PARACETAMOL, CODEINE AND CAFFEINE 500MG/8MG/30MG
SOLUBLE TABLETS

PL 08137/0270

UKPAR

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PARACETAMOL, CODEINE AND CAFFEINE 500MG/8MG/30MG
SOLUBLE TABLETS

PL 08137/0270

LAY SUMMARY

On 13 July 2011, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Neolab Limited a Marketing Authorisation (licence) for the medicinal product Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets (PL 08137/0270). This is a pharmacy only (P) medicine used for the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone. It is used to relieve migraine, headache, dental pain, period pain, backache, rheumatic pain, strains and sprains and sciatica.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
PARACETAMOL, CODEINE AND CAFFEINE 500MG/8MG/30MG SOLUBLE TABLETS

PL 081370270

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Neolab Limited a Marketing Authorisation for the medicinal product Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets (PL 08137/0270) on 13 July 2011. This product is supplied through pharmacies only (P) and is indicated for the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets are recommended for the relief of migraine, headache, backache, rheumatic pain, period pain, dental pain, strains and sprains and sciatica.

The application was submitted according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets contain the active ingredients paracetamol, caffeine and codeine phosphate. Paracetamol is a well established analgesic, caffeine has a stimulating effect on the central nervous system and possesses a weak diuretic action. Codeine phosphate has moderate analgesic and weak cough-suppressant effects.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this was a bibliographic application for a product containing active ingredients of well-established use.

No new or unexpected safety concerns were raised during the assessment of this application and it was, therefore, judged that the benefits of using Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE: PARACETAMOL
INN: Paracetamol
Chemical name: N-(4-hydroxyphenyl)acetamide.
Molecular formula: C₈H₉NO₂
Molecular weight: 151.2
Appearance: White, crystalline powder.
Solubility: Paracetamol is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in dichloromethane.

Paracetamol is the subject of a European Pharmacopoeia monograph.

The manufacture and control of paracetamol by all suppliers is covered by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability.

ACTIVE SUBSTANCE: CODEINE PHOSPHATE HEMIHYDRATE
INN: Codeine phosphate
Chemical name: 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol
Molecular formula: C₁₈H₂₁NO₃, H₃PO₄, ½ H₂O
Molecular weight: 406.4
Appearance: White or almost white crystalline powder or small colourless crystals.
Solubility: Soluble in water

Codeine phosphate hemihydrate is the subject of a European Pharmacopoeia monograph

The manufacture and control of codeine phosphate hemihydrate by all suppliers is covered by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability.
ACTIVE SUBSTANCE: CAFFEINE
INN: Caffeine
Chemical name: 1,3,7-trimethyl-3,7-dihydropurine-2,6-dione or 1,3,7-trimethylxanthine.

Structure:

Molecular formula: $\text{C}_8\text{H}_{10}\text{N}_4\text{O}_2$
Molecular weight 194.2
Appearance: White or almost white, crystalline powder.
Solubility: Sparingly soluble in water, freely soluble in boiling water and slightly soluble in ethanol.

Caffeine is the subject of a European Pharmacopoeia monograph

The manufacture and control of caffeine is covered by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability.

MEDICINAL PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients, namely citric acid (anhydrous), povidone (K30), sodium hydrogen carbonate, saccharin sodium, sodium carbonate anhydrous, simeticone, polysorbate 80 and aspartame (E951).

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable product containing the active ingredients paracetamol 500mg, codeine phosphate hemihydrate 8mg and caffeine 30mg.

Suitable pharmaceutical development data have been provided for this application.

Manufacturing Process
A description and flow-chart of the manufacturing method have been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation on pilot scale batches has been provided.
Finished Product Specification
The finished product specification proposed is satisfactory. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications.

Container Closure System
The finished product is packaged in 4 ply laminate (paper/LDPE/aluminium/LDPE) blister strips and is available in pack sizes of 16, 24 or 32 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the Product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with the storage conditions, “Store below 30°C. Store in the original package.”

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this application.

Summary of Product Characteristics (SmPC), Product Information Leaflets (PILs) and Labelling
The SmPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical data were submitted, which is acceptable given that this was a bibliographic application for a product containing active substances of well-established use.

NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No new clinical pharmacology data were submitted or required for this application.

EFFICACY
No new efficacy data were submitted or required for this application.

SAFETY
No new safety data were submitted or required for this application. The applicant has provided an acceptable safety review from the literature. No new safety issues have been raised from this application.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for this product.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PRODUCT FORMATION LEAFLETS (PILs) AND LABELS
The SmPC, PIL and labels are acceptable.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none were required for this type of application. A non-clinical overview has been provided by an appropriately qualified person and consists of a review of the published literature.

EFFICACY
No new data were submitted and none were required for this type of application.

The analgesic efficacy of the actives in this combination is well described and no new studies have been conducted. The applicant has summarised the current state of knowledge in their literature review.

SAFETY
The safety profiles of paracetamol, codeine phosphate and caffeine are well-known. The literature review identified no new or unexpected safety issues or concerns.

PRODUCT LITERATURE
The approved SmPC is satisfactory. The PIL and labelling texts are satisfactory, and consistent with the approved SmPC.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Paracetamol, codeine phosphate and caffeine are well-known active substances. Extensive clinical experience with paracetamol, codeine phosphate and caffeine is considered to have demonstrated the therapeutic value of the product. The benefit-risk is, therefore, considered to be positive.
PARACETAMOL, CODEINE AND CAFFEINE 500MG/8MG/30MG SOLUBLE TABLETS

PL 08137/0270

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 02 November 2009.

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 15 December 2009.

3. Following assessment of the application the MHRA requested further information relating to the quality dossier on 12 February 2010 and 06 January 2011 and the clinical dossier on 25 March 2010.

4. The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 15 September 2010 and 11 February 2011 and the clinical dossier on 15 September 2010.

5. The application was determined and granted on 13 July 2011.
PAR Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains paracetamol 500mg, codeine phosphate hemihydrate 8mg and caffeine 30mg.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Effervescent tablet.

White to off-white coloured circular flat bevelled tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

Paracetamol, Codeine & Caffeine Soluble Tablets are recommended for the relief of migraine, headache, backache, rheumatic pain, period pain, dental pain, strains and sprains and sciatica.

4.2 Posology and method of administration
Adults (including the elderly)
2 tablets dissolved in at least half a tumbler of water. These doses may be given up to 3 or 4 times a day if necessary. The dose should not be repeated more frequently than every 4 hours. Do not take for more than 3 days without consulting a doctor.

Children
Not to be given to children under 12 years of age.
Do not take for more than 3 days continuously without medical review.

4.3 Contraindications
Hypersensitivity to paracetamol, codeine, caffeine, opioid analgesics or any of the other constituents.

Use of codeine containing products is contraindicated in mothers who are breast feeding unless prescribed by a doctor.

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 hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Do not exceed the stated dose.

Patients should be advised to consult their doctor if their headaches become persistent.

Patients should be advised not to take other paracetamol or codeine containing products concurrently.

If symptoms persist, consult your doctor.

Keep out of the reach of children.

Patients with obstructive bowel disorders or acute abdominal conditions should consult a doctor before using this product.
Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients. Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.

Each tablet contains 403.24 mg of sodium and may be harmful to people on a low sodium diet.

The tablets also contain aspartame (a source of phenylalanine) and so should not be taken by people with phenylketonuria.

The label will state:
*Front of Pack*
- Can cause addiction.
- For three days use only.

*Back of Pack*
- For the short term treatment of acute moderate pain when other painkillers have not worked. Do not take less than four hours after taking other painkillers.
- For the treatment of migraine, headache, dental pain, period pain, backache, rheumatic pain, strains and sprains and sciatica.
- If you need to take this medicine continuously for more than three days you should see your doctor or pharmacist.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. If you take this medicine for headaches for more than three days it can make them worse.

The leaflet will state:

*Headlines section (to be prominently displayed)*
- This medicine can only be used for the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.
- You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should see your doctor or pharmacist for advice.
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take this medicine for headaches for more than three days it can make them worse.

*Section 1: What the medicine is for*
Paracetamol, Codeine and Caffeine Tablets are for the short term treatment of acute moderate pain which is not relieved by paracetamol, ibuprofen or aspirin alone.

They are used to relieve migraine, headache, dental pain, period pain, strains and sprains, backache, rheumatic pain and sciatica.

*Section 2: Before taking*
- This medicine contains codeine which can cause addiction if you take it continuously for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.
- If you take a painkiller for headaches for more than three days it can make them worse.

*Section 3: Dosage*
- Do not take for more than 3 days. If you need to use this medicine for more than three days you must speak to your doctor or pharmacist.
- This medicine contains codeine and can cause addiction if you take it continuously for more than three days. When you stop taking it you may get withdrawal symptoms. You should talk to your doctor or pharmacist if you think you are suffering from withdrawal symptoms.

*Section 4: Side effects*
- Some people may have side-effects when taking this medicine. If you have any unwanted side-effects you should seek advice from your doctor, pharmacist or other healthcare
professional. Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side-effects via the internet at www.yellowcard.gov.uk; alternatively you can call Freephone 0808 100 3352 (available between 10am-2pm Monday – Friday) or fill in a paper form available from your local pharmacy.

**How do I know if I am addicted?**

If you take the medicine according to the instructions on the pack it is unlikely that you will become addicted to the medicine. However, if the following apply to you it is important that you talk to your doctor:

- You need to take the medicine for longer periods of time
- You need to take more than the recommended dose

When you stop taking the medicine you feel very unwell but you feel better if you start taking the medicine again.

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

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

Opioid analgesics should be given with care to patients receiving monoamine oxidase inhibitors. The effect of CNS depressants (including alcohol) may be potentiated by codeine; these interactions are unlikely to be significant at the dosage involved.

**4.6 Pregnancy and lactation**

**Pregnancy**

Use during pregnancy should be avoided, unless advised by a physician. This includes maternal use during labour because of the potential for respiratory depression in the neonate. The safety of paracetamol-caffeine-codeine during pregnancy has not been established relative to the possible adverse effects of foetal development and should be avoided during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption.

**Lactation**

Codeine-containing products must not be used while breast feeding unless prescribed by a doctor.

In nursing mothers, who are ultra-rapid metabolisers of codeine, higher than expected serum and breast milk morphine levels can occur. Morphine toxicity in babies can cause excessive somnolence, hypotonia and difficulty breast feeding or breathing. In severe cases respiratory depression and death can occur. The lowest effective dose should be used, for the shortest possible time. Nursing mothers should be informed about carefully monitoring the infant during treatment for any sign and symptoms of morphine toxicity such as increased drowsiness or sedation, difficulty breast feeding, breathing difficulties, and decreased tone, and seeking immediate medical care if such symptoms or signs are noticed.

Although significant caffeine toxicity has not been observed in breastfed infants, caffeine may have a stimulating effect on the infant. Due to the caffeine content of this product it should not be used if you are pregnant or breast feeding.

**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**

Adverse events 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. The frequency of these adverse events is not known (cannot be estimated from available data).
Paracetamol

<table>
<thead>
<tr>
<th>Body System</th>
<th>Undesirable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Cutaneous hypersensitivity reactions including skin rashes, angiodema and Stevens Johnson syndrome/toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm*</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic dysfunction</td>
</tr>
</tbody>
</table>

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

Caffeine

<table>
<thead>
<tr>
<th>Body System</th>
<th>Undesirable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Nervousness</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
</tbody>
</table>

When the recommended paracetamol-caffeine-codeine 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.

Codeine

Adverse reactions identified during post-marketing use are listed below by MedDRA system organ class. The frequency of these reactions is not known.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Undesirable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>Drug dependency can occur after prolonged use of codeine at higher doses</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>Constipation, nausea, vomiting, dyspepsia, dry mouth, acute pancreatitis in patients with a history of cholecystectomy</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>Dizziness, worsening of headache with prolonged use, drowsiness</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td>Pruritus, sweating</td>
</tr>
</tbody>
</table>

4.9 Overdose

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

Codeine

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms

An overdose of codeine is characterised, in the first phase, by nausea and vomiting. An acute depression of the respiratory centre can cause cyanosis, slower breathing, drowsiness, ataxia and, more rarely, pulmonary oedema. Respiratory pauses, miosis, convulsion, collapse and urine retention. Signs of histamine release have been observed as well.
Management
This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of 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 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 preparation has been taken.

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

Risk Factors:
If the patient
Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
Or
Regularly consumes ethanol in excess of recommended amounts.
Or
Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
Symptoms of paracetamol overdose 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
Overdose of caffeine may result in epigastric pain, vomiting, diuresis, 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.
Management
Patients should receive general supportive care (e.g. hydration and maintenance of vital signs). The administration of activated charcoal may be beneficial when performed within one hour of the overdose, but can be considered for up to four hours after the overdose. The CNS effects of overdose may be treated with intravenous sedatives.

Summary
Treatment of overdose with Paracetamol, Codeine & Caffeine Tablets requires assessment of plasma paracetamol levels for antidote treatment, with signs and symptoms of codeine and caffeine toxicity being managed symptomatically.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Paracetamol is a well established analgesic, caffeine has a stimulating effect on the central nervous system and possesses a weak diuretic action. Codeine phosphate has moderate analgesic and weak cough-suppressant effects.

5.2 Pharmacokinetic properties
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Concentration of the drug in plasma reaches a peak in 30 - 60 minutes and the plasma half-life is 1 - 4 hours. Paracetamol is relatively uniformly distributed throughout most body fluids and exhibits variable protein binding. Excretion is almost exclusively renal, in the form of conjugated metabolites.

Codeine phosphate is well absorbed after administration and distributes widely throughout the body. 86% of an oral dose is excreted in the urine within 24 hours, 40 - 70% of this being free or conjugated codeine, 5 - 15% free or conjugated morphine, 10 - 20% free or conjugated norcodeine, and trace amounts may be free or conjugated normorphine.

Caffeine is rapidly but irregularly absorbed after oral administration, absorption is pH-related. After an oral dose of 100mg, peak plasma concentrations of 1.5 - 2 μg/ml are attained within 1 - 2 hours. Plasma half-life = 4 - 10 hours. Caffeine rapidly distributes throughout the body water, and is approximately 15% bound to plasma proteins. In 48 hours, 45% of a dose is excreted in the urine as l-methylxanthine and l-methyluric acid.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Citric Acid (anhydrous)
Povidone (K30)
Sodium Hydrogen Carbonate
Saccharin Sodium
Sodium Carbonate Anhydrous
Simeticone
Polysorbate 80
Aspartame (E951)

6.2 Incompatibilities
None stated.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30°C. Store in the original package.
6.5 Nature and contents of container
Strip formed from 4 ply laminate (paper/LDPE/aluminium/LDPE).
Pack sizes of 16, 24 or 32 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Neolab Limited
57 High Street
Odiham
Hants
RG21 1LF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 08137/0270

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/07/2011

10 DATE OF REVISION OF THE TEXT
13/07/2011
PRODUCT INFORMATION LEAFLET

PARACETAMOL, CODEINE & CAFFEINE 500mg/8mg/30mg Soluble Tablets

The name of this medicine is Paracetamol, Codeine & Caffeine 500mg/8mg/30mg Soluble Tablets which will be referred to as 'Paracetamol, Codeine & Caffeine Tablets' in this leaflet.

Read all of this leaflet carefully because it contains important information for you.

• This medicine can only be used for the short-term treatment of adults moderate pain which is not relieved by paracetamol, aspirin or ibuprofen alone.
• You should only take this product for a maximum of three days at a time. If you need to take it for longer than three days you should take your doctor or pharmacist for advice.
• Take several times a day to cover the duration of the fever.
• Do not take this medicine for more than three days at a time. This can give you withdrawal symptoms from the medicine when you stop taking it.
• If you take this medicine for headaches for more than three days it can make you dependent.
• Keep this leaflet. You may need to refer to it again.

In this leaflet: 3.
• What Paracetamol, Codeine & Caffeine Tablets are and what they are used for
• How to stop taking Paracetamol, Codeine & Caffeine Tablets
• Possible side effects
• How to store Paracetamol, Codeine & Caffeine Tablets
• Further information

1. WHAT PARACETAMOL, CODEINE & CAFFEINE TABLETS ARE AND WHAT THEY ARE USED FOR

Paracetamol, Codeine & Caffeine Tablets contain the active ingredients paracetamol 500mg, codeine phosphate 8mg and caffeine 30mg.

Paracetamol, Codeine & Caffeine Tablets are a short-term treatment of moderate pain which is not relieved by paracetamol, aspirin or ibuprofen alone. They are used to relieve migraine headache, dental pain, post-procedural pain, trauma, musculoskeletal pain and fever.

2. BEFORE YOU TAKE PARACETAMOL, CODEINE & CAFFEINE TABLETS

This medicine contains codeine which can cause addiction if you take it for more than three days. This can give you withdrawal symptoms from the medicine when you stop taking it.

If you take a particular dosage for more than three days it can make you dependent.

Do not take Paracetamol, Codeine & Caffeine Tablets if:
• you are allergic to codeine or paracetamol, codeine, caffeine or any of the other ingredients in this medicine
• you have recently taken any other paracetamol or codeine containing products
• you are taking or have recently taken any other paracetamol or codeine containing products

3. HOW TO TAKE PARACETAMOL, CODEINE & CAFFEINE TABLETS

Take special care with Paracetamol, Codeine & Caffeine Tablets

• Carefully read the leaflet before you take this medicine. If you have any questions, ask your doctor or pharmacist.
• Do not exceed the recommended dose of 3 tablets per day
• Do not use this medicine for more than 3 days
• Do not use more than 4 tablets for each treatment
• Do not take this medicine with alcohol
• Do not give this medicine to children under 12 years of age
• Do not exceed the recommended dose of 3 tablets per day.

4. POSSIBLE SIDE EFFECTS

Some people may have side effects when taking this medicine. If you have any new unusual side effects you should seek advice from your doctor, pharmacist or other healthcare professional. Anyone who can help you to be sure that medicines remain safe and effective by reporting any unusual side effects. Visit the internet at www.random.gov.uk or by telephone to 0845 60 30 302

Coughing or sneezing
• If you have any of the following symptoms after taking these tablets, you should consult your doctor immediately:
• any sudden alteration, difficulty in breathing or difficulty in swallowing, swelling of the face, lips, eyes, hands, feet or trunk;
• an acute allergic reaction (anaphylaxis) or swelling of the skin;
• severe abdominal pain, nausea and vomiting if you have recently had a gall bladder removal;
• impaired breathing or bleeding;
• nausea, sweat, blood loss, loss of appetite and yellowing of the eyes and skin

The following side effects have also been reported:
• constipation
• if any of these side effects gets worse, or if you notice any side effects not listed in this leaflet, then please tell your doctor or pharmacist.

5. HOW TO STORE PARACETAMOL, CODEINE & CAFFEINE TABLETS

Do not take this medicine above 30°C. Store in the original package.

6. FURTHER INFORMATION

1. What Paracetamol, Codeine & Caffeine Tablets are and what they are used for
2. How to stop taking Paracetamol, Codeine & Caffeine Tablets
3. Possible side effects
4. How to take Paracetamol, Codeine & Caffeine Tablets
5. How to store Paracetamol, Codeine & Caffeine Tablets
6. Further information

If you have any questions, ask your doctor or pharmacist.
Paracetamol, Codeine and Caffeine 500mg/8mg/30mg Soluble Tablets

PL 08137/0270

**LABELLING**

**Carton:**

16 effervescent tablets
Paracetamol, Codeine & Caffeine
500mg/8mg/30mg SOLUBLE TABLETS

**Warnings**
- Do not exceed the stated dose.
- Contains paracetamol. See warnings on the paracetamol-containing products.
- Store below 25°C in the original packaging.

**Directions for use**
- For oral use.
- Paracetamol, Codeine & Caffeine is a short-term treatment of adults and children over 12 years of age for mild to moderate pain, headache, toothache, and menstrual pain.

**Other information**
- For children under 12 years, use in a child-formulated product.
- If symptoms persist, consult your doctor.

**Manufactured by:**
- REHAB A/S
- PO Box 3000
- 2100 Copenhagen
- Denmark

**Date of dispensing:**
- The batch number and date of dispensing are on the carton.
Blister: