PARACETAMOL 120MG/5ML ELIXIR
PL 19348/0044

UKPAR

TABLE OF CONTENTS

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LAY SUMMARY

The MHRA granted LPC Medical (UK) Ltd a Marketing Authorisation (licence) for the medicinal product Paracetamol 120mg/5ml Elixir (PL 19348/0044) on 10 March 2008. This product is available through pharmacies (P) for the treatment of mild to moderate pain, including headache, migraine, neuralgia, toothache, teething pains, sore throats and aches. It can also be used to relieve the symptoms of influenza, feverishness and feverish colds.

Paracetamol 120mg/5ml Elixir contains the active ingredient paracetamol, which is an analgesic (relieves pain) and an antipyretic (lowers your temperature when you have a fever).

This application is a duplicate of a previously granted application for Paracetamol Elixir paediatric 120mg/5ml (Rusco Ltd, trading as Rusco Pharmaceuticals) and as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Paracetamol 120mg/5ml Elixir outweigh the risks, hence a Marketing Authorisation has been granted.

PARACETAMOL 120MG/5ML ELIXIR
PL 19348/0044

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Paracetamol 120mg/5ml Elixir to LPC Medical (UK) Ltd on 10 March 2008. The product is available through pharmacies.

The application was submitted as a simple abridged application according to article 10c of Directive 2001/83/EC as amended, referring to Paracetamol Elixir paediatric 120mg/5ml (Rusco Ltd, trading as Rusco Pharmaceuticals), approved on 02 October 1996.

No new data were submitted nor were any necessary for this simple application since the data are identical to that of the previously granted reference product. As the reference product was granted prior to the introduction of current legislation, a Public Assessment Report (PAR) has not been generated for it.

The product contains the active ingredient paracetamol which is an analgesic and antipyretic and is indicated for the treatment of mild to moderate pain, including headache, migraine, neuralgia, toothache, pain in teething, sore throat, aches and pains. It is also indicated for the symptomatic relief of influenza, feverishness and feverish colds.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as an oral solution containing 120mg/5ml of the active pharmaceutical ingredient paracetamol. The excipients present are alcohol 96%, propylene glycol, potassium sorbate, sorbitol, glycerol, saccharin sodium, raspberry flavour, citric acid hydrated, amaranth ariavit and purified water.

Paracetamol 120mg/5ml is presented in an amber glass bottle with either a plastic cap or an aluminium ROPP cap in pack sizes of 60ml, 100ml and 200ml.

DRUG SUBSTANCE

Paracetamol

All aspects of the manufacture and control of paracetamol are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of paracetamol for inclusion in this medicinal product.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards with the exception of raspberry flavour and amaranth ariavit which are tested as per suitable in house specifications.

No excipients used contain material of animal or human origin.

Manufacture

The proposed manufacturing process is consistent with the details registered for the reference product and the maximum batch size is stated.

Finished product specification

The proposed finished product specification is in line with the details registered for the reference product.

Stability

Finished product stability data support the proposed shelf-life of 36 months with storage conditions of “Do not store above 25°C. Keep the bottle tightly closed. Store in the original container.”

Bioequivalence/bioavailability

A bioequivalence study was not required for this application.

SPC, PIL and Labels

The SPC and labels are pharmaceutically acceptable.

The product does not have a separate Patient Information Leaflet (PIL) as the relevant information is detailed on the label. This is acceptable.

The Marketing Authorisation holder has provided a commitment to update the Marketing Authorisation with a Patient Information Leaflet/label in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet/label shall reflect the results of consultation with target patient groups, no later than 01 July 2008.

CONCLUSION

It is recommended that a Marketing Authorisation should be granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

As this is a duplicate application, no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application are consistent with those previously assessed for the reference product and as such have been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

This application is identical to the previously granted application for Paracetamol Elixir paediatric 120mg/5ml in which the applicant provided clinical data.

No new or unexpected safety concerns arise from this application.

The SPC and labelling are satisfactory and consistent with that for the reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the reference product. Clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

PARACETAMOL 120MG/5ML ELIXIR
PL 19348/0044

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Marketing Authorisation application on 10 November 2003.
2	Following standard checks and communication with the applicant, the MHRA considered the application valid on 26 January 2004.
3	Following assessment of the application, the MHRA requested further information on 02 March 2004 and 29 January 2008.
4	The applicant responded to the MHRA's requests, providing further information on 04 October 2007 and 29 January 2008.
5	The application was determined on 10 March 2008.

PARACETAMOL 120MG/5ML ELIXIR
PL 19348/0044

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 120mg/5ml Elixir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains:

Paracetamol 120mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution
Clear red liquid with raspberry flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of mild to moderate pain, including headache, migraine, neuralgia, toothache, pain in teething, sore throat, aches and pains Symptomatic relief of influenza, feverishness, feverish colds.

4.2 Posology and method of administration

Children 3-12 months: 2.5ml to 5.0ml every four hours.

Children 1 year – under 6 years: 5.0 ml to 10.0ml every four hours

Children 6 years – 12 years: 10.0ml to 20.0ml every four hours

Dosage for children under 3 months is at Physicians discretion.

Not more than 4 doses should be administered in any 24-hour period**.**

4.3 Contraindications

Hypersensitivity to Paracetamol or any of the excipients.

Contains sorbitol: Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.4 Special warnings and precautions for use

Use with caution in patients with severe renal or hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

The risk of hepatotoxicity with single doses or prolonged administration of paracetamol may be increased in chronic alcoholics, or in patients regularly taking other hepatotoxic medications, or hepatic-enzyme inducing agents.

Do not exceed the recommended dose
If symptoms persist consult your doctor
Keep out of reach and sight of children

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 cholestyramine.

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.

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 approx. 60 %.

Other substances with enzyme-inducing properties, e.g. rifampicine 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.

Acute alcohol intake may diminish an individual’s ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged..

The risk of hepatotoxicity with single doses or prolonged administration of paracetamol may be increased in chronic alcoholics, or in patients regularly taking other hepatotoxic medications, or hepatic-enzyme inducing agents.

4.6 Pregnancy and lactation

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but However, in one study, eight cases of constriction and complete occlusion of the ductus arteriosus associated with maternal use of paracetamol. All were recovered. Hence, patients should follow the advice of their doctors regarding its use.

Paracetamol is excreted in breast milk, but not in a clinically significant amount. Available published data do not contraindicate breast-feeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causality related to paracetamol.

Allergic reactions may include skin rashes, and urticaria, anaphylaxis, angioneurotic oedema, toxic epidermal necrosis, erythema multiforme, and vasculitis have been rarely reported.

There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis but these were not necessarily causality related to paracetamol.

Most reports of adverse reactions to paracetamol relate to overdosage with the drug.

Nephrotoxicity following therapeutic doses of paracetamol is very rare, but papillary necrosis has been reported after prolonged administration.

4.9 Overdose

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

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

- Long-term treatment with enzyme-inducing drugs such as some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine), rifampicin and St. John's wort (hypericum). Even subacute "therapeutic" overdose has resulted in severe intoxication with doses varying from 6 g/24 hours for a week, 20 g for 2-3 days, etc
- Regular consumption of ethanol in excess of recommended amounts
- The existence of conditions that may lead to glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, and 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 ,coma and death. Acute renal failure with acute

tubular necrosis may develop even in the absence of severe liver damage. This is strongly suggested by lion pain, haematuria, and Protenuria. Cardiac arrhythmias and pancreatitis have been reported.

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.

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 for overdose, or 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesic and Antipyretic
ATC code: N02BE01
Paracetamol has analgesic and antipyretic effects but has only weak anti- inflammatory effects.
These actions are considered to be due to inhibition of the Biosynthesis of Prostaglandins.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30minutes 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 Parcetamol. The elimination half-life varies from 1-4 hours. Plasma protein binding is negligible at usual therapeutic concentrations but increase with increasing concentrations. A minor hyroxylated metabolite, which is usually produced in very small amounts by mixed function, oxidises in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following Paracetamol overdosage and cause liver damage.

Particularly no Paracetamol is excreted unchanged, and the bulk is excreted after hepatic conjugation with glucuronic acid (about 60%) sulphuric acid (about 35%) or cysteine (about 3%)

Children have less capacity for glucuronidation of the dugs than do adults. When high doses are ingested Paracetamol undergoes N-Hydroxylation t form (for further details see product licence file).

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Alcohol 96%,

Propylene Glycol,

Potassium Sorbate,

Sorbital,

Glycerol,

Saccharin Sodium,

Raspberry Flavour (IFF 17.40.0478),

Citric Acid Hydrated,

Amaranth Ariavit 311801,

Purified Water.

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C. Keep the bottle tightly closed. Store in the original container.

6.5 Nature and contents of container

Amber glass bottle with plastic cap
Amber glass bottle with Aluminium ROPP cap

Pack sizes: 60ml, 100ml, and 200ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

LPC Medical (UK) Ltd

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Bedfordshire

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United Kingdom

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e-mail: info@lpcpharma.com

8 MARKETING AUTHORISATION NUMBER(S)

PL 19348/0044

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/03/2008

10 DATE OF REVISION OF THE TEXT

10/03/2008

PATIENT INFORMATION LEAFLET/LABELLING

INGREDIENTS: Each 5ml of oral solution contains: Active Ingredient 120mg Paracetamol. Inactive Ingredients: Ethanol (8.4% w/v), Propylene Glycol, Potassium Sorbate (E202), Sorbitol (E420), Glycerol (E422), Saccharin Sodium, Raspberry flavour, Citric Acid Hydrated (E330), Ariavit Amaranth (E123) & Water.

WARNINGS: Do not give to your child if they are hypersensitive to Paracetamol or any of the other ingredients (check the list above). Please consult your doctor before taking this medicine if you are suffering from kidney or liver disorders or if you are pregnant or planning to become pregnant or breast-feeding. This medicinal product contains 8.4% vol of Ethanol (alcohol), i.e. up to 421mg per 5ml, equivalent to 8.4ml beer, 3.5ml wine per 5ml. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. This product contains 1.72g of Sorbitol. When taken according to dosage recommendation each dose supplies up to 6.9g of Sorbitol. If your child has an intolerance to some sugars, contact your doctor before giving this medicinal product. May have a mild laxative effect. Calorific value 2.6 Kcal/g Sorbital. This product contains Amaranth, which may cause allergic reactions. This product contains Propylene Glycol, which may cause alcohol-like symptoms. It also contains Glycerol which may cause headache, stomach upset and diarrhoea.

INTERACTIONS: Paracetamol may interact with metoclopramide, domperidone, colestyramine, warfarin or other blood thinning medicines, antiepileptic drugs, rifampicin or alcohol.

SIDE EFFECTS: Side effects are rare but blood disorders, skin rashes, hives, serious allergic reaction which causes difficulty in breathing or dizziness and other allergic reactions may occasionally occur. If you notice any of these or any other side effect please contact your doctor or pharmacist immediately. Do not use after the expiry date shown.

Date of preparation: OCTOBER 2007

MA Holder and Batch Release Site: LPC Medical (UK) Ltd, 30 Chaul End Lane, Luton, Bedfordshire, LU4 8EZ, UK.

Rusco

Paracetamol 120mg/5ml Elixir

FOR PAEDIATRIC USE - SUGAR FREE

For oral administration.

For the treatment of mild to moderate pain, including headache, migraine, neuralgia, toothache, teething pains, sore throats & aches.

Relieves the symptoms of influenza, feverishness and feverish colds.

HOW MUCH TO GIVE

DO NOT EXCEED THE STATED DOSE. NOT SUITABLE FOR DIABETICS.

AGE	DOSAGE
CHILDREN 6 TO 12 YEARS	Two to four 5ml teaspoons every four hours.
CHILDREN 1 TO 6 YEARS	One to two 5ml teaspoons every four hours.
CHILDREN 3 TO 12 MONTHS	Half to one 5ml teaspoon every four hours.
CHILDREN UNDER 3 MONTHS	**Not to be given except on medical advice.**

PL 19348/0044

IF SYMPTOMS PERSIST CONSULT YOUR DOCTOR

CONTAINS PARACETAMOL - Do not give with any other Paracetamol-containing products.

IMMEDIATE MEDICAL ADVICE SHOULD BE SOUGHT IN THE EVENT OF AN OVERDOSE, EVEN IF THE CHILD SEEMS WELL, BECAUSE OF THE RISK OF DELAYED, SERIOUS LIVER DAMAGE.

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200 ml ℮ P

DO NOT STORE ABOVE 25°C. KEEP THE BOTTLE TIGHTLY CLOSED. STORE IN THE ORIGINAL CONTAINER. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

BN:

EXP: