PARACETAMOL 10MG/ML SOLUTION FOR INFUSION
PL 20240/0004

UKPAR

TABLE OF CONTENTS

Lay Summary ......................................................... Page 2
Scientific discussion .............................................. Page 3
Steps taken for assessment ...................................... Page 10
Steps taken after authorisation – summary .............. Page 11
Summary of Product Characteristics .....................
Product Information Leaflet ............................
Labelling .............................................................
On 1st February 2011, the MHRA granted Interdos Pharma BV a Marketing Authorisation (licence) for the medicinal product Paracetamol 10mg/ml Solution for Infusion (PL 20240/0004). This medicine is only available on prescription from your doctor.

This medicine is an analgesic (it relieves pain) and an anti-pyretic (it lowers fever). It is indicated for:
- short-term treatment of moderate pain, especially following surgery
- short-term treatment of fever

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Paracetamol 10mg/ml Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction .......................................................... Page 4
Pharmaceutical assessment ........................................ Page 5
Preclinical assessment .............................................. Page 7
Clinical assessment (including statistical assessment) .......... Page 8
Overall conclusions and risk benefit assessment ................. Page 9
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Paracetamol 10mg/ml Solution for Infusion (PL 20240/0004) to Interos Pharma BV on the 1st February 2011. This is a prescription-only medicine (POM) indicated for the short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

This application was submitted under Article 10.1, claiming to be a generic medicinal product of Efferalgan 500mg comprime, which was first licensed to Bristol-Myers Squibb, France, on 15th June 1982.

Paracetamol 10 mg/ml Solution for Infusion provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours. It also reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

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.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
INN: Paracetamol
Chemical Name: N-(4-hydroxyphenyl)acetamide.
Structure:

![Chemical Structure](image)

Molecular Formula: C₈H₉NO₂
Molecular Weight: 151.2
Physical form: a white, crystalline powder. It is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in dichloromethane.

All aspects of the manufacture and control of the drug substance are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of pharmaceutical excipients, namely mannitol, disodium phosphate dihydrate, hydrochloric acid 0.1M, water for injection, sodium hydroxide solution 0.1M and nitrogen.

All excipients are controlled to their respective European Pharmacopoeia specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

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

Pharmaceutical Development
The objective of the pharmaceutical development programme was to obtain stable intravenous product similar to Perfalgan 10mg/ml solution for Infusion.

Suitable pharmaceutical development data have been provided for this application.

Manufacture
A description and flow-chart of the manufacturing method has been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on three pilot batches of product. The marketing authorisation holder has made a commitment to provide data for validation performed on full-scale batches.
**Finished Product Specification**
The finished product specification is satisfactory. 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.

**Container Closure System**
The solution is contained in a Type I colourless glass vial with bromobutyl stopper and an aluminium/plastic flip-off cap, containing pack sizes of 1 and 12 vial.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with guidelines concerning materials in contact with parenteral products.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months has been set, with storage conditions of “Do not store above 30°C” “Store in the original package” and “Do not refrigerate or freeze”.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are pharmaceutically satisfactory.

**Marketing Authorisation Application Form (MAA)**
The MAA form is pharmaceutically 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**
There is no objection to the approval of the product from a pharmaceutical point of view.
PRECLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well-known. Thus, the applicant has not provided any new pre-clinical data and none are required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There is no objection to the approval of the product from a pre-clinical viewpoint.
CLINICAL ASSESSMENT

Pharmacokinetics
No new data have been submitted and none are required for applications of this type. This application is for a generic medicinal product of Efferalgan 500mg comprime, which was first granted to Bristol-Myers Squibb, France on 15th June 1982. The use of the reference product is well-established.

According to the Committee for Proprietary Medicinal Products Notes for Guidance on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), there is no requirement for a bioequivalence study for products where the active ingredient is present in solution.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.

Clinical safety
No new data have been submitted and none are required for applications of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

The applicant has submitted results of PIL user testing. The results indicate that the PIL 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.

Marketing Authorisation Application (MAA) Forms
The MAA form is medically satisfactory.

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

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Paracetamol 10mg/ml Solution for Infusion 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 applications of this type.

EFFICACY
This application is for a generic medicinal product of Efferalgan 500mg comprime, which was first granted to Bristol-Myers Squibb, France on 15th June 1982. The use of the reference product is well-established.

According to the Committee for Proprietary Medicinal Products Notes for Guidance on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), there is no requirement for a bioequivalence study for products where the active ingredient is present in solution.

No new safety data are supplied or required for this generic application. Paracetamol has well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.
<table>
<thead>
<tr>
<th></th>
<th>STEPS TAKEN FOR ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 2\textsuperscript{nd} December 2008</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 17\textsuperscript{th} December 2008</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information on the quality section on the 29\textsuperscript{th} September 2009 and 10\textsuperscript{th} December 2010 and for the clinical section on the 3\textsuperscript{rd} October 2009 and 10\textsuperscript{th} November 2010</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality section on the 3\textsuperscript{rd} October 2009 and 14\textsuperscript{th} January 2011 and on the clinical section on the 3\textsuperscript{rd} October 2009 and 7\textsuperscript{th} December 2010</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 1\textsuperscript{st} February 2011</td>
</tr>
</tbody>
</table>
PARACETAMOL 10MG/ML SOLUTION FOR INFUSION
PL 20240/0004

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### SUMMARY OF PRODUCT CHARACTERISTICS

1. **NAME OF THE MEDICINAL PRODUCT**
   Paracetamol 10 mg/ml Solution for Infusion

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   One ml contains 10 mg paracetamol
   One 100ml vial contains 1000mg paracetamol.
   Excipients: Sodium 0.04mg/ml
   For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**
   Solution for infusion.
   The solution is clear.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**
   Paracetamol 10 mg/ml Solution for Infusion is indicated for the short-term treatment of
   moderate pain, especially following surgery, and for the short-term treatment of fever, when
   administration by intravenous route is clinically justified by an urgent need to treat pain or
   hyperthermia and/or when other routes of administration are not possible.

4.2. **Posology and method of administration**
   Intravenous use.
   The 100 ml vial is restricted to adults, adolescents, and children weighing more than 33 kg.

   **Posology:**

<table>
<thead>
<tr>
<th>Body weight or age</th>
<th>Single dose</th>
<th>Maximum daily dose (taking all medicinal products containing paracetamol into account)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term newborn infants</td>
<td>No safety efficacy data are available for pre-term newborn infants (see section 5.2).</td>
<td></td>
</tr>
<tr>
<td>Term newborn infants, infants, toddlers and children weighing up to 10 kg (up to approximately 1 year old)</td>
<td>The use of 100 ml vial is not recommended in this group of patients.</td>
<td></td>
</tr>
<tr>
<td>Children weighing more than 10 kg (approximately 1 year old) and up to 33 kg</td>
<td>The use of 100 ml vial is not recommended in this group of patients.</td>
<td></td>
</tr>
</tbody>
</table>
   | Children weighing more than 33 kg (approximately 11 years old), adolescents and adults weighing up to 50 kg | 15 mg/kg paracetamol per administration, i.e 1.5 ml solution per kg. | -Up to four times a day
   |                                                         |                                                         | -The minimum interval between each administration must be 4 hours
   |                                                         |                                                         | -The maximum daily dose must not exceed 60 mg/kg (i.e. maximum daily dose 3 g). |
   | Adolescents and adults weighing more than 50 kg         | 1 g paracetamol per administration, i.e. one 100 ml vial. | -Up to four times a day
   |                                                         |                                                         | -The minimum interval between each administration must be 4 hours
   |                                                         |                                                         | -The maximum daily dose must not exceed 4 g. |
Severe renal insufficiency: it is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance \( \leq 30 \text{ mL/min} \)), to increase the minimum interval between each administration to 6 hours (See section 5.2 Pharmacokinetic properties).

Method of administration:
The paracetamol solution is administered as a 15-minute intravenous infusion. As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the infusion applies particularly for central route infusions, in order to avoid air embolism.

4.3 Contraindications
in patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients,
in cases of severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use
It is recommended that a suitable analgesic oral treatment be used as soon as this route of administration is possible.
In order to avoid the risk of overdose, check that no other medicines administered do not contain paracetamol.
Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of liver damage are not usually seen until two days, and up to a maximum of 4-6 days, after administration. Treatment with antidote should be given as soon as possible (See section 4.9 Overdose).
This medicinal product contains less than 1mmol sodium (23mg) per 100ml of Paracetamol 10 mg/ml Solution for Infusion i.e. essentially 'sodium free'.

Precautions for use
Paracetamol should be used with caution in cases of:
hepatocellular insufficiency,
severe renal insufficiency (creatinine clearance \( \leq 30 \text{ mL/min} \)) (see sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties),
chronic alcoholism,
chronic malnutrition (low reserves of hepatic glutathione),
dehydration.

4.5 Interaction with other medicinal products and other forms of interaction
Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction in the paracetamol dose should be considered if it is to be used concomitantly with probenecid.
Salicylamide may prolong the elimination t½ of paracetamol.
Caution should be taken with the concomitant intake of enzyme-inducing substances (see section 4.9 Overdose).
Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued.

4.6 Pregnancy and lactation
Pregnancy:
Clinical experience of the intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects in pregnancy or on the health of the foetus / newborn infant.
Prospective data on pregnancies exposed to overdoses did not show any increase in the risk of malformation.
No reproductive studies with the intravenous form of paracetamol have been performed in animals. However, studies with the oral route did not show any malformation or foetotoxic effects.
Nevertheless, Paracetamol 10 mg/ml Solution for Infusion should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

**Lactation**

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, Paracetamol 10 mg/ml Solution for Infusion may be used in breast-feeding women.

4.7 **Effects on ability to drive and use machines**

Not relevant.

4.8 **Undesirable effects**

The frequency of adverse events listed below is defined using the following convention:

- very common (≥ 1/10);
- common (≥ 1/100 to /10);
- uncommon (≥ 1/1,000 to 1/100);
- rare (≥ 1/10,000 to < 1/1,000);
- very rare (< 1/10,000),

Not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Malaise</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Increased levels of hepatic transaminases</td>
<td></td>
</tr>
<tr>
<td>Platelet/blood</td>
<td>Thrombocytopenia Leucopenia, Neutropenia</td>
<td></td>
</tr>
</tbody>
</table>

Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment.

4.9 **Overdose**

There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor and abdominal pain.

Overdose, 7.5 g or more of paracetamol in a single administration in adults or 140 mg/kg of body weight in a single administration in children, causes hepatic cytolysis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration.

Clinical symptoms of liver damage are usually evident initially after two days, and reach a maximum after 4 to 6 days.

**Emergency measures**

**Immediate hospitalisation.**

Before beginning treatment, take a blood sample for plasma paracetamol assay, as soon as possible after the overdose.

The treatment includes administration of the antidote, N-acetylcysteine (NAC) by the i.v. or oral route, if possible before the 10th hour. NAC can, however, give some degree of protection even after 10 hours, but in these cases prolonged treatment is given.

**Symptomatic treatment.**

Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours. In most cases hepatic transaminases return to normal in one to two weeks with full return of normal liver function. In very severe cases, however, liver transplantation may be necessary.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: OTHER ANALGESICS AND ANTIPYRETICS, ATC Code: N02BE01

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established: it may involve central and peripheral actions. Paracetamol 10 mg/ml Solution for Infusion provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.

Paracetamol 10 mg/ml Solution for Infusion reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

5.2 Pharmacokinetic properties

Adults

Absorption:
Paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours.
The bioavailability of paracetamol following infusion of 500mg and 1 g of Paracetamol 10 mg/ml Solution for Infusion is similar to that observed following infusion of 1 g and 2 g propacetamol (containing 500mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500mg and 1 g of Paracetamol 10 mg/ml Solution for Infusion is about 15 μg/ml and 30 μg/ml respectively.

Distribution:
The volume of distribution of paracetamol is approximately 1 L/kg.
Paracetamol is not extensively bound to plasma proteins.
Following infusion of 1 g paracetamol, significant concentrations of paracetamol (about 1.5 μg/mL) were observed in the cerebrospinal fluid at and after the 20th minute following infusion.

Metabolism:
Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, during massive overdosing, the quantity of this toxic metabolite is increased.

Elimination:
The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted within 24 hours, mainly as glucuronide (60-80%) and sulphate (20-30%) conjugates. Less than 5% is eliminated unchanged. Plasma half-life is 2.7 hours and total body clearance is 18 L/h.

Neonates, infants and children:
The pharmacokinetic parameters of paracetamol observed in infants and children are similar to those observed in adults, except for the plasma half-life that is slightly shorter (1.5 to 2 h) than in adults. In neonates, the plasma half-life is longer than in infants i.e. around 3.5 hours. Neonates, infants and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.
Table - Age related pharmacokinetic values (standardised clearance, *CL_{std}/Foral (L.h⁻¹ 70kg⁻¹)

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>CL_{std}/Foral (L.h⁻¹ 70kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 weeks PCA</td>
<td>3.3</td>
<td>5.9</td>
</tr>
<tr>
<td>3 months PNA</td>
<td>6</td>
<td>8.8</td>
</tr>
<tr>
<td>6 months PNA</td>
<td>7.5</td>
<td>11.1</td>
</tr>
<tr>
<td>1 year PNA</td>
<td>10</td>
<td>13.6</td>
</tr>
<tr>
<td>2 years PNA</td>
<td>12</td>
<td>15.6</td>
</tr>
<tr>
<td>5 years PNA</td>
<td>20</td>
<td>16.3</td>
</tr>
<tr>
<td>8 years PNA</td>
<td>25</td>
<td>16.3</td>
</tr>
</tbody>
</table>

*CL_{std} is the population estimate for CL.

Special populations:
Renal insufficiency:
In cases of severe renal impairment (creatinine clearance 10-30 mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤30 mL/min), the minimum interval between each administration should be increased to 6 hours (see section 4.2, Posology and method of administration).

Elderly subjects:
The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC. Studies on local tolerance of Paracetamol 10 mg/ml Solution for Infusion in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Disodium phosphate dihydrate
Hydrochloric acid
Mannitol
Sodium hydroxide
Water for Injections

6.2 Incompatibilities
Paracetamol 10 mg/ml Solution for Infusion should not be mixed with other medicinal products.

6.3 Shelf life
18 months.
From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package. Do not refrigerate or freeze.
6.5 **Nature and contents of container**

100 ml Type I colourless glass vial with bromobutyl stopper and an aluminium/plastic flip-off cap.

Pack size: pack of 1, 12 vials.

6.6 **Special precautions for disposal**

Before administration, the product should be visually inspected for any particulate matter and discolouration. For single use only. Any unused solution should be discarded.

7 **MARKETING AUTHORISATION HOLDER**

Interdos Pharma BV,

Burg. Lemmensstraat 352,

6163 JT Geleen,

The Netherlands.

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 20240/0004

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

01/02/2011

10 **DATE OF REVISION OF THE TEXT**

01/02/2011
UKPAR Paracetamol 10mg/ml Solution for Infusion PL 20240/0004

PATIENT INFORMATION LEAFLET (PIL)

Package leaflet: information for the user

Paracetamol 10 mg/ml Solution for Infusion
Paracetamol

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Paracetamol 10 mg/ml Solution for Infusion is and what it is used for
2. Before you take Paracetamol 10 mg/ml Solution for Infusion
3. How to take Paracetamol 10 mg/ml Solution for Infusion
4. Possible side effects
5. How to store Paracetamol 10 mg/ml Solution for Infusion
6. Further information

1. What Paracetamol 10 mg/ml Solution for Infusion is and what it is used for

Paracetamol 10 mg/ml Solution for Infusion is used in:
This medicine is an analgesic (it relieves pain) and an anti-pyretic (it lowers fever).
It is indicated for:
- short-term treatment of moderate pain, especially following surgery
- short-term treatment of fever.

2. Before you take Paracetamol 10 mg/ml Solution for Infusion

Do not take Paracetamol 10 mg/ml Solution for Infusion:
- If you are allergic (hypersensitive) to paracetamol or any of the other ingredients of Paracetamol 10 mg/ml Solution for Infusion. An allergic reaction may include a rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue.
- If you are allergic (hypersensitive) to propacetamol (another analgesic and a precursor of paracetamol)
- If you suffer from a severe liver disease.

Take special care with Paracetamol 10 mg/ml Solution for Infusion
Use a suitable analgesic oral treatment as soon as this administration route is possible.
- If you are taking other medicines containing paracetamol,
- In cases of nutritional problems (malnutrition) or dehydration.

Inform your doctor before treatment if any of the above mentioned conditions apply to you.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or herbal medicines and natural products.
Take particular care if you are taking the following medicines while under treatment with Paracetamol 10 mg/ml Solution for Infusion:
- This medicine should not be given to you if you are taking other paracetamol-containing products, in order not to exceed the recommended daily dose (see following section).
- Inform your doctor if you are taking other medicines containing paracetamol.
- A dose reduction should be considered for concomitant treatment with probenecid.
- Please inform your doctor or pharmacist if you are taking oral anticoagulants. More check-ups to look at the effect of the anticoagulant might be needed.
Pregnancy
Inform your doctor if you are pregnant. Paracetamol 10 mg/ml Solution for Infusion may be used during pregnancy. However, in this case the doctor must evaluate if the treatment is advisable.

Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding
Paracetamol 10 mg/ml Solution for Infusion may be used during breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Not applicable.

Important information about some of the ingredients of Paracetamol 10 mg/ml Solution for Infusion
This medicinal product contains less than 1 mmol sodium (23mg) per 100ml of Paracetamol 10 mg/ml Solution for Infusion i.e. is essentially ‘sodium free’.

3. How to take Paracetamol 10 mg/ml Solution for Infusion
For Intravenous Use.
The use of the 100 ml vial is restricted to adults, adolescents, and children weighing more than 33 kg.
The usual dose is:

<table>
<thead>
<tr>
<th>Body weight or age</th>
<th>Single dose</th>
<th>Maximum daily dose (taking all medicinal products containing paracetamol into account)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term newborn infants</td>
<td>No safety efficacy data are available for pre-term newborn infants (see section 5.2)</td>
<td></td>
</tr>
<tr>
<td>Term newborn infants, infants, toddlers and children weighing up to 15 kg (up to approximately 1 year old)</td>
<td>The use of 100 ml vial is not recommended in this group of patients</td>
<td></td>
</tr>
<tr>
<td>Children weighing more than 10 kg (approximately 1 year old) and up to 33 kg</td>
<td>The use of 100 ml vial is not recommended in this group of patients</td>
<td></td>
</tr>
</tbody>
</table>
| Children weighing more than 33 kg (approximately 11 years old), adolescents and adults weighing up to 60 kg | 15 mg/kg paracetamol per administration, i.e. 1.3 ml solution per kg. | - Up to four times a day  
- The minimum interval between each administration must be 4 hours  
- The maximum daily dose must not exceed 60 mg/kg (i.e. maximum daily dose 3 g). |
| Adolescents and adults weighing more than 50 kg | 1 g paracetamol per administration, i.e. one 100 ml vial | - Up to four times a day  
- The minimum interval between each administration must be 4 hours  
- The maximum daily dose must not exceed 4 g. |

Do not exceed the stated dose.
Kidney disease:
It is recommended when giving paracetamol to patients with severe renal impairment (creatinine clearance 30 mL/min), to increase the minimum interval between each administration to 6 hours.

Administration:
The paracetamol solution is administered as a 15-minute intravenous infusion.
As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the infusion applies particularly for central route infusions, in order to avoid air embolism.
Do not use Paracetamol 10 mg/ml Solution for Infusion if you notice any particulate matter and discolouration.
For single use only. The product should be used immediately after opening. Any unused solution should be discarded.

If you use more Paracetamol 10 mg/ml Solution for Infusion than you should
talk to your doctor or pharmacist immediately. In overdose cases, symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, abdominal pain. Immediate medical advice should be sought in the event of overdose, because of the risk of irreversible liver damage.

If you forget to use Paracetamol 10 mg/ml Solution for Infusion
If you forget to use Paracetamol 10 mg/ml Solution for Infusion, pain or fever is likely to return. Do not take a double dose to make up for forgotten individual doses.

If you have any further questions on the use of Paracetamol 10 mg/ml Solution for Infusion, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, Paracetamol 10 mg/ml Solution for Infusion can cause side effects, although not everybody gets them.
The side effects of medicines are classified as follows:

<table>
<thead>
<tr>
<th>very common</th>
<th>common</th>
<th>uncommon</th>
<th>rare</th>
<th>very rare</th>
<th>not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>more than 1 in 10 treated patients</td>
<td>less than 1 in 10, but more than 1 in 100 treated patients</td>
<td>less than 1 in 100, but more than 1 in 1,000 treated patients</td>
<td>less than 1 in 1,000, but more than 1 in 10,000 treated patients</td>
<td>less than 1 in 10,000 treated patients</td>
<td>(cannot be estimated from the available data)</td>
</tr>
</tbody>
</table>

Rare:
- Malaise;
- A drop in blood pressure;
- Changes in laboratory test results: abnormally high levels of hepatic enzymes found during blood checks. Should this occur, inform your doctor as regular blood checks may be required later.

Very rare:
- A serious skin rash or allergic reaction may occur. Stop the treatment immediately and inform your doctor.

In isolated cases, other changes in laboratory test results have been observed which have necessitated regular blood checks: abnormally low levels of some types of blood cells (platelets, white cells) can occur, possibly leading to bleeding from the nose or gums. Should this occur, inform your doctor.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. How to store Paracetamol 10 mg/ml Solution for Infusion

Keep out of the reach and sight of children.
Do not use Paracetamol 10 mg/ml Solution for infusion after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C. Store in the original package. Do not refrigerate or freeze.

Before administration:
The product should be inspected visually. Do not use Paracetamol 10 mg/ml Solution for Infusion if your notice any particulate matter and discoloration.
For single-use only. The product should be used immediately after opening. Any unused solution should be discarded.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Paracetamol 10 mg/ml Solution for Infusion contains

• The active substance is paracetamol.
  One ml contains 10 mg paracetamol, this vial contains 1000 mg paracetamol in 100 ml.
• The other ingredients are: Disodium phosphate dihydrate, Hydrochloric acid, Mannitol, Sodium hydroxide, Water for Injections.

What Paracetamol 10 mg/ml Solution for Infusion looks like and contents of the pack

Paracetamol 10 mg/ml Solution for Infusion is a clear solution.
Paracetamol 10 mg/ml Solution for Infusion vials are supplied as 100 ml glass vials in packs of 1 or 12 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Intendis Pharma BV
Burg Lemmensaat 352
6103 JT Geleen
The Netherlands

Manufacturer
Delpharm Tours
La Baraudière, Rue Paul Langevin
37170 Charbray-lès-Tours
France

This leaflet was last approved in MM/YYYY
Paracetamol 10mg/ml Solution for Infusion

For single use

10 ml contains 100 mg paracetamol
1 ml contains 10 mg paracetamol
See leaflet

Excipients: Disodium phosphate dihydrate, Hydrochloric acid, Mannitol, Sodium hydroxide, Water for Injections.

EXP: (MM/YYYY)

BN: xxxxx