Rx PARACETAMOL

AMGESIC

300 mg/ 2 mL Solution for Injection (IM/IV)

Analgesic

Formulation:
Each 2 mL ampoule contains:
Paracetamol CP.....300 mg

Product Description:
Amgesic Solution for Injection is a clear, colorless with charactestic odor solution.

Indications: Paracetamol is used for the relief of mild to moderate pain and fever.

Pharmacokinetics: Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours. Paracetamol is metabolised predominantly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. A minor hydroxylated metabolite (*N*-acetyl-*p*-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate following paracetamoloverdosage and cause tissue damage.

Absorption: The absorption of paracetamol was slow and incomplete in vegetarian subjects compared with non-vegetarian subject.

Dosage and Administration:
Recommended Dose: 10 mg/Kg body weight/dose, to be given by slow IV push or by deep IM Injection, every 4 to 6 hours while symptoms persist, or approximately as follows:

Age Group	IV/IM dose every 4 to 6 hrs
Children:	
Below 6 mos.	0.25 to 0.5 mL
6 to 12 mos.	0.5 to 0.75 mL
1 to 2 yrs	0.75 to 1 mL
3 to 6 yrs	1 to 1.25 mL
7 to 12 yrs	1.25 to 2 mL
Adults:	2 to 4 mL
Or as prescribed by physician	

Do not exceed 5 doses in each 24-hr period and do not give for more than 5 days unless directed by physician.
Note: Strict aseptic technique should be observed when drawing up the contents of the ampule. If injection ampules become contaminated, they have the potential to become a source of infection to patients.

For Children:
Must be given every 4 to 6 hours when necessary up to maximum of 4 doses in 24 hours.

3months to 1 year: 60 to 120mg
1 to 5 years: 120mg to 250mg
6 to 12 years: 250mg to 500mg

For Neonates:
(28 to 32 week) postmenstrual age:
20mg/kg as a single dose then 10 to 15 mg/kg every 8 to 12 hours if necessary up to a max.of 30mg/kg daily.

Over 32 weeks postmenstrual age: 20mg/kg as a single dose then 10 to 15mg/kg every 6 to 8 hours if necessary up to max. of 60mg/kg daily.
1 to 3 months of age: 30 to 60mg every 8 hours if necessary.
Children with more *severe* symptoms: children aged 1 to 3 months may be given 20 mg/kg as a single dose followed by 15 to 20 mg/kg every 6 to 8 hours if necessary up to a maximum of 60 mg/kg daily; older children may also be given 20 mg/kg every 6 hours to a maximum of 90 mg/kg daily for 48 hours or longer if necessary followed by 15 mg/kg every 6 hours.
For post-immunisation pyrexia, a dose of 60 mg has been recommended for children 2 to 3 months of age. If necessary a second dose may be given after six hours; if the pyrexia persists after that dose, medical advice should be sought.
Paracetamol may also be given as suppositories in an adult **rectal** dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily.
Rectal doses in younger children:
neonates 28 to 32 weeks postmenstrual age, 20 mg/kg as a single dose then 15 mg/kg every 12 hours if necessary to a maximum of 30 mg/kg daily
neonates over 32 weeks postmenstrual age, 30 mg/kg as a single dose then 20 mg/kg every 8 hours if necessary to a maximum of 60 mg/kg daily
1 to 3 months of age, 30 to 60 mg every 8 hours if necessary to a maximum of 60 mg/kg daily
3 to 12 months of age, 60 to 125 mg every 4 to 6 hours if necessary to a maximum of 4 doses in 24 hours
5 to 12 years of age, 250 to 500 mg every 4 to 6 hours if necessary to a maximum of 4 doses in 24 hours
for *severe* symptoms, children aged 1 to 3 months may be given 30 mg/kg as a single dose followed by 20 mg/kg every 8 hours to a maximum of 60 mg/kg daily; older children may be given 40 mg/kg as a single dose followed by 20 mg/kg every 4 to 6 hours to a maximum of 90 mg/kg daily for 48 hours or longer, if necessary, before reducing to 15 mg/kg every 6 hours. Again, the usual adult maximum would apply in heavier children.
Paracetamol by **intravenous** infusion to adults and children over 10 kg in weight. Dosage may be calculated by weight as follows:
patients weighing over 50 kg, single doses of 1 g every 4 or more hours, to a maximum of 4 g daily
from 33 to 50 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 3 g daily (whichever is less)
between 10 and 33 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 2 g daily (whichever is less).

Overdosage:
Acute overdosage with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and **toxic doses**. Ingestion of as little as 10 to 15 g of paracetamol by adults may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Patients should be considered at risk of severe liver damage if they have ingested more than 150 mg/kg of paracetamol or 12 g or more in total, whichever is the smaller. The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses; however, chronic use of supratherapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity.
Early **signs** of overdosage (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Hepatic failure, encephalopathy, coma, and death may result. Complications of hepatic failure include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. Prothrombin time increases with deteriorating liver function and some recommend that it be measured regularly.
Measurement of serum concentrations of aspartate aminotransferase and alanine aminotransferase is also of value.Patients receiving enzyme-inducing drugs or those with a history of alcohol abuse are at special risk of hepatic damage, as may be patients suffering from malnutrition such as those with anorexia or AIDS. It has also been suggested that fasting may predispose to hepatotoxicity.
Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage.
Other non-hepatic symptoms that have been reported following paracetamoloverdosage include myocardial abnormalities and pancreatitis.
The **mechanism** of toxicity in overdosage with paracetamol is thought to be the production of a minor but highly reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NABQI) by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4)in the liver and kidney. The amount of NABQI produced after normal doses of paracetamol is usually completely detoxified by conjugation with glutathione and excreted as mercaptopurine and cysteine conjugates. In paracetamoloverdosage, tissue stores of glutathione become depleted, allowing NABQI to accumulate and bind to sulfhydryl groups within hepatocytes causing cell damage. Substances capable of replenishing depleted stores of glutathione, such as acetylcysteine or methionine, are therefore used as antidotes in paracetamoloverdosage. Acetylcysteine may also be involved in the repair of damaged tissue.

Treatment of ParacetamolOverdosage:
Prompt treatment is essential, even when there are no obvious symptoms, and all patients should be admitted to hospital; full supportive measures should also be instituted.
Activated charcoal may be used to reduce gastrointestinal absorption, if it can be given within 1 hour of the overdose, and if more than 150 mg/kg of paracetamol has been ingested. However, if acetylcysteine or methionine is to be given by mouth the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote
There is little evidence that gastric lavage is of benefit in those who have overdosed solely with paracetamol
The plasma-paracetamol concentration should be determined as soon as possible, but not within 4 hours of ingestion, to ensure that peak concentrations are recorded. The risk of liver damage is determined by comparison with a nomogram reference line on a plot of plasma-paracetamol concentration against hours after ingestion. A semi-logarithmic plot or a linear plot may be used. Generally, antidote treatment is required if the patient's plasma-paracetamol concentration is higher than the appropriate line (but see below)
Patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, rifampicin, and St John's wort, or those with malnutrition or a history of alcohol abuse, are considered at high risk, and should receive an antidote even if their plasma-paracetamol concentrations are up to 50% below the standard reference line
Plasma-paracetamol concentrations measured more than 15 hours after ingestion are not reliable indicators of hepatic toxicity. Furthermore, the nomogram may not be suitable for use when patients have taken modified-release preparations of paracetamol.Some suggestions for modified strategies for the use of the Rumack-Matthew nomogram in the face of overdosage with modified-release preparations have been made.
Plasma-paracetamol concentrations are also of little value in patients who have taken several overdoses of paracetamol over a short period of time: such patients should be considered as at serious risk and given antidote treatment
Deaths from liver failure have occurred in patients presenting with plasma-paracetamol concentrations below the treatment line: suggested explanations include inadequate patient histories and a need for a lower treatment threshold.
If there is any doubt about timing or the need to treat, then a patient **should** be treated with an antidote. In some centres, patients who have ingested 150 mg/kg or more of paracetamol are treated

regardless of plasma-paracetamol concentrations.
Antidote treatment should be started as soon as possible after suspected paracetamol ingestion and should not be delayed while awaiting the results of plasma assays. Once the results become available, treatment may be stopped if the initial concentration was below the nomogram reference line. However, if the initial concentration is above the reference line, the full course of antidote must be given and should not be stopped when subsequent plasma concentrations fall below the reference line.
*Choice of antidote.*Acetylcysteine is usually the antidote of choice but the route of administration varies, and the best protocol has yet to be determined.Intravenous use has been associated with anaphylactic reactions but is the preferred route in the UK because of fears that oral absorption might be reduced by vomiting or activated charcoal. However, in the USA the oral route is usual, and is clearly effective. The use of methionine by mouth is licensed in the UK, despite the same risks of impaired absorption due to vomiting or activated charcoal. It is cheaper and easier to give than intravenous acetylcysteine and may be used in situations where a patient cannot be transferred to hospital, provided it is given within 10 to 12 hours of the overdose and the patient is not vomiting.
Acetylcysteine is most effective when given during the first 8 hours after taking the overdose and the effect diminishes progressively thereafter. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might aggravate the risk of hepatic encephalopathy. However, late treatment was subsequently shown to be safe,and studies of patients treated up to 36 hours after ingestion suggest that benefit may be obtained up to and possibly beyond 24 hours.Furthermore, giving intravenous acetylcysteine to patients who had already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.
In the UK, an initial dose of 150 mg/kg of acetylcysteine in 200 mL of glucose 5% is given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg in one litre over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable. The volume of intravenous fluids should be modified for children. If an anaphylactoid reaction develops, the infusion should be stopped and an antihistamine given; it may be possible to continue the acetylcysteine infusion at a slower rate

In the USA, acetylcysteine is given by mouth in an initial dose of 140 mg/kg as a 5% solution followed by 70 mg/kg every 4 hours for an additional 17 doses. Somehave suggested increasing the loading dose of oral acetylcysteine when it is given after activated charcoal, whereas othershave found that the efficacy of acetylcysteine is not reduced by use of activated charcoal beforehand and consider a larger acetylcysteine dose unnecessary.
Methionine, like acetylcysteine, is most effective when given as early as possible after paracetamoloverdosage. However, it is not as effective if treatment is delayed and hepatic damage is more frequent and severe if treatment with methionine is started more than 10 hours after ingestion; it may also precipitate hepatic encephalopathy.
The usual dose of methionine in adults and children over 6 years is 2.5 g by mouth every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol and provided the patient is not vomiting. Children under 6 years should be given 1 g every 4 hours for 4 doses. It has also been given intravenously.

The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. In the UK, the doses quoted above refer to DL-methionine. Preparations containing both methionine and paracetamol (co-methiamol) have been formulated for use in situations where overdosage may occur. However, the issue of whether methionine should be routinely added to paracetamol preparations is contentious for medical and ethical reasons.
Histamine H_2-antagonists. It has been suggested that since cimetidine blocks the hepatic cytochrome P450 mixed function oxidase system, it might be of use as an adjunct to acetylcysteine for patients whose production of the toxic metabolite of paracetamol is increased due to enzyme induction. Although there have been several anecdotal reports claiming benefit for cimetidine in patients with paracetamol poisoning, there is no current evidence to support these claims.
Liver transplantation may be considered as a last recourse in some patients.

Adverse Effects and Treatment:
Haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes, and other hypersensitivity reactions occur occasionally.
Effects on the kidneys:
Can produce nephropath

Hypersensitivity
Reactions, characterised by urticaria, dyspnoea, and hypotension, have occurred following the use of paracetamol in adultsand children.Angioedema has also been reported. Fixed drug eruptions, confirmed by rechallenge, have been described and toxic epidermal necrolysis.

Reporting of Suspected Adverse Reactions:
To allow continued monitoring of the benefit/risk balance of the medicinal product, reporting of suspected adverse reaction is necessary. Healthcare professionals are encouraged to report any suspected adverse reactions directly to the importer/distributor and/or report to FDA: www.fda.gov.ph.
Patients are advised to seek immediate medical attention at first sign/s of adverse reactions.

Precautions:
Paracetamol should be given with care to patients with impaired kidney or liver function patients with alcohol dependence.

Breast feeding:
No adverse effects have been observed in breast-feeding infants whose mothers were receiving paracetamol.

Pregnancy:
Paracetamol is generally considered to be the analgesic of choice in pregnant patients. However, the frequent use of paracetamol (defined as most days or daily use) in late pregnancy may be associated with an increased risk of persistent wheezing in the infant.Should use the analgesic of choice for pregnant.

Renal impairment:
Plasma concentrations of paracetamol and its glucuronide and sulfate conjugates are increased in patients with moderate renal failure and in patients on dialysis. It has been suggested that paracetamol itself may be regenerated from these metabolites.

Interactions:
The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Antibacterials:
The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing drugs such as *rifampicin*. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving *isoniazid*, aloneor with other drugs for tuberculosis.

Anticoagulants:
Many NSAIDs inhibit platelet function to some extent and have an irritant effect on the gastrointestinal tract, so increasing the risk of haemorrhage and also hypoprothrombinaemic effect of warfarin, possibly by an intrinsic effect on coagulation or by displacement of warfarin from plasma protein-binding sites.

Antiepileptics:
The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme-inducing drugs such as *carbamazepine, phenobarbital, phenytoin,* or *primidone*.
Paracetamol reduced the area under the plasma concentration-time curve for lamotrigine, reduced lamotrigine's half-life, and increased the percentage of lamotrigine recovered in the urine.

Antivirals:
Patients will experience hepatotoxicity.

Probenecid:
Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life.Although urinary excretion of the sulfate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

Pharmacodynamics:
Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies.
Single doses of acetaminophen up to 3,000mg and repeated doses of 1,000mg every 6 hours for 48 hours have not been shown to cause a significant effect on platelet aggregation. Acetaminophen does not have any immediate or delayed effects on small-vessel hemostasis. Clinical studies of both healthy subjects and patients with hemophilia showed no significant changes in bleeding time after receiving multiple doses of oral acetaminophen.

Warning: Risk of Medication Errors and Hepatotoxicity
Take care when prescribing, preparing, and administering Acetaminophen Injection to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that:
- The dose in milligrams (mg) and milliliters (mL) is not confused;
- The dosing is based on weight for patients under 50kg;
- Infusion pumps are properly programmed; and
- The total daily dose of acetaminophen from all sources does not exceed maximum daily limits

Acetaminophen injection contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limits, and often involve more than one acetaminophen-containing product.

Storage: Store at temperatures not exceeding 30°C.

Availability:
2 mL in USP Type I Amber Glass Ampoule (Box of 10's)

FDA Registration Number: DRP-4340-02
Date of Initial of Authorization: 10 May 2022
Date of Revision of Package Insert: 30 March 2023

Manufactured by:
Zhejiang Ruixin Pharmaceutical Co., LTD
168 Kaifa Road Tianning Industrial Zone,
Lishui, Zhejiang, China

Imported by:
SAHAR INTERNATIONAL TRADING INC.
354 Aguirre Ave., Phase III, BF Homes,
Paranaque City

Distributed by:
AMSON PHARMACEUTICALS
356 Aguirre Ave., Phase III BF Homes,
Paranaque City