ACULIFE HEALTHCARE PVT. LTD.
Sachana, Gujarat - 382150, India.

ACULIFE™ HEALTHCARE

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Art work Preparation Date:	06/09/2018		**Superseded code:**	NA	
Approved By	Prepared By PMD	Head/Designee Marketing	Head/Designee Regulatory Affairs	PM Quality Control	Site QA Head/Designee
Sign & Date					

Art work Description :	FEVERACH Glass Bottle Insert For Global
Type of packing material	Maplitho Paper
GSM of packing material	54 GSM ± 10%
Dimension of packing material in mm	L: 250 x W: 200 mm
Colour / Pantone Shade for Printing	Black or (Screen of Black)
Reason For Change in A.W./Initiation	New Artwork
Effective Date	

FRONT

cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of paracetamol.

Anticoagulants: Chronic oral paracetamol use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of paracetamol infusion in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.

OVERDOSAGE:
Signs and Symptoms: In acute paracetamol overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma paracetamol levels > 300 µg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 µg/mL or < 37.5 µg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.
Treatment: If paracetamol overdose is suspected, obtain a serum paracetamol assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24-hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the paracetamol level can be plotted against time since oral ingestion on a nomogram (Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the paracetamol level is below the lower line.

PRESENTATION:
FEVERACH available in 100 mL transparent glass bottle.

STORAGE CONDITIONS:
Store below 30°C. Do not refrigerate or freeze. Protect from Light.
Keep out of reach of children.

SHELF LIFE: 24 Month

DATE OF PUBLICATION: August 2015

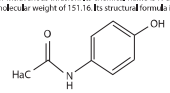
ACULIFE®
Manufactured in India by:
Aculife Healthcare Pvt. Ltd.
Sachana, Gujarat 382150, India.

For the use only of Registered Medical Practitioners or Hospital or Laboratory.

PARACETAMOL INFUSION 10 mg/mL

FEVERACH®

DESCRIPTION:
Paracetamol is a non-salicylate antipyretic and non-opioid analgesic agent. Paracetamol Infusion is a sterile, clear, colorless, non-pyrogenic, isotonic formulation of paracetamol intended for intravenous infusion. Its chemical name is N-acetyl-p-aminophenol. Paracetamol has a molecular weight of 151.16. Its structural formula is:



COMPOSITION:
FEVERACH
Each mL contains:

Paracetamol BP	10 mg
Water for Injections BP	q. s.

PHARMACOLOGICAL CLASSIFICATION:
Analgesic and Antipyretic agent

PHARMACOLOGICAL ACTION:
The precise mechanism of the analgesic and antipyretic properties of paracetamol is not established but is thought to primarily involve central actions.
Paracetamol 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 Infusion reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

PHARMACOKINETIC:
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 Infusion 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 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 Cerebro Spinal Fluid as and from the 20th minute following infusion.

Metabolism: Paracetamol is metabolized 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 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.

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

BACK

INDICATIONS:
Paracetamol 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.

CONTRAINDICATIONS:
Paracetamol Infusion 10 mg/mL is contraindicated:
- In patients with known hypersensitivity to paracetamol or to any of the excipients in the intravenous formulation.
- In patients with severe hepatic impairment or severe active liver disease.

SPECIAL PRECAUTIONS AND WARNING:
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. The maximum recommended daily dose of paracetamol includes all routes of paracetamol administration and all paracetamol -containing products administered, including combination products. Use caution when administering paracetamol in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min)

Serious Skin Reactions: Rarely, paracetamol may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Allergy and Hypersensitivity: There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of paracetamol. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. Discontinue Paracetamol Infusion immediately if symptoms associated with allergy or hypersensitivity occurs. Do not use Paracetamol Infusion in patients with paracetamol allergy.

Use in Pediatric: The safety and effectiveness of Paracetamol Infusion for the treatment of acute pain and fever in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of Paracetamol Infusion in adults. The effectiveness of Paracetamol Infusion for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age.

Use in the Elderly: No overall differences in safety or effectiveness were observed between these elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Hepatic Impairment: Paracetamol is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. A reduced total daily dose of paracetamol may be warranted.

Patients with Renal Impairment: In cases of severe renal impairment (creatinine clearance ≤ 30 mL/min), longer dosing intervals and a reduced total daily dose of paracetamol may be warranted.

Pregnancy: Pregnancy Category C. There are no studies of intravenous paracetamol in pregnant women; however, epidemiological data on oral paracetamol use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IV paracetamol, and it is not known whether Paracetamol Infusion can cause fetal harm when administered to a pregnant woman. Paracetamol Infusion should be given to a pregnant woman only if clearly needed.

Labor and Delivery: There are no adequate and well-controlled studies with Paracetamol Infusion during labor and delivery; therefore, it should be used in such settings only after a careful benefit-risk assessment.

Lactation: While studies with Paracetamol Infusion have not been conducted, paracetamol is secreted in human milk in small quantities after oral administration. Caution should be exercised when Paracetamol Infusion is administered to a nursing woman.

DOSAGE AND DIRECTIONS FOR USE:
General Dosing Information:
Paracetamol Infusion may be given as a single or repeated dose for the treatment of acute pain or fever. No dose adjustment is required when converting between oral paracetamol and Paracetamol Infusion dosing in adults and adolescents who weigh 50 kg and above. Calculated maximum daily dose of paracetamol is based on all routes of administration (i.e., intravenous, oral, and rectal) and all products containing paracetamol. Exceeding the maximum mg/kg daily dose of paracetamol as described in below Tables may result in hepatic injury, including the risk of liver failure and death. To avoid the risk of overdose, ensure that the total amount of paracetamol from all routes and from all sources does not exceed the maximum recommended dose.

Recommended Dosage: Adults and Adolescents:

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of paracetamol (by all routes)
Adults and adolescents (13 years and older) weighing ≥ 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 years and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

Recommended Dosage: Children

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of paracetamol (by all routes)
Children 2 to 12 years of age	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

Administration:
For adult and adolescent patients weighing > 50 kg requiring 1000 mg doses of Paracetamol Infusion, administer the dose by inserting a vented intravenous set through the septum of the 100 mL vial. Paracetamol Infusion may be administered without further dilution. Examine the vial contents before dose preparation or administering. DO NOT USE if particulate matter or discoloration is observed. Administer the contents of the vial intravenously over 15-minutes. Use aseptic technique when preparing Paracetamol Infusion for intravenous infusion. Do not add other medications to the Paracetamol Infusion vial or infusion device.
For doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed Paracetamol Infusion vial and place the measured dose in a separate empty, sterile container (e.g., glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100 mL vial of Paracetamol Infusion is not intended for use in patients weighing less than 50 kg. Paracetamol Infusion is a single use vial and the unused portion must be discarded.
Place small volume pediatric doses up to 60 mL in volume in a syringe and administer over 15 minutes using a syringe pump.
Monitor the end of the infusion in order to prevent the possibility of an air embolism, especially in cases where the Paracetamol Infusion is the primary infusion.
Once the vacuum seal of the glass vial has been penetrated, or the contents transferred to another container, administer the dose of Paracetamol Infusion within 6 hours.
Do not add other medications to the Paracetamol Infusion solution. Diazepam and chlorpromazine hydrochloride are physically incompatible with Paracetamol Infusion, therefore do not administer simultaneously.

ADVERSE EFFECTS:
Blood and lymphatic system disorders: Anemia
Cardiac disorders: Tachycardia
Gastrointestinal disorders: Nausea, vomiting, abdominal pain, diarrhea
General disorders and administration site conditions: Fatigue, infusion site pain, edema peripheral, pyrexia
Investigations: Hepatic enzyme increase, aspartate aminotransferase increased, breath sounds abnormal
Metabolism and nutrition disorders: Hypokalemia, hypoalbuminemia, hypomagnesemia, hypophosphatemia, hypervolemia
Musculoskeletal and connective tissue disorders: Muscle spasms, trismus, pain in extremity
Nervous system disorders: Headache
Psychiatric disorders: Anxiety, insomnia
Renal and urinary disorders: Oliguria
Respiratory, thoracic and mediastinal disorders: Dyspnea, pulmonary edema, hypoxia, pleural effusion, stridor, wheezing
Skin and subcutaneous tissue disorders: Periorbital edema, rash
Vascular disorders: Hypertension, hypotension

DRUG INTERACTIONS:
Effects of other Substances on Paracetamol: Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of paracetamol and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic