PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM

INTRAMOL (Solution for Intravenous Infusion)

COMPOSITION

Each 100 ml vial contains 1000 mg paracetamol as active ingredient (each 1 ml of infusion solution contains 10 mg of paracetamol)

Excipients: Mannitol; anhydrous disodium hydrogen phosphate; water for injection.

Contains mannitol.

PHARMACOLOGICAL CLASSIFICATION

A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Paracetamol, also known as acetaminophen, has analgesic and antipyretic properties.

The mechanism of analgesic and antipyretic action has not been fully determined.

Pharmacokinetic properties

Absorption

Paracetamol pharmacokinetics is linear up to 2 g after a single administration and after repeated administration during 24 hours.

The maximal plasma concentration (C_{max}) of about 30 µg/ml paracetamol is observed after 15 minutes of an intravenous infusion of 1 g of paracetamol.

Distribution

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of paracetamol to plasma proteins is variable. Only about 20 % is bound to plasma proteins. The volume of distribution is about 0,95 l/kg.

Significant concentrations of paracetamol of about 1,5 µg/ml are observed in the cerebrospinal fluid after about 20 minutes of a 1 g paracetamol intravenous infusion.

Metabolism

Paracetamol is metabolised in the liver by conjugation with glucuronic acid (60 %), sulphuric acid (35 %), and cysteine (± 3 %).

A minor hydroxylated metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive intermediate, is usually produced in very small amounts by cytochrome P450 isoenzymes in the liver.

NAPQI is usually detoxified by conjugation with glutathione. After paracetamol overdosage, this metabolite accumulates, depletes hepatic glutathione sulfhydryl groups and contributes significantly to the toxic effects of overdose.

Neonates, infants and children up to ten years have less glucuronidation capacity of paracetamol and more sulphate conjugates than adults.

Elimination

Less than 5 % is excreted as unchanged paracetamol.

Some 90 % to 100 % of the dose may be recovered in the urine as metabolites within the first 24 hours of administration, mainly as the glucuronide (60 to 80 %) and sulphate (20 to 30 %) conjugates.

The plasma half-life of paracetamol is 2,7 hours for adults, 1,5 to 2 hours for infants and children.

Special populations

Renal insufficiency

In cases of severe renal impairment (creatinine clearance 10 to 30 ml/min), the elimination of paracetamol is 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 to leave an interval of at least 6 hours between administrations in

patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) (see "DOSAGE AND DIRECTIONS FOR USE").

Hepatic impairment

Paracetamol should be administered with caution to patients with hepatic impairment (see "CONTRAINDICATIONS" and "DOSAGE AND DIRECTIONS FOR USE"). Hepatic impairment may decrease the clearance of paracetamol or increase the probability of hepatic toxicity.

INDICATIONS

INTRAMOL is indicated for the short-term treatment (not exceeding 24 hours) of mild to moderate pain e.g. after dental procedures and minor orthopaedic procedures, and the short-term treatment of fever, when the oral route is unsuitable.

CONTRAINDICATIONS

INTRAMOL is contraindicated in

- cases of hypersensitivity to paracetamol or to paracetamol hydrochloride (prodrug of paracetamol) or to any of the excipients of INTRAMOL
- cases of severe hepatocellular insufficiency, decompensated active liver disease including alcoholic hepatitis and hepatic failure
- children weighing less than 33 kg (approximately 11 years old) as safety and efficacy have not been established

WARNINGS

Dosages of INTRAMOL in excess of those recommended may cause severe liver damage.

Clinical symptoms and signs of liver damage are usually seen first after two days with a maximum usually after 4 to 6 days. Treatment with an antidote should be given as soon as possible (see "KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT").

In order to avoid the risk of overdose, check that the other medicines administered do not contain paracetamol.

INTRAMOL contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

It is recommended to use a suitable oral analgesic treatment as soon as this administration route is possible.

Renal impairment

In patients with renal impairment with a creatinine clearance of 30 ml/minute or less, the elimination of paracetamol is delayed, therefore a 6 hourly dose interval is recommended (see "DOSAGE AND DIRECTIONS FOR USE").

INTRAMOL should be administered with caution in patients suffering from renal disease, prolonged excessive use of INTRAMOL can produce nephropathy. Paracetamol-induced renal function impairment may be severe and could result in uraemia, especially with prolonged use of high doses (see "INTERACTIONS").

Hepatotoxicity

The risk of paracetamol toxicity may be increased in patients receiving potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes (see "INTERACTIONS").

Patients suffering from alcoholism, liver disease or malnutrition are at special risk of hepatic damage and should not be administered excessive quantities of INTRAMOL.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with INTRAMOL must immediately be discontinued and appropriate treatment instituted.

INTERACTIONS

Alcohol, hepatic enzyme inducers or hepatotoxic medications: Patients have an increased risk of hepatotoxicity with concurrent use of high doses or prolonged use of INTRAMOL concurrently with chronic alcohol abuse, taking hepatic enzyme inducers (such as barbiturates, isoniazid, zidovudine, phenytoin, rifampicin, carbamazepine, primidone) - or hepatotoxic medications.

Warfarin: The anticoagulant effect may be increased when high doses of INTRAMOL are used together with anticoagulants, such as warfarin. Increased monitoring of INR values should be conducted during and one week after concomitant use.

This does not apply to occasional use or if chronic use doses are below 2 g INTRAMOL per day.

Non-steroidal anti-inflammatory medicine (NSAID's), aspirin or other salicylates: Salicylates in prolonged treatments together with INTRAMOL significantly increased the risk of analgesic nephropathy, renal papillary necrosis, end-stage renal diseases, and cancer of the urinary bladder. Do not exceed the recommended individual dosages for salicylates and INTRAMOL.

Prolonged use of INTRAMOL and other NSAID's may increase the risk of adverse renal effects.

Probenecid: Probenecid causes an almost 2-fold reduction in paracetamol clearance and increases its plasma half-life by decreasing the urinary excretion of the sulphate and glucuronide conjugates of paracetamol. A decrease in INTRAMOL dose should be considered when administered concomitantly with probenecid.

PREGNANCY AND LACTATION

Pregnancy

Clinical experience of intravenous administration of INTRAMOL is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects of pregnancy or on the health of the foetus/new-born infant. Nevertheless, INTRAMOL 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 breastfed infants have been reported. However, caution should be used when administering INTRAMOL to women who are breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE

DO NOT EXCEED THE RECOMMENDED DOSE.

The prescribed dose must be based on the patient's weight.

Unintentional overdose

Unintentional overdose can lead to serious liver damage and death. Unintentional overdose has a significant reduced survival compared with intentional overdose. The weight-related dose recommendations, individual patient risk factors for hepatotoxicity (see "SPECIAL PRECAUTIONS") and pattern of overdose should be taken into account when assessing patients with paracetamol-induced hepatotoxicity. Irrespective of the patient's admission paracetamol concentrations, patients with unintentional overdose should be managed as high-risk cases due to their significant increased mortality (see "KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT").

Adults and adolescents weighing more than 50 kg

1 g INTRAMOL 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 in 24 hours.

Children weighing more than 33 kg, adolescents and adults weighing less than 50 kg

INTRAMOL: 15 mg/kg per administration, i.e. 1,5 ml solution per kg up to 4 times per day. The minimum interval between each administration must be 4 hours for these patients (underweight adults etc.). The maximum daily dose must not exceed 60 mg/kg and must not exceed 3 g in 24 hours.

The dosage should be calculated on non-oedematous weight.

The maximum daily dose takes into account all the medicines containing paracetamol.

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

Recommended dosage in patients with severe renal insufficiency

It is recommended to leave a minimum interval of 6 hours between each administration in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) (see "WARNINGS" and "Pharmacokinetic properties").

Recommended dosage in patients with hepatic impairment

In patients with chronic or compensated active hepatic disease, the maximum daily dose should not exceed 3 g per day. Hepatic failure or decompensated active liver disease should be regarded as a contraindication to INTRAMOL use (see "CONTRAINDICATIONS").

Method of administration

INTRAMOL should be administered as a 15-minute intravenous infusion. It is intended for single-use only.

Before administration, the product should be visually inspected for any particulate matter and discolouration e.g. yellowing.

Once opened, the vial should be used immediately.

Careful monitoring to avoid air embolism is needed, notably at the end of the infusion, especially if a central venous catheter is used for the infusion.

Any unused solution should be discarded.

INTRAMOL should not be mixed with other medicinal products.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects

Blood and lymphatic system disorders

Less frequent: Agranulocytosis, anaemia, thrombocytopenia

Leukopenia, pancytopenia, neutropenia

Vascular disorders

Less frequent: Hypotension

Cardiac disorders

Less frequent: Tachycardia

Hepato-biliary disorders

Less frequent: Hepatitis, hepatic necrosis, hepatic failure

Pancreatitis, increased levels of hepatic transaminases

Gastrointestinal disorders

Frequency unknown: Nausea, vomiting

Skin and subcutaneous tissue disorders

Less frequent: Dermatitis, allergic skin rash, erythema, flushing, pruritus, urticaria

Renal and urinary disorders

Less frequent: Renal colic, renal failure, sterile pyuria

Immune system disorders

Less frequent: Hypersensitivity, anaphylactic shock, angioedema

General disorders and administrative site conditions

Less frequent: Malaise, administration site reaction

Post-marketing experience:

Skin and subcutaneous tissue disorders

Frequency unknown: Acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE.

Special Precautions

INTRAMOL should be used with caution in cases of:

- hepatocellular insufficiency (see "WARNINGS")
- anorexia, bulimia or cachexia, chronic malnutrition, (low reserves of hepatic glutathione)

- severe renal insufficiency (creatinine clearance ≤ 30 ml/min) (see "WARNINGS" and "DOSAGE AND DIRECTIONS FOR USE")
- chronic alcoholism, excessive alcohol intake (3 or more alcoholic drinks every day)
- hypovolaemia
- dehydration
- glucose-6-phosphate dehydrogenase (G6PD) deficiency may lead to haemolytic anaemia

Effects on ability to drive and use machines

INTRAMOL should have no influence on the ability to drive and the use of machines. No unwanted effects which could influence the ability to drive and to operate machinery have been reported by patients using INTRAMOL.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Prompt treatment is essential in the event of an overdosage. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 10 g per day) of paracetamol for several days. There is a risk of poisoning, particularly in chronic alcoholism, chronic liver disease, AIDS, malnutrition, elderly subjects, young children and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine. Overdosing may be fatal in these cases.

Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours, or later after administration of INTRAMOL, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin

concentration and prolongation of the prothrombin or INR time. These changes may appear only in 12 to 48 hours after administration. Clinical symptoms of liver damage are usually evident initially only after 2 days, and reach a maximum after 4 to 6 days. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

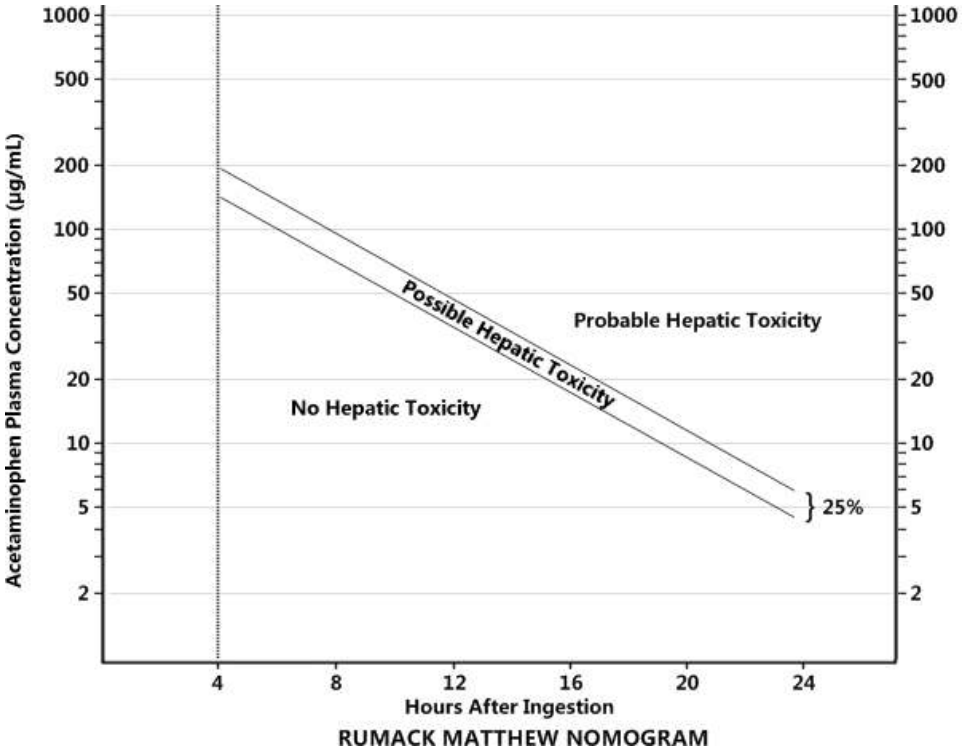
Treatment for paracetamol overdosage following IV administration of INTRAMOL

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

N-acetylcysteine (NAC) should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after the overdose may still be of benefit, especially if more than 150 mg/kg of paracetamol was administered and taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose 5 % *w/v* injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose 5 % *w/v* injection over the next four hours, and then 100 mg/kg in 1 000 ml dextrose 5 % *w/v* injection over the next sixteen hours. Sodium chloride 0,9 % *w/v* may be used where glucose 5 % *w/v* is unsuitable. **The volume of intravenous fluid should be modified for children.**

Though the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

After an overdosage with an intravenous infusion, the standard nomogram used for determining treatment from paracetamol plasma concentrations following oral ingestion of an overdose of paracetamol, may not be appropriate. Paracetamol plasma concentrations more than 4 hours after intravenous injection may be lower than those predicted for the same oral dose at the same time point after ingestion.



Adapted from the following sources: Martindale, The Complete Drug Reference, 36th Edition, page 109, fig. 1.2 and Goodman and Gilman 11th Edition, page 694, fig 26.2.

Those whose plasma paracetamol levels are above the "normal treatment line" (the top plotted line), should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the "high risk treatment line" (the bottom plotted line). Prothrombin index correlates best with survival.

Monitor all patients with significant overdose for at least ninety six hours.

- Treatment is symptomatic and supportive.
- 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 the liver function. In very severe cases however liver transplantation may be necessary.

IDENTIFICATION

INTRAMOL (1 % *w/v*) is in the form of sterile infusion solution. The product is clear colourless to yellowish solution, free of visible particulate matter.

PRESENTATION

INTRAMOL is presented in transparent 100 ml low density polyethylene (LDPE) bottles sealed with a white, low density polyethylene (LDPE) cap. The bottle is packed in an outer polyethylene bag in an outer cardboard carton.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from light. Do not refrigerate or freeze.

Single use only, discard any remaining portion.

Store the bottle in the outer carton until required for use.

Use immediately after opening.

Do not use the bottle if the plastic bag is missing or tampered with.

Do not administer if the solution contains any visible particulate matter.

KEEP OUT OF SIGHT AND REACH OF CHILDREN

REGISTRATION NUMBER

47/2.7/0570

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