National Agency for Food & Drug Administration & Control (NAFCAC)

Registration & Regulatory Affairs (R & R)

Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT:

EBECOLD TABLETS (Paracetamol 500 mg, Phenylephrine HCl 5 mg, Caffeine 30 mg & Chlorpheniramine Maleate 2 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated chewable tablet contains:
Paracetamol BP 500 mg
Phenylephrine Hydrochloride BP 5 mg
Caffeine (anhydrous) BP 30 mg
Chlorpheniramine Maleate BP 2 mg
Excipients q.s
Colour: Ponceau 4R.

Excipients:

1. Colour Ponceu 4R (supra)
2. Maize Starch
3. Sodium Methyl Paraben
4. Gelatin
5. Purified Talc
6. Polyvinyl Pyrrolidone K-30
7. Magnesium Stearate
8. Colloidal Silicon Dioxide (Aerosil)
9. Sodium Starch Glycollate

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EBECOLD tablet is used in the symptomatic management of pain and fever.
EBECOLD tablet is a cold preparation to prevent any influenza symptoms such as nasal congestion, nasal hypersecretion, sneezing, headache, dizziness, muscle pain, sluggishness, weariness, fever, throat itches.

4.2 Posology and method of administration:

According to the physician's instructions, the recommended dose is:

Adults: 1 tablet 3-4 times daily.

Children 6-12 years: 1/2 tablet 3-4 times daily.

Children 2-6 years: 1/4 tablet 3-4 times daily.

If the fever continues for more than 3 days or if there is no pain relief within 5 days, refer to your doctor.

If you forget to take this medicine at the specified time, take the dose as soon as you remember, but never take a double dose to compensate for a missed one.

4.3 Contraindications:

Hypersensitivity to any of the ingredients. Avoid in patients with cardiovascular disease, hypertension, diabetes, hyperthyroidism, phaeochromocytoma, closed angle glaucoma, prostatic enlargement and liver failure.

Patients being treated with monoamine oxidase inhibitors, or within 14 days of ceasing such treatment.

4.4 Special warnings and precautions for use

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 non-cirrhotic alcoholic liver

disease. Do not take with any other paracetamol-containing products.

Contains paracetamol.

This medicine should be used with caution in patients with occlusive vascular disease including Raynaud's Phenomenon.

Keep all medicines out of the reach of children.

If symptoms persist for more than 7 days, consult your doctor. Do not exceed the

stated dose.

Label:

Immediate medical advice should be sought in the event of an overdose, even

if you feel well. Leaflet or combined label/leaflet:

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

4.5 Interaction with other product and other forms of interaction

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestryramine.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Should not be given to patients being treated with monoamine oxidase inhibitors or within 14 days of stopping such treatment. May also interfere with the hypotensive effects of antihypertensive drugs. May enhance the effects of anticholinergic drugs such as tricyclic antidepressants. The product may increase the possibility of arrhythmias in digitalised patients. May enhance the cardiovascular effects of other sympathomimetic amines (e.g. decongestants).

4.6 Pregnancy and Lactation:

This product is not recommended for use in pregnancy due to the phenylephrine and caffeine content. There is a potential increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption during pregnancy.
This product should not be used while breast-feeding without medical advice. Caffeine in breast milk may have a stimulating effect on breast-fed infants.
Phenylephrine may be excreted in 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.

4.8 Undesirable effects:

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. The frequency of these adverse events is not known (cannot be estimated from available data).

Paracetamol

Body System	**Undesirable effect**
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis These are not necessarily causally related to paracetamol.
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema and Stevens Johnson syndrome, toxic epidermal necrolysis
Respiratory, thoracic and mediastinal disorders	Bromchospasm*
Hepatobiliary disorders	Hepatic dysfunction

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

Caffeine

Adverse reactions identified through post-marketing use with caffeine are listed below. The frequency of these reactions is unknown.

Central Nervous system	Nervousness and anxiety Irritability, Restlessness and Excitability Dizziness

When the recommended paracetamol-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine- related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

Phenylephrine

The following adverse events have been observed in clinical trials with phenylephrine and may therefore represent the most commonly occurring adverse events.

Body System	**Undesirable effect**
Psychiatric disorders	Nervousness
Nervous system disorders	Headache, dizziness, insomnia
Cardiac disorders	Increased blood pressure
Gastrointestinal disorders	Nausea, vomiting, diarrhoea

Adverse reactions identified during post-marketing use are listed below. The frequency of these reactions is unknown.

Eye disorders	Mydriasis, acute angle closure glaucoma, most likely to occur in those with closed angle glaucoma
Cardiac disorders	Tachycardia, palpitations
Skin and subcutaneous disorders	Allergic reactions (e.g. rash, urticaria, allergic dermatitis). Hypersensitivity reactions – including that cross-sensitivity may occur with other sympathomimetics
Renal and urinary disorders	Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

<u>Chlorpheniramine</u>

Blood and lymphatic system

disorders Unknown: haemolytic

anaemia, blood dyscrasias

Immune system disorders:

Unknown: allergic reaction, angioedema, anaphylactic reactions

Metabolism and nutritional disorders:
Unknown: anorexia.

Psychiatric disorders:

Unknown: confusion*, excitation*, irritability*, nightmares*, depression

Nervous system disorders*:

Very common: sedation, somnolence

Common: disturbance in attention, abnormal coordination, dizziness, headache.

Eye disorders:

Common: blurred vision

Ear and labyrinth disorders

Unknown: tinnitus

Cardiac disorders:

Unknown: palpitations, tachycardia, arrythmias

Vascular disorders:

Unknown: Hypotension

Respiratory, thoracic and Mediastinal disorders: Unknown: thickening of bronchial secretions Gastrointestinal disorders:

Common: nausea, dry mouth

Unknown: vomiting, abdominal pain, diarrhoea, dyspepsia

Hepatobiliary disorders:

Unknown: hepatitis including jaundice

Skin and subcutaneous disorders:

Unknown: exfoliative dermatitis, rash, urticaria, photosensitivity,

Musculoskeletal and connective tissue disorders:

Unknown: muscular twitching, muscle weakness.

Renal and Urinary disorders:

Unknown: Urinary retention

General disorders and administration site conditions:

Common: fatigue Unknown: chest tightness

*Children and the elderly are more susceptible to neurological anticholinergic effects and paradoxical excitation (eg increased energy, restlessness, nervousness)

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:

Paracetamol

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

Risk factors:

If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b, Regularly consumes ethanol in excess of recommended amounts.

Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

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. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, 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 and pancreatitis 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.

Caffeine

Symptoms and signs

Overdose of caffeine may result in epigastric pain, vomiting, diurese, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Treatment

No specific antidote is available, but supportive measures may be used.

Phenylephrine

Symptoms and signs

Phenylephrine overdosage is likely to result in effects similar to those listed under adverse reactions. Additional symptoms may include hypertension, and possibly reflex bradycardia. In severe cases confusion, hallucinations, seizures and arrhythmias may occur. However the amount required to produce serious phenylephrine toxicity would be greater than that required to cause paracetamol-related liver toxicity.

Treatment

Treatment should be as clinically appropriate. Severe hypertension may need to be treated with alpha blocking drugs such as phentolamine.

Chlorpheniramine

Symptoms and signs

The estimated lethal dose of chlorphenamine is 25 to 50mg/kg body weight. Symptoms and signs include sedation, paradoxical excitation of the CNS, toxic psychosis, convulsions, apnoea, anticholinergic effects, dystonic reactions and cardiovascular collapse including arrhythmias.

Treatment

Symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions and fluid and electrolyte balance. If overdosage is by the oral route, treatment with activated charcoal should be considered provided there are no contraindications for use and the overdose has been taken recently (treatment is most effective if given within an hour of ingestion.) Treat hypotension and arrhythmias vigorously CNS convulsions may be treated with i.v. diazepam. Haemoperfusion may be used in severe cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynemic properties

Paracetamol: An analgesic and antipyretic.
Caffeine: A mild stimulant
Phenylephrine hydrochloride: A sympathomimetic decongestant.
Chlorphenamine is a potent antihistamine (H1-antagonist).
The active ingredients are not known to cause sedation.

5.2 Pharmacokinetic Properties:

Paracetamol: is readily absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine, mainly as glucoronide and sulphate conjugates.

Caffeine: is absorbed readily after oral administration, maximal plasma concentrations are achieved within one hour and the plasma half-life is about 3.5 hours. 65-80% of administered caffeine is excreted in the urine as 1-methyluric acid and 1-methylxanthine.

Phenylephrine Hydrochloride: is irregularly absorbed from the gastrointestinal tract and undergoes first-pass metabolism by monoamine oxidase in the gut and liver; orally administered phenylephrine thus has reduced bioavailability. It is excreted in the urine almost entirely as the sulphate conjugate.

Chlorpheniramine: Chlorphenamine is well absorbed from the gastro-intestinal tract, following oral administration. The effects develop within 30 minutes, are maximal within 1 to 2 hours and last 4 to 6 hours. The plasma half-life has been estimated to be 12 to 15 hours. Chlorphenamine is metabolised to the monodesmethyl and didesmethyl derivatives. About 22% of an oral dose is excreted unchanged in the urine.

5.3 Preclinical safety data

Pre-clinical safety data on these active ingredients in the literature have not revealed any pertinent and conclusive findings which are of relevance to the recommended dosage and use of the product and which have not already been mentioned elsewhere in this Summary.

The toxicity of paracetamol has been extensively studied in numerous animal species. Pre- clinical studies in rats and mice have indicated single dose oral LD50 values of 3.7 g/kg and 338 mg/kg, respectively. Chronic toxicity in these species at large multiples of the human therapeutic dose, occurs as degeneration and necrosis of hepatic, renal and lymphoid tissue, and blood count changes. The metabolites believed responsible for these effects have also been demonstrated in man. Paracetamol should not, therefore, be taken for long periods of time, and in excessive doses. At normal therapeutic doses, paracetamol is not associated with genotoxic or carcinogenic risk. There is no evidence of embryo-or foetus-toxicity from paracetamol in animal studies.

6. PHARMACEUTICAL PARTUCULARS

6.1 List of excipients

1. Colour Ponceu 4R (supra)
2. Maize Starch
3. Sodium Methyl Paraben
4. Gelatin
5. Purified Talc
6. Polyvinyl Pyrrolidone K-30
7. Magnesium Stearate
8. Colloidal Silicon Dioxide (Aerosil)
9. Sodium Starch Glycollate

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 Months from the date of manufacturing.

6.4 Special precautions for storage:

Do not store above 25°C.
Keep out of reach of children
Do not refrigerated
Discard outdated medicines.

6.5 Nature and contents of container:

Alu Strip of 4 Tablets.

Style: 1 x 4 Tablets

6.6 Special precaution for disposal

No Special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer:

Name & address:

LESANTO LABORATORIES
Plot No. 9,10,11 & 20,
Survey No. 53,
Palghar (E) – 401 404,
Maharashtra, India.