Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Docpharma 10 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 10 mg paracetamol
One 100 ml vial contains 1000 mg paracetamol.
Excipients: sodium 0.04 mg/ml.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
The solution is clear and slightly yellowish.
pH= 5.0-6.0 ; osmolarity = 280-320 mOsmol/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Paracetamol Docpharma 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.
Paracetamol Docpharma is restricted to adults, adolescents and children weighing more than 33 kg (approximately 11 years old).

Posology:

- Adolescents and adults weighing more than 50 kg:
  Per administration 1000 mg paracetamol, 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.

  In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration:
  The maximum daily dose must not exceed 3 g (see section 4.4).

- Children weighing more than 33 kg (approximately 11 years old), adolescents and adults weighing less than 50 kg:
  Per administration 15 mg/kg paracetamol, 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 (without exceeding 3 g).
- Severe renal insufficiency:
  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 (see section 5.2).

Method of administration:
The paracetamol solution is administered as a 15-minute intravenous infusion.
Before administration, the product should be visually inspected for any particulate matter and discolouration. For

single use only.
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

Paracetamol Docpharma is contraindicated:
- 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

Warnings:
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 other medicines administered do not contain either paracetamol or propacetamol.
Doses higher than those recommended entail the risk of very serious liver damage. Clinical signs and symptoms of liver damage **(**including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are - usually first seen afterl two days of drug administration with a peak seen with a maximum usually after 4 - 6 days., a treatment with antidote should be given as soon as possible (see section 4.9).
This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml of Paracetamol Docpharma i.e. essentially 'sodium free'.

Precautions for use:
Paracetamol should be used with caution in cases of:
- hepatocellular insufficiency,
- severe renal insufficiency (creatinine clearance ≤ 30 ml/min) (see sections 4.2 and 5.2),
- chronic alcoholism,
- chronic malnutrition (low reserves of hepatic glutathione),
- dehydration.

In children treated with 60 mg/kg daily of paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness."

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).
- 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.

- **Hormonal contraceptives/oestrogens**: reduce plasma paracetamol levels, with possible inhibition of its effect, due to possible induction of its metabolism.
-Antiepileptic drugs (**phenytoin, phenobarbital, methylphenobarbital, primidone**): reduction of the bioavailability of paracetamol as well as potentiation of overdose hepatotoxicity due to the induction of hepatic metabolism.
-Chloramphenicol: potentiation of chloramphenicol toxicity, possibly by inhibiting its metabolism in the liver.
-Isoniazid: reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver.
- **Lamotrigine**: decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible

induction of its metabolism in the liver.
- Metoclopramide and **domperidone**: increase the absorption of paracetamol in the small intestine due the effects of these medications on gastric emptying.
- Propranolol: increases plasma paracetamol levels, possibly by inhibiting its metabolism in the liver.
- Rifampicin: increases paracetamol clearance and formation of its hepatotoxic metabolites due to a possible induction of its metabolism in the liver.
- Zidovudine: although a possible increase in the toxicity of zidovudine (neutropenia, hepatotoxicity) has been described in isolated cases, there seems to be no kinetic type interaction between these two drugs.

Interactions with diagnostic tests:
Paracetamol may affect the values of the following analytical determinations:
- Blood: increase (biological) in transaminases (ALT and AST), alkaline phosphatase, ammonia, bilirubin, creatinine, lactate-dehydrogenase (LDH) and urea; increase (interference with test) in glucose, theophylline and uric acid. Increase in prothrombin time (in patients on maintenance warfarin therapy, but with no clinical significance). Reduction (interference with test) of glucose when using the oxidase-peroxidase method.
- Urine: false increases in metadrenaline and uric acid may appear.
- Bentiromide test for assessing pancreatic dysfunction: paracetamol, like bentiromide, is also metabolized to an arylamine, and thus the apparent quantity of paraaminobenzoic acid (PABA) recovered is increased; it is recommended that paracetamol be discontinued at least three days prior to administration of bentiromide.
- Urine 5-hydroxyindoleacetic acid (5-HIAA) determinations: paracetamol may cause false-positive results in qualitative screening tests using nitrosonaphthol reagent. The quantitative test is unaffected.

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 Docpharma 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 Docpharma may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Paracetamol has no influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

As with all paracetamol products, adverse drug reactions are rare (=1/10000, <1/1000) or very rare (1<1/10000). Or not known (cannot be estimated from the available data) They are described below:

Organ System	Rare ≥1/10000 to <1/1000	Very rare <1/10000
Blood and lymphatic system disorders	Platelet disorders, Stemm cell disorders	Thrombocytopenia Leucopenia Neutropenia
Immune system disorders	Allergies (excluding Angioedema)	
Psychiatric disorders	Depression, confusion, hallucinations	

Nervous system disorders	Tremor, Headache	
Eye disorders	Abnormal vision	
Cardiac disorders	Oedema	
Gastrointestinal disorders	Haemorrhage, abdominal pain, diarrhoea, nausea, vomiting	
Hepatobiliary disorders	Abnormal hepatic function, hepatic failure, hepatic necrosis,	Hepatotoxicity, jaundice
Renal and urinary disorders		Sterile pyuria (cloudy urine)
Skin and subcutaneous disorders	Pruritis, rash, sweating, purpura, angioedema, urticaria	
General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, myrexia, sedation, drug interaction	Hypersensitivity reactions (requiring discontinuation of treatment)
Injury, poisoning and procedural complications	Overdose and poisoning	

Cases of erythema, flushing, pruritus and tachycardia have been reported.

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 liver injury (including fulminant hepatitis, hepatic failure,cholestatic hepatitis, cytolytic hepatitis), 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. Immediate emergency measures are necessary even when no symptoms are present.

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. *Doses over 20-25 g are potentially fatal.*

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; anilides,
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 provides onset of pain relief within 5 to 10 minutes after the start of administration by infusion. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.
Paracetamol reduces fever within 30 minutes after the start of administration by infusion with 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 1 g of paracetamol is similar to that observed following infusion of 2 g propacetamol (containing 1 g paracetamol respectively). The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 1 g of paracetamol is about 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.

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).
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 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 3.8%, for pH adjustment
Mannitol
Sodium hydroxide 4.2%, for pH adjustment
Water for Injections

6.2 Incompatibilities

Paracetamol Docpharma must not be mixed with other medicinal products., except for those mentioned in section 6.6.

6.3 Shelf Life

Unopened: 18 months.

From a microbiological point of view, , the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

If diluted in 9 mg/ml (0,9%) sodium chloride solution or 50mg/ml (5%) glucose solution , the solution should be use immediately.

6.4 Special precautions for storage

Do not store above 30°C. Keep vial in the outer carton, in order to protect from light.
For storage conditions after first opening/dilution see section 6.3.

6.5 Nature and contents of container

100 ml type I clear glass vial with bromobutyl rubber stopper, aluminium cap and plastic flip-off.

Pack size: pack of 1 or 12 vials.
Not all pack size may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Any unused solution should be discarded.
The product can be diluted in 9 mg/ml (0,9%) sodium chloride solution or in 50mg/ml (5%) glucose solution ; the diluted solution should be used immediately.
Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

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Terhulpsesteenweg 6A
1560 Hoeilaart
Belgium

8 MARKETING AUTHORISATION NUMBER

PA 1506/2/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 2010

10 DATE OF REVISION OF THE TEXT