment of menthol intoxication. The benefits of gastric decontamination are uncertain, but oral activated charcoal after
potentially life-threatening overdose, may be considered if the patient presents within 1 hour of ingestion; any convulsions must be controlled first. Haemodialysis with a lipid dialysate or haemoperfusion have been tried but are of doubtful value.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

R05F B 02- Cough suppressants and expectorants

Codeine depresses the cough reflex, partly by a direct effect on a cough centre in the medulla; the exact mechanism is not entirely clear. It has been suggested that the usual doses of opioids produce their major effect on the patients subjective reactions to the cough, rather than on the frequency and intensity of coughing.

Codeine phosphate is absorbed from the gastro-intestinal tract, it is metabolised by O- and 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.

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

Menthol acts to ventilate the bronchial passages and is excreted in the urine and bile as a glucuronide.

Terpin hydrate is stated to increase bronchial secretions and assist expectoration.

5.2 Pharmacokinetic properties

Ingestion of codeine phosphate produces peak plasma-codeine concentrations in about one hour. The plasma half-life has been reported to be between 2½ and 4 hours after ingestion.

Menthol - no information available.
Terpin hydrate - no information available.

5.3 Preclinical safety data

No data of relevance, which is additional to that on other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cineole
Alcohol 96%
Glycerin
Pumilio Pine Oil
Syrup
Purified Water

6.2 Incompatibilities
No major incompatibilities known.

6.3 Shelf life
200ml: 36 months unopened.

6.4 Special precautions for storage
Store below 25ºC.
Protect from light.

6.5 Nature and contents of container
200ml: amber glass bottle with white 28mm child resistant tamper evident cap with EPE /Saranex liner.

6.6 Special precautions for disposal
None.

7 MARKETING AUTHORISATION HOLDER
Thornton & Ross Ltd
Linthwaite Laboratories
Huddersfield
HD7 5QH

8 MARKETING AUTHORISATION NUMBER(S)
PL 00240/5026R

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/08/1989 / 14/09/2007