ZAPAIN 500MG/5ML ORAL SOLUTION PARACETAMOL

PL 12762/0173

UKPAR

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ZAPAIN 500MG/5ML ORAL SOLUTION PARACETAMOL

PL 12762/0173

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Goldshield Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Zapain 500mg/5ml Oral Solution Paracetamol (Product Licence number: 12762/0173).

Paracetamol is used to relieve pain and to reduce an increased body temperature. This formulation can be used to treat mild to moderate pain and is also used to help reduce fever, headache and to help relieve the symptoms of flu and cold.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Zapain 500mg/5ml Oral Solution Paracetamol outweigh the risks, hence a Marketing Authorisation has been granted.

ZAPAIN 500MG/5ML ORAL SOLUTION PARACETAMOL

PL 12762/0173

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Zapain 500mg/5ml Oral Solution Paracetamol (PL 12762/0173) to Goldshield Pharmaceuticals Limited on 13 February 2007. This medicinal product is available without prescription from pharmacies.

Zapain 500mg/5ml Oral Solution Paracetamol contains the active ingredient paracetamol, which reduces the feeling of pain in your body. It also acts on the heat regulating part of the brain to reduce sweating and temperature during fever.

This is a bibliographic application, submitted according to Article 10a of EC Directive 2001/83. The product is qualitatively and quantitatively the same as Paracetamol Infant Drops 100 mg/ml, Infadrops (PL 12762/0135), differing only in pack size

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Zapain 500mg/5ml Oral Solution Paracetamol outweigh the risks, hence a Marketing Authorisation was granted.

PHARMACEUTICAL ASSESSMENT REPORT

DRUG SUBSTANCE

A Certificate of Suitability for the drug substance has been issued. This means that the paracetamol used in this product complies with the monographs of the European Pharmacopoeia and Directives 2001/83/EC and 2001/82/EC.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active paracetamol is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated confirming the stability of the drug substance.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely purified water, glycerol, sodium citrate, Macrogol 400, citric acid monohydrate, propylene glycol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, raspberry flavour No. 1, saccharin sodium and erythrosine E127.The inclusion of each excipient is justified.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of Raspberry Flavour No. 1 and erythrosine E127, which comply with satisfactory in-house standards. Satisfactory certificates of analysis have been provided for all excipients.

A letter confirming that the glycerine used in this product is of vegetable origin has been provided.

Manufacture

A description and flow-chart of the manufacturing method has been provided. The manufacturing procedure is the same as Infant Drops 100 mg/ml, Infadrops (PL 12762/0135) differing only in fill volume (the proposed is 300ml, Infant Drops 100 mg/ml, Infadrops are 15 or 20 ml.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used. The specification is similar to Infant Drops 100 mg/ml, Infadrops and is acceptable.

Container closure system

The product is packed into 300 ml amber glass bottles with LD-polyethylene, tamper evident and child resistant caps. The bottle is packed in an outer carton. A spoon with a 5 ml and 2.5 ml measure is supplied with this pack. This is appropriate for a product of this nature.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set for the product when it remains unopened, which is satisfactory. Once the container is opened the shelf life is 3 months. Storage conditions are "Do not store above 25 ^{o}C. Store in the original container."

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

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

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of the product 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.

PRECLINICAL

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

EFFICACY AND SAFETY

Paracetamol is a well-known drug and its efficacy has been well documented in the past. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-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 products are identical to the reference product. Extensive clinical experience with paracetamol is considered to have demonstrated its therapeutic value.

ZAPAIN 500MG/5ML ORAL SOLUTION PARACETAMOL

PL 12762/0173

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 13 February 2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 18 March 2003
3	Following assessment of the application the MHRA requested further information on the quality dossier on 23 May 2003. The applicant responded to the MHRA's requests, providing further information on 9 February 2005
5	The MHRA requested further information on the quality dossier on 14 July 2005, 31 July 2006 and 30 November 2006. The applicant responded to the MHRA's requests, providing further information on 26 September 2006, 21 October 2006, 14 December 2006 and 7 February 2007
9	The application was determined on 13 February 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zapain 500mg/5ml Oral Solution
Paracetamol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol oral solution contains 500 mg paracetamol in each 5 ml
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Oral solution.
A clear, pink, viscous solution with an odour of raspberry.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol solution is indicated in the management of pain and fever associated with such conditions as the common cold, influenza and headache.

4.2 Posology and method of administration

For oral administration only.

Shake well before use.

Recommended Doses and Dosage Schedules

Adults and children 12 years and over:
The Optimal dosage range is 500 mg to 1 g paracetamol, i.e. 5 ml to 10 ml of Paracetamol oral solution (maximum 1g), which may be repeated every 4 to 6 hours to a maximum of 4 g paracetamol/ day (40 ml paracetamol oral solution).

Children aged 6 to 12 years:

The optimal dosage range is 250-500mg, i.e. 2.5 ml to 5 ml of paracetamol oral solution; these doses may be repeated every 4-6 hours when necessary up to a maximum of 4 doses per 24 hours.

Children under 6 years:

Not recommended.

The Elderly:

In the elderly, the rate and extent of paracetamol absorption is normal but plasma half-life is longer and paracetamol clearance is lower than in young adults.

4.3 Contraindications

Hypersensitivity to paracetamol or any of the other components of the preparation.

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.

Prolonged use except under medical supervision could be harmful.

If symptoms persist for more than 3 days or worsen at any time, consult your doctor.

Do not exceed the recommended dose.

Keep out of the reach and sight of children.

This product contains Glycerol and this is known to be harmful in high doses. It can cause headache, stomach upset and diarrhoea.

The label shall say: "Do not take with any other paracetamol-containing products" and "Immediate medical advice should be sought in the event of an overdose, even if you feel well."

The leaflet shall say: "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."

4.5 Interaction with other medicinal products and other forms of interaction

Patients who have taken barbiturates, tricyclic antidepressants and alcohol may show diminished ability to metabolize large doses of paracetamol, the plasma half-life of which can be prolonged.

Alcohol can increase the hepatotoxicity of paracetamol overdosage.

Chronic ingestion of anticonvulsants or oral steroid contraceptives induces liver enzymes and may prevent attainment of therapeutic paracetamol levels by increasing first pass metabolism or clearance.

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.

4.6 Pregnancy and lactation

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

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

4.7 Effects on ability to drive and use machines

None known.

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

4.9 Overdose

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 the risk factors.

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 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, coma and death. Acute renal failure with acute tubular necrosis, strongly suggested with 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. Any patient who had ingested around 7.5 g or more or paracetamol in the preceding 4 hours should undergo gastric lavage.

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 however 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 represent with serious hepatic dysfunction beyond 24h ingestion should be discussed with the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Classification: N02B E01 other analgesics and antipyretics; Anilides

The site and mechanism of the analgesic effect of paracetamol is unclear. Paracetamol reduces fever by a direct action on the hypothalamic heat-regulating centers, which increases dissipation of body heat (via vasodilation and sweating). The action of endogenous pyrogen on heat-regulating centers is inhibited.

Paracetamol is almost as potent as aspirin in inhibiting prostaglandin synthetase in the CNS but its peripheral inhibition of prostaglandin synthesis is minimal, which may account for its lack of clinically significant anti-rheumatic or anti-inflammatory effects.

Paracetamol dose not inhibit platelet aggregation, affect prothrombin response or produce GI ulceration.

5.2 Pharmacokinetic properties

Absorption: Paracetamol is rapidly an almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur within 0.5 to 2 hours, with slightly faster absorption of liquid preparations.

Distribution : Usual analgesic doses produce total serum concentrations of 5 to 20 mcg/ ml; a good correlation between serum concentration and analgesic effect has not been found. Serum protein binding varies from 20 to 50% at toxic serum concentrations.

Metabolism: Paracetamol is extensively metabolized in the liver by glucuronisation and conjugation with sulphates. Approximately 4% is metabolized via cytochrome P-450 to a toxic metabolite which is normally detoxified by preferential conjugation with hepatic glutathione and excreted in the urine as conjugates of cysteine and mercapturic acid. When paracetamol is used chronically or taken acutely in large doses, glutathione stores are depleted and hepatic necroses may occur.

Elimination: Paracetamol is excreted in the urine, mostly as metabolites; 2 to 4 % is excreted unchanged. The average elimination half-life is 1 to 4 hours; half-life is slightly prolonged in neonates (2.2 to 5 hours) and in cirrhotics.

5.3 Preclinical safety data

Data in the literature on toxic doses and serum levels of Paracetamol is limited, but Paracetamol is relatively non-toxic in therapeutic doses.

Paracetamol toxicity may result from a single toxic dose or from long term ingestion of the drug. It has been reported in the literature that children may be less susceptible to acute Paracetamol poisoning than adults. Hepatic necrosis is dose dependent and is the most serious acute toxic effect associated with over dosage. It is potentially fatal, and nausea, vomiting and abdominal pain usually occur within 2-3 hours after ingestion of toxic doses of the drug.

Acute toxic doses of Paracetamol in laboratory animals produce animals produce death from liver and renal damage.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Erythrosine (E127)
Glycerol
Macrogol 400
Propylene Glycol
Methyl parahydroxybenzoate
Propyl parahydroxbenzoate
Raspberry flavor No.1
Saccharin Sodium
Sodium citrate
Purified Water

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

Unopened: 24 months
Opened: 3 months

6.4 Special precautions for storage

Do not store above 25 ^{o}C. Store in the original container.

6.5 Nature and contents of container

Amber glass bottle with LD-polyethylene, tamper evident and child resistant cap.The bottle is packed in an outer carton.
A spoon with a 5 ml and 2.5 ml measure is supplied with this pack.
Pack size: 300ml

6.6 Special precautions for disposal

No special instruction.

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
NLA Tower
12-16 Addiscombe Road
Croydon
Surrey
CRO OXT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0173

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/02/2007

10 DATE OF REVISION OF THE TEXT

13/02/2007

PATIENT INFORMATION LEAFLET

GOLDSHIELD
Pharmaceuticals

Item Code to go here

SUMMARY OF PRODUCT CHARACTERISTICS

Zapain 500mg/5ml Oral Solution Paracetamol

Pharma Code to go here

Product Summary

1. TRADE NAME OF THE MEDICINAL PRODUCT

Zapain 500mg/5ml Oral Solution Paracetamol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol oral solution contains 500 mg paracetamol in each 5 ml. For excipients, see 6.1

3. PHARMACEUTICAL FORM

Oral solution.

A clear, pink, viscous solution with an odour of raspberry.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Paracetamol solution is indicated in the management of pain and fever associated with such conditions as the common cold, influenza and headache.

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Adults and children 12 years and over:

The Optimal dosage range is 500 mg to 1 g paracetamol, i.e. 5 ml to 10 ml of Paracetamol oral solution (maximum 1g), which may be repeated every 4 to 6 hours to a maximum of 4 g paracetamol/ day (40 ml paracetamol oral solution).

Children aged 6 to 12 years:

The optimal dosage range is 250-500mg, i.e. 2.5 ml to 5 ml of paracetamol oral solution; these doses may be repeated every 4-6 hours when necessary up to a maximum of 4 doses per 24 hours.

Children under 6 years: Not recommended.

The Elderly: In the elderly, the rate and extent of paracetamol absorption is normal but plasma half-life is longer and paracetamol clearance is lower than in young adults.

4.3 Contra-Indications

Hypersensitivity to paracetamol or any of the other components of the preparation.

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.

Prolonged use except under medical supervision could be harmful.

If symptoms persist for more than 3 days or worsen at any time, consult your doctor.

Do not exceed the recommended dose.

Keep out of the reach and sight of children.

This product contains Glycerol and this is known to be harmful in high doses. It can cause headache, stomach upset and diarrhoea.

The label shall say: "Do not take with any other paracetamol-containing products" and "Immediate medical advice should be sought in the event of an overdose, even if you feel well."

The leaflet shall say: "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."

4.5 Interactions with other Medicaments and other forms of Interaction

Patients who have taken barbiturates, tricyclic antidepressants and alcohol may show diminished ability to metabolize large doses of paracetamol, the plasma half-life of which can be prolonged.

Alcohol can increase the hepatotoxicity of paracetamol overdosage.

Chronic ingestion of anticonvulsants or oral steroid contraceptives induces liver enzymes and may prevent attainment of therapeutic paracetamol levels by increasing first pass metabolism or clearance.

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.

4.6 Pregnancy and Lactation

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

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

4.7 Effects on Ability to Drive and Use Machines

None known.

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 causally related to paracetamol.

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

4.9 Overdosage

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 the risk factors.

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 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,

Patient Information Leaflet

Zapain 500mg/5ml Oral Solution Paracetamol

This leaflet must be read carefully before taking this medicine and kept in a handy place for reference

This leaflet has been prepared to help you use this medicine correctly. However, this leaflet does not tell you everything about your medicine. If you do have any questions, please ask your doctor or pharmacist.

If symptoms persist for more than three days or worsen at any time, consult your doctor.

The name of this medicine is Paracetamol Oral Solution:

Paracetamol oral solution contains paracetamol 500 mg/5ml.

A spoon with 2.5 ml and 5 ml measure is included in the pack so that the medicine can be given accurately.

The active ingredient is: Paracetamol. Each 5 ml of paracetamol oral solution contains 500mg paracetamol. Each 300ml bottle contains 30,000mg paracetamol.

What else is in this medicine?

As well as paracetamol, also contains citric acid monohydrate (E330), purified water, glycerol (E422), sodium citrate (E3311), polyethylene glycol 400, propylene glycol, methylparaben (E21B), propylparaben (E216), raspberry flavour no. 1, saccharin sodium (EB541), erythrosine (E127).

Paracetamol oral solution is raspberry flavoured and sugar free. It is orally available from your pharmacist, in bottles of 300ml.

Pharma Code to go here

Holder of Product Authorisation:

Goldshield Pharmaceuticals Ltd.; NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT, United Kingdom.

Product Licence Number : PL 12762/0173

Manufactured by:

Universal Production (Lytham),

Fairfield, Bradshaw Lane, Greenhaigh,

Kirkham, Proston, Lancashire, PR4, 3JA, UK

Marketed by:

Goldshield Pharmaceuticals Limited.

NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT, United Kingdom.

How Does Your Medicine Work?

Paracetamol oral solution can be used to treat mild to moderate pain and is also used to help reduce fever, headache and to help relieve symptoms of flu and cold.

Paracetamol reduces the feeling of pain in your body. It also acts on the heat regulating part of the brain to reduce sweating and temperature, during fever.

Before using this medicine:

If the answer to any of the following questions is YES, or you are not sure about the answer, tell your doctor, pharmacist, or healthcare professionals:

Are you or the child sensitive (allergic) to products containing paracetamol, or any of the other ingredients listed above?

Are you taking any other products containing paracetamol?

Do you suffer from liver or kidney problem?

Do you take any of the following medicines?

- Barbiturates e.g., Phenobarbitone
- Tricyclic antidepressants e.g., Amitriptyline, Imipramine
- Anticonvulsants e.g., Carbamazepine, Sodium Valproate
- Metoclopramide
- Domperidone
- Cholestyramine

haemorrhage, hypoglycaemia, coma and death. Acute renal failure with acute tubular necrosis, strongly suggested with 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. Any patient who had ingested around 7.5 g or more or paracetamol in the preceding 4 hours should undergo gastric lavage.

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 however 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 represent with serious hepatic dysfunction beyond 24h ingestion should be discussed with the NPIS or a liver unit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

ATC Classification: N02B E01 other analgesics and antipyretics; Anilides

The site and mechanism of the analgesic effect of paracetamol is unclear. Paracetamol reduces fever by a direct action on the hypothalamic heat-regulating centers, which increases dissipation of body heat (via vasodilation and sweating). The action of endogenous pyrogen on heat-regulating centers is inhibited.

Paracetamol is almost as potent as aspirin in inhibiting prostaglandin synthetase in the CNS but its peripheral inhibition of prostaglandin synthesis is minimal, which may account for its lack of clinically significant anti-rheumatic or anti-inflammatory effects.

Paracetamol dose not inhibit platelet aggregation, affect prothrombin response or produce GI ulceration.

5.2 Pharmacokinetic Properties

Absorption: Paracetamol is rapidly an almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur within 0.5 to 2 hours, with slightly faster absorption of liquid preparations.

Distribution : Usual analgesic doses produce total serum concentrations of 5 to 20 mcg/ ml; a good correlation between serum concentration and analgesic effect has not been found. Serum protein binding varies from 20 to 50% at toxic serum concentrations.

Metabolism : Paracetamol is extensively metabolized in the liver by glucuronisation and conjugation with sulphates. Approximately 4% is metabolized via cytochrome P-450 to a toxic metabolite which is normally detoxified by preferential conjugation with hepatic glutathione and excreted in the urine as conjugates of cysteine and mercapturic acid. When paracetamol is used chronically or taken acutely in large doses, glutathione stores are depleted and hepatic necroses may occur.

Elimination : Paracetamol is excreted in the urine, mostly as metabolites; 2 to 4% is excreted unchanged. The average elimination half-life is 1 to 4 hours; half-life is slightly prolonged in neonates (2.2 to 5 hours) and in cirrhotics.

Pharma Code to go here

5.3 Preclinical Safety Data

Data in the literature on toxic doses and serum levels of Paracetamol is limited, but Paracetamol is relatively non-toxic in therapeutic doses.

Paracetamol toxicity may result from a single toxic dose or from long term ingestion of the drug. It has been reported in the literature that children may be less susceptible to acute Paracetamol poisoning than adults. Hepatic necrosis is dose dependent and is the most serious acute toxic effect associated with over dosage. It is potentially fatal, and nausea, vomiting and abdominal pain usually occur within 2-3 hours after ingestion of toxic doses of the drug.

Acute toxic doses of Paracetamol in laboratory animals produce animals produce death from liver and renal damage.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Citric acid monohydrate
Erythrosine (E127)
Glycerol
Macrogol 400
Propylene Glycol
Methyl parahydroxybenzoate
Propyl parahydroxbenzoate
Raspberry flavor No.1
Saccharin Sodium
Sodium citrate
Purified Water

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

Unopened : 24 months
Opened: 3 months

6.4 Special Precautions for Storage

Do not store above 25^{o}C. Store in the original container.

6.5 Nature and Contents of Container

Amber glass bottle with LD-polyethylene, tamper evident and child resistant cap.The bottle is packed in an outer carton.

A spoon with a 5ml and 2.5ml measure is supplied with this pack.

Pack size: 300ml

6.6 Instruction for Use/Handling

No special instruction.

Administrative Data

7. MARKETING AUTHORIZATION HOLDER

Goldshield Pharmaceuticals Limited
NLA Tower 12-16 Addiscombe Road Croydon
Surrey CR0 0XT United Kingdom

8. MARKETING AUTHORIZATION NUMBER

PL 12762/0173

9. Date of first authorization /renewal of authorization

10. Date of revision of the text

September, 2006

Legal Category

P - Pharmacy only.

- Warfarin and other medicines called coumarins
- This medicine contains Propylene glycol which may cause alcohol like symptoms
- This medicine contains Methyl Paraben and Propyl Paraben which may cause allergic reactions (possible delayed)
- This medicine contains Glycerol which may cause headache, upset stomach and diarrhoea

What precautions should be taken?

Always use the measures spoon to give an accurate dosage.

Do not give with any other paracetamol containing product.

Do not exceed the recommended dosage.

Do not use for a prolonged period of time (more than 3 days) without medical supervision.

If symptoms persist or worsen consult your doctor. 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.

How to use paracetamol oral solution:

Ensure the tamper-evident seal on the bottle is intact before first use.

Paracetamol solution has to be taken orally only.

Please follow the dosage instructions exactly.

Always check the dosage before use.

Consult your doctor or pharmacist if you are unsure of the correct dose.

Adults and Children over 12 years:

0.5-1g every 4–6 hours to a max. of 4 g daily

The dose must not be repeated more than 3-4 times in any 24 hour period, and should not be given at intervals of less than 4 hours, unless directed by your doctor.

Pharma Code to go here

Children aged 6 to 12 years:

The optimal dosage range is 250-500mg, i.e. 2.5 ml to 5 ml of paracetamol oral solution; these doses may be repeated every 4-6 hours when necessary up to a maximum of 4 doses per 24 hours.

A spoon with 2.5 ml and 5 ml measure is given so that the medicine can be given accurately.

If too much paracetamol is taken it can harm the liver-this effect is worsened if alcohol is taken at the same time.

Patients who are pregnant or breast feeding should not take paracetamol without first consulting their doctor.

While giving this medicine:

If you have to go to a doctor or hospital, tell them that you have taken this medicine.

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

Immediate medical advice should be sought in the event of an overdose, even if the child seems well.

Undesirable effects:

As with most medicines, paracetamol may cause some undesirable effects such as blood disorders, skin rashes and other allergic reactions. These are usually rare and mild with paracetamol, but tell your doctor if they last more than a few days. Also consult your doctor or pharmacist it you notice any other unwanted effects.

How to store this medicine:

Store at room temperature (below 25ºC) in a dry place and protect from light.

Keep all medicines out of the sight and reach of children.

Do not use the medicine after the "Use before" date printed on the carton.

Remember this medicine is only for you. Never give this medicine to a child or someone else. It could harm them even if their symptoms seem the same as yours

Further Information:

We suggest that you return any unused medicine to your pharmacist.

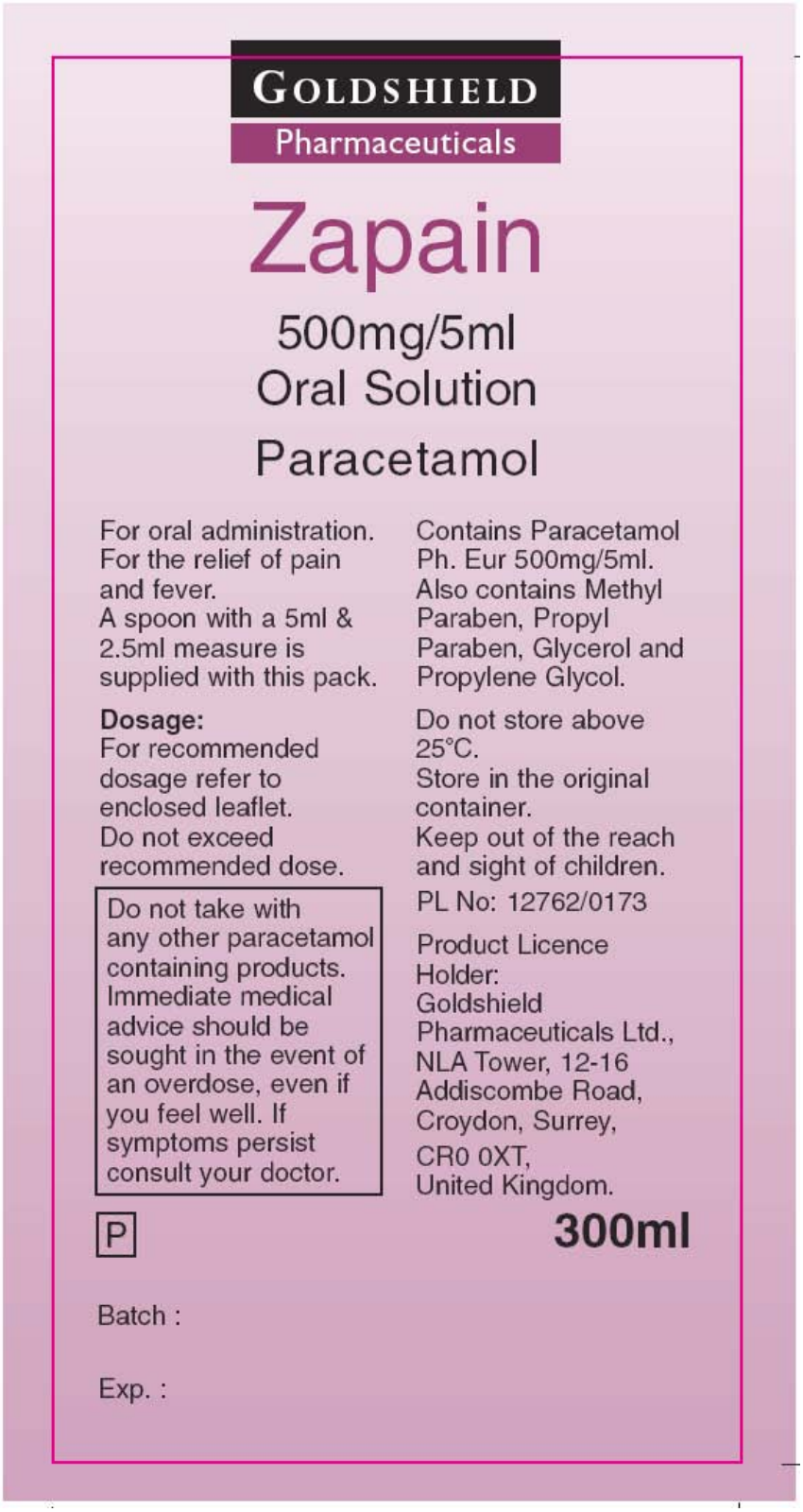
For further information about this product contact:

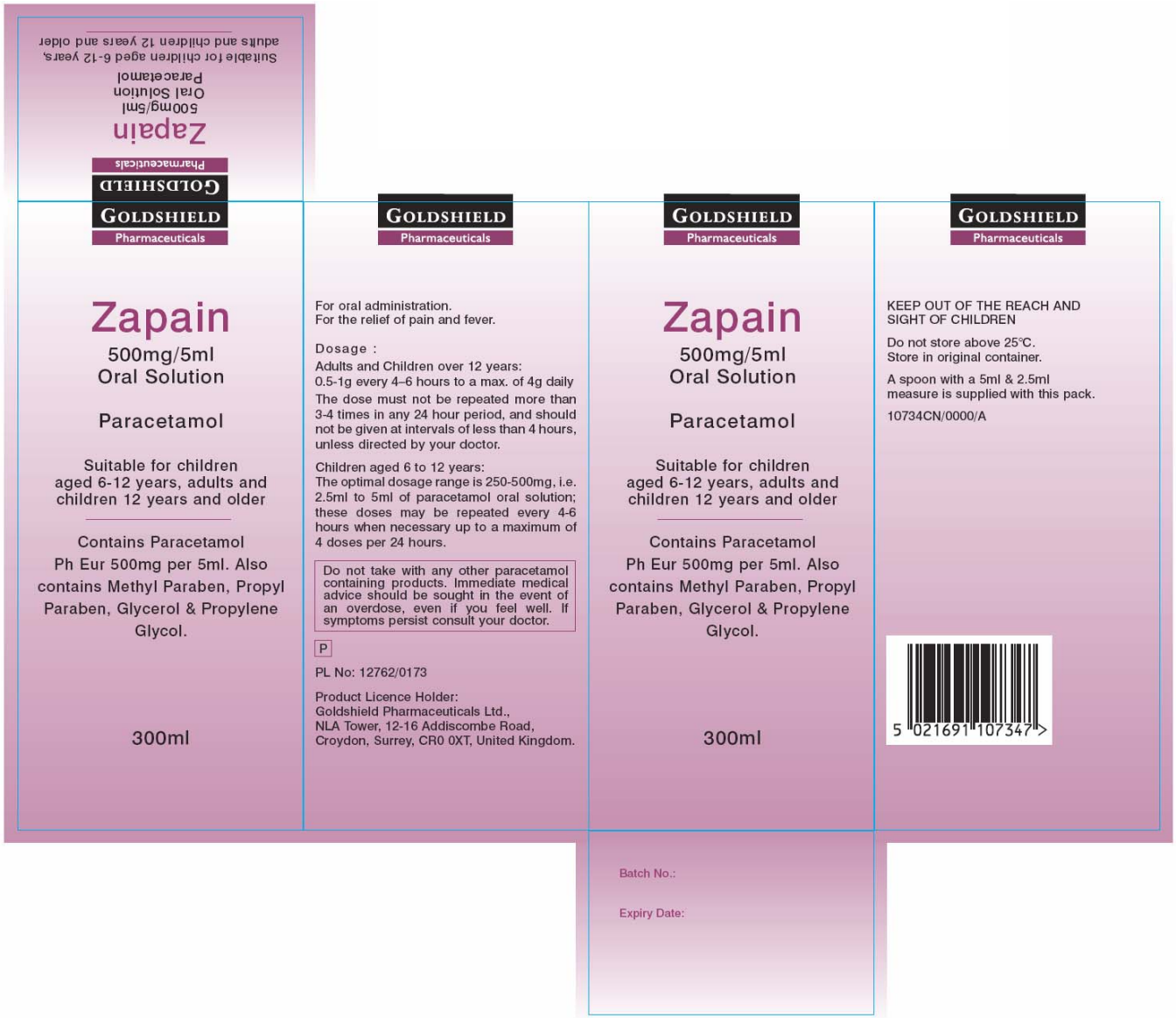
Goldshield Pharmaceuticals Ltd.

NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT, United Kingdom.

Date of last revision: September, 2006. 10734LF/0000/A

LABELLING


GOLDSHIELD
Pharmaceuticals
Zapain
500mg/5ml
Oral Solution
Paracetamol
For oral administration.
For the relief of pain and fever.
A spoon with a 5ml & 2.5ml measure is supplied with this pack.
Dosage:
For recommended dosage refer to enclosed leaflet.
Do not exceed recommended dose.
Do not take with any other paracetamol containing products. Immediate medical advice should be sought in the event of an overdose, even if you feel well. If symptoms persist consult your doctor.
Contains Paracetamol Ph. Eur 500mg/5ml. Also contains Methyl Paraben, Propyl Paraben, Glycerol and Propylene Glycol.
Do not store above 25°C.
Store in the original container.
Keep out of the reach and sight of children.
PL No: 12762/0173
Product Licence Holder:
Goldshield Pharmaceuticals Ltd.,
NLA Tower, 12-16 Addiscombe Road,
Croydon, Surrey,
CR0 0XT,
United Kingdom.
P
300ml
Batch :
Exp. :


Zapain
500mg/5ml
Oral Solution
Paracetamol
Suitable for children aged 6-12 years, adults and children 12 years and older
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300ml
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For the relief of pain and fever.
Dosage :
Adults and Children over 12 years:
0.5-1g every 4–6 hours to a max. of 4g daily
The dose must not be repeated more than 3-4 times in any 24 hour period, and should not be given at intervals of less than 4 hours, unless directed by your doctor.
Children aged 6 to 12 years:
The optimal dosage range is 250-500mg, i.e. 2.5ml to 5ml of paracetamol oral solution; these doses may be repeated every 4-6 hours when necessary up to a maximum of 4 doses per 24 hours.
Do not take with any other paracetamol containing products. Immediate medical advice should be sought in the event of an overdose, even if you feel well. If symptoms persist consult your doctor.
P
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10734CN/0000/A
5 021691 107347
Batch No.:
Expiry Date: