IFIMOL® IV

Paracetamol Infusion IP 10 mg/ml

COMPOSITION

Each ml contains:

Paracetamol IP……..……10mg

Water for Injection IP……..…..q.s.

DOSAGE FORM AND STRENGTH

Solution for infusion

THERAPEUTIC INDICATIONS

Ifimol IV 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.

PSOLOGY AND METHOD OF ADMINISTRATION

Intravenous route.

The 100 ml FFS bottle is restricted to adults, adolescents and children weighing more than 33 kg.

Dosing based on patient weight (please see the dosing table here below)

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of Paracetamol (10 mg/mL) per administration based on upper weight limits of group (mL)****	**Maximum Daily Dose *****
> 33 kg to 50kg	15 mg/kg	1.5mL/kg	75 mL	60mg/kg not exceeding 3g

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume per administration ****	**Maximum Daily Dose *****
> 50 kg with additional risk factors for hepatotoxicity	1 g	100 mL	100 mL	3 g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100 mL	100 mL	4 g

** Patients weighing less will require smaller volumes.

The minimum interval between each administration must be at least 4 hours. No more than 4 doses to be given in 24 hours.

The minimum interval between each administration in patients with severe renal insufficiency must be at least 6 hours.

*** Maximum daily dose: The maximum daily dose as presented in the table above is for patients that are not receiving other paracetamol containing products and should be adjusted accordingly taking such products into account.

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.

Hepatic insufficiency

In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration:

The maximum daily dose must not exceed 3 g

Method of administration

Take care when prescribing and administering paracetamol IV to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume.

The paracetamol solution is administered as a 15minute intravenous infusion.

Text for the 100ml FFS bottle:

To remove solution, use a 0.8 mm needle (21 gauge needle) and vertically perforate the stopper at the spot specifically indicated.

As for all solutions for infusion presented in FFS bottle, 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 perfusion applies particularly for central route infusion, in order to avoid air embolism.

The solution is to be inspected visually for particulate matter and discolouration prior to administration and should only be used if it is clear and free from particles.

CONTRAINDICATIONS

Ifimol IV is contraindicated:

- In patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to one of the excipients.
- In cases of severe hepatocellular insufficiency.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

RISK OF MEDICATION ERRORS

Take care to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and death.

It is recommended to use a suitable analgesic oral treatment as soon as this administration route 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 the recommended entails risk for very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually first seen after two days of drug administration with a peak seen usually after 4-6 days. Treatment with antidote should be given as soon as possible.

Hepatic Injury: Administration of paracetamol in doses higher than recommended may result in hepatic injury, including the risk of liver failure and death. Do not exceed the maximum recommended daily dose of paracetamol.

Text for the 100ml FFS bottle:

As for all solutions for infusion presented in FFS bottle, a close monitoring is needed notably at the end of the infusion.

Precautions for use

Paracetamol should be used with caution in cases of:

- Hepatocellular insufficiency,
- Severe renal insufficiency (creatinine clearance ≤ 30 mL/min),
- Chronic alcoholism,
- Chronic malnutrition (low reserves of hepatic gluthatione),
- Dehydration.

DRUG INTERACTIONS

Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.

Salicylamide may prolong the elimination $t_{1/2}$ of paracetamol.

Caution should be paid to the concomitant intake of enzyme-inducing substances.

Concomitant use of paracetamol (4g 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.

USE IN SPECIFIC POPULATIONS

Pregnancy:

Clinical experience of intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus / newborn infant.

Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any malformation of foetotoxic effects. Nevertheless, paracetamol IV should only be used during pregnancy after a careful benefit risk assessment. In this case, the recommended dosage 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 IV may be used in breast-feeding women.

UNDESIRABLE EFFECTS

As all paracetamol products, adverse drug reactions are rare (>1/10000, <1/1000) or very rare (<1/10000), they are described below:

Organ system	**Rare >1/10000, <1/1000**	**Very rare <1/10000**
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased levels of hepatic transaminases	
Platelet / blood		Thrombocytopenia, Leucopenia, Neutropenia

Frequent adverse reactions at injection site have been reported during clinical trials (pain and burning sensation).

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

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, abdominal pain. Overdose, 7.5 g or more of paracetamol in a single administration in adults and 140 mg/kg of body weight in a single administration in children, cause 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 tube of blood 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 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 restitution of liver function. In very severe cases, however, liver transplantation may be necessary.

CLINICAL PHARMACOLOGY

Pharmacodynamics properties

Pharmacotherapeutic group: other analgesics and antipyretics.

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

Paracetamol IV 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 IV reduces fever within 30 minutes after the start of administration with duration of the antipyretic effect of at least 6 hours.

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 500 mg and 1 g of paracetamol is similar to that observed following infusion of 1 g and 2 g propacetamol (corresponding to 500 mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15 minutes intravenous infusion of 500 mg and 1 g of paracetamol 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 (25%) to plasma proteins.

Following infusion of 1 g paracetamol, significant concentrations of paracetamol (about 1.5 µg/mL) were observed in the Cerebro Spinal Fluid as and from 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 in 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 2h) 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 (standardized clearance, *CLstd/Foral ($l.h^{-1}$ 70 kg^{-1}), are presented below.*

Age	Weight (kg)	CL_{std}/Foral ($l.h^{-1}$ 70 kg^{-1})
40 weeks PCA	3.3	5.9
3 months PNA	6	8.8
6 months PNA	7.5	11.1
1 year PNA	10	13.6
2 years PNA	12	15.6
5 years PNA	20	16.3
8 years PNA	25	16.3

*CLstd 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, 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.

Elderly subjects

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

NONCLINICAL PROPERTIES

Animal Toxicology and/or Pharmacology

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the pack insert.

Studies on local tolerance of paracetamol IV in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

DESCRIPTION

Paracetamol, also known as acetaminophen. Paracetamol is a p-aminophenol derivative with analgesic and antipyretic activities. The molecular formula is $C_8H_9NO_2$. IUPAC name is N-(4-hydroxyphenyl) acetamide.

INCOMPATABILITIES

Paracetamol IV should not be mixed with other medicinal products.

STORAGE AND HANDLING INSTRUCTIONS:

Store below 30°C. Protect from light & moisture. Do not freeze.

Keep out of reach of children.

PACKAGING INFORMATION:

100 ml bottle

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

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Note: This prescribing information is applicable for India Market only.