FEVAGO Suspension/Drops (Paracetamol)

**Composition**

FEVAGO Suspension
Each 5 ml contains:
Paracetamol, IP ........ 120 mg
(In a flavoured syrup base)
Colour: Erythrosine

FEVAGO DS Suspension
Each 5 ml contains:
Paracetamol, IP ........ 250 mg
(In a flavoured syrup base)
Colour: Erythrosine

FEVAGO Drops
Each ml contains:
Paracetamol, IP ........ 100 mg
(In a flavoured syrup base)
Colour: Sunset yellow FCF

**Dosage Form**

Suspension and drops

**Pharmacology**

**Pharmacodynamics**

Paracetamol (acetaminophen) is a centrally acting analgesic and antipyretic agent and has been clinically proven to be effective for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps, and for the reduction of fever. Acetaminophen is an effective antipyretic in infants, children, and adults.

**Mechanism of Action**

**Analgesic**

The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain-impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation.
Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation, resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

Pharmacokinetics

Oral acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract primarily in the small intestine. This absorption process occurs by passive transport. The relative bioavailability ranges from 85% to 98%. Acetaminophen appears to be widely distributed throughout most body fluids except fat. The apparent volume of distribution of acetaminophen is 0.95 L/kg. A relatively small proportion (10% to 25%) of acetaminophen is bound to plasma proteins and binding is only slightly increased in plasma concentrations associated with overdose. The sulphate and glucuronide metabolites do not bind to plasma proteins even at relatively high concentrations.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: (a) conjugation with glucuronide; (b) conjugation with sulphate; and (c) oxidation via the cytochrome (CY) P450-dependent, mixed-function oxidative enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways. Two additional minor pathways also are possibly involved in acetaminophen metabolism: (a) hydroxylation to form 3-hydroxy-acetaminophen; and (b) methoxylation to form 3-methoxy-acetaminophen.

These metabolites are further conjugated with glucuronic acid or sulphate.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulphate. These glucuronide-, sulphate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulphate conjugate predominates.

The biologic half-life of acetaminophen in normal adults is approximately 2 to 3 hours in the usual dosage range. It is somewhat shorter in children and somewhat longer in neonates and in patients with cirrhosis. The elimination half-life is approximately 3 hours for the extended-release product. The elimination half-life of acetaminophen in the cerebrospinal fluid according to pooled data is 3.2 hours.

Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulphate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Indications

FEVAGO Suspension/Drops temporarily relieves mild-to-moderate aches and pains due to common cold or influenza, backache, headache, earache, migraine, menstrual and premenstrual cramps, muscular aches, sore throat, toothache, teething; temporarily, also reduces fever, including post-immunization fever.

Dosage And Administration

Dosage

The recommended dose of FEVAGO Suspension/Drops is 10 to 15 mg/kg every 4 to 6 hours, not to exceed 5 doses (50 to 75 mg/kg) in 24 hours.

Find the right dosage from the chart below (If possible, use weight to dose; otherwise, use age).
## For Infants Aged Between 1 And 12 Months

<table>
<thead>
<tr>
<th>Age (Months)</th>
<th>Average Weight (kg)</th>
<th>Dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 3</td>
<td>3.8 to 5.5</td>
<td>0.6 to 0.8</td>
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<tr>
<td>3 to 9</td>
<td>5.5 to 8.3</td>
<td>0.8 to 1.2</td>
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<tr>
<td>9 to 12</td>
<td>8.3 to 10</td>
<td>1.2 to 1.5</td>
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## FEVAGO Suspension

### For Children Aged Between 1 And 5 Years

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Average Weight (kg)</th>
<th>Dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2</td>
<td>10 to 12</td>
<td>6 to 8</td>
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<tr>
<td>2 to 3</td>
<td>12 to 14</td>
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<td>3 to 4</td>
<td>14 to 18</td>
<td>9 to 11</td>
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<tr>
<td>4 to 5</td>
<td>18 to 20</td>
<td>11 to 13</td>
</tr>
</tbody>
</table>

## FEVAGO DS Suspension

### For Children Aged Between 5 and 12 Years

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Average Weight (kg)</th>
<th>Dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 7</td>
<td>20 to 25</td>
<td>6 to 8</td>
</tr>
<tr>
<td>7 to 9</td>
<td>25 to 32</td>
<td>8 to 10</td>
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</table>
Administration
Use the calibrated measuring cup provided with the pack of FEVAGO DS Suspension/FEVAGO Suspension for appropriate dosing. FEVAGO DS Suspension/FEVAGO Suspension should not be administered for more than 48 hours without the doctor's advice.

Use only the enclosed dropper for use with FEVAGO Drops. Do not use any other dosing device. Fill to dose level. Dispense liquid slowly into the child's mouth, towards the inner cheek. Replace the bottle cap tightly after each use. FEVAGO Drops should not be administered without the doctor's advice.

Contraindications
Hypersensitivity to paracetamol or any of the constituents.

Warnings And Precautions
Acetaminophen at recommended doses has no obvious effects on the CNS function. In an overdose situation, CNS effects are uncommon. Coma or other evidence of CNS depression usually is not present unless the patient has taken a massive overdose, has taken other CNS-active agents concomitantly, or is experiencing CNS effects secondary to fulminant hepatic failure.

Most studies do not show any cross-reactivity with the use of acetaminophen in aspirin-sensitive patients. In one study, when asthmatic patients who were sensitive to very low doses of aspirin were challenged with doses of 1,000 to 1,500 mg of acetaminophen, a proportion had evidence of decreased pulmonary forced expiratory volume at 1 second (FEV₁), but, in contrast to the aspirin reactions, the reactions to acetaminophen were generally mild and easily reversed. No reactions were seen with acetaminophen at doses of 650 mg or less. Acetaminophen is recommended as the analgesic/antipyretic of choice in aspirin/NSAID-sensitive patients.

In recommended therapeutic doses, acetaminophen does not cause gastric irritation, gastric erosions, occult or overt gastrointestinal blood loss, or ulcers. In a placebo-controlled, randomized, double-blind, crossover, endoscopy study in 12 healthy volunteers, 1,000 mg of aspirin evoked a lesion score of 2.5 (possible scores ranged from 0 to 3 ), whereas 1,000 mg of acetaminophen and placebo resulted in scores of 1.0 and 0.92, respectively. Several case-controlled studies have established that gastrointestinal bleeding is a significant risk with both regular and occasional aspirin or NSAID use, whereas acetaminophen is not associated with a risk for gastrointestinal bleeding. A case-controlled study evaluating first-time peptic ulcer patients found no significant risk associated with acetaminophen use prior to gastric ulcer occurrence, whereas this was not the case with aspirin. An American College of Gastroenterology survey found that over-the-counter (OTC) aspirin and NSAIDs were used significantly more often by patients in the gastrointestinal bleeding population than in controls. However, this was not the case with acetaminophen.

A case-controlled, multicentre study established that acetaminophen is not associated with agranulocytosis or aplastic anaemia. Although there have been infrequent reports (primarily letters to the editor), in which thrombocytopenia was noted in patients receiving acetaminophen, no causality was established.

In various clinical conditions, acetaminophen may be preferred because it does not have any immediate or delayed
effects on small-vessel haemostasis, as measured by bleeding time. In normal volunteers receiving a single dose of acetaminophen (975 or 1,950 mg) or multiple doses of acetaminophen (1,950 mg daily for 6 weeks), no change in bleeding time or platelet aggregation was observed. In another study, a single 1,000 mg dose of acetaminophen was given to normal volunteers and did not affect the bleeding time or platelet aggregation. Patients with haemophilia receiving multiple doses of acetaminophen showed no significant changes in bleeding time.

In clinical studies in adults, acetaminophen when taken in therapeutic doses of up to 4,000 mg/day demonstrated no adverse hepatic effects. In a large clinical study, more than 84,000 febrile children were enrolled in a randomized, double-blind, acetaminophen-controlled trial to assess the risks of rare but serious adverse events following the use of paediatric ibuprofen. Of the children included in the analysis, 28,130 received acetaminophen and none experienced serious adverse hepatic effects.

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Acetaminophen in massive overdosage may cause hepatotoxicity in some patients. In adults and adolescents, hepatotoxicity may occur following ingestion of greater than 7.5 to 10 g over a period of 8 hours or less. Fatalities are infrequent (less than 3% to 4% of untreated cases) and have rarely been reported with overdoses less than 15 g. In children, amounts less than 150 mg/kg are highly unlikely to produce hepatotoxicity. In both adults and children, toxicity associated with acetaminophen is almost invariably caused by ingestion of quantities of the drug that are significantly above the recommended dosage range. Hepatotoxicity, ranging from transient sharp transaminase elevations to fatal, fulminant hepatic failure, is the most common result of clinically significant overdosage.

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Although it is suggested that alcoholics may be at increased risk from therapeutic doses, reports usually involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Studies evaluating the metabolism of doses up to 20 mg/kg of acetaminophen in chronic alcohol abusers and a study evaluating the effects of 2 days of acetaminophen dosing at 4,000 mg daily in chronic alcoholics undergoing detoxification do not support an increased risk of hepatotoxicity with recommended doses of acetaminophen.

A report has suggested that hepatotoxicity following greater than the recommended dose of acetaminophen may be enhanced by both fasting and/or chronic alcohol ingestion. Review of this case series revealed that in all patients reported taking overdoses of acetaminophen, most had reported prolonged periods of fasting, and the majority had a history of the abuse of alcohol.

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally are controlled by discontinuation of the drug and, when necessary, symptomatic treatment.

Clinical data have established that acetaminophen in recommended doses is not nephrotoxic. In a single-blind study, the effect of acetaminophen (4,000 mg/d) was compared with indomethacin (150 mg/d) and placebo on renal function in healthy volunteers. Acetaminophen did not have the adverse renal effects generally associated with NSAIDs. In one of the study, renal function was measured in patients taking at least 1,000 mg of acetaminophen daily for at least 1 year. There was no evidence of clinically significant renal impairment in 18 patients who each consumed a cumulative total of 2 to 30 kg of acetaminophen over prolonged periods.

Acute nephrotoxicity has been reported following massive overdose either as a sequela of hepatic failure or, occasionally, in the absence of hepatic failure.

Some studies suggest an association between the chronic long-term use of acetaminophen and renal effects. Results, however, are conflicting, limited by recall bias and confounded by the inability to determine whether analgesic use preceded or followed the onset of renal disease.

There is negligible clinical evidence to suggest that the habitual use of acetaminophen causes analgesic nephropathy. However, use of antipyretic analgesic combinations (i.e. analgesics that contain aspirin and acetaminophen combined with caffeine or codeine) in large doses for prolonged periods of time is thought to be associated with an increased risk
of renal papillary necrosis, resulting in analgesic nephropathy. In one of the position paper, acetaminophen was recommended as the non-narcotic analgesic of choice for episodic use in patients with underlying renal disease. In therapeutic doses, acetaminophen does not shorten the lifespan of red blood cells and does not produce any clinically perceptible destruction of circulating red blood cells.

Acetaminophen can be used in patients with liver disease and has been studied in both one-time single (1,500 mg) and multiple doses (4,000 mg/d) in adult patients with chronic stable liver disease. A double-blind, two-period, crossover study evaluated the use of 4,000 mg/d of acetaminophen for 13 days in patients with stable chronic liver disease. There were no abnormalities indicative of an adverse reaction to acetaminophen. Comparison of acetaminophen metabolism following a single 1,500 mg dose in normal subjects, patients with mild liver disease, and patients with severe liver disease was done. There were no significant differences in overall 24-hour urinary excretion of acetaminophen and glucuronide, sulphate, cysteine, and mercapturic acid conjugates of acetaminophen. Following a single (10 mg/kg) dose of acetaminophen, the pharmacokinetic profiles in paediatric patients with mild, moderate or severe liver disease were not significantly different. Although the plasma half-life of acetaminophen was prolonged in patients with severe liver disease, there were no significant differences in the 24-hour (adult) and 36-hour (children) urinary excretion of acetaminophen or its conjugates (e.g. glucuronide, sulphate, cysteine, mercapturic acid).

Based on available clinical data, acetaminophen can be used in patients with chronic renal disease without dosage adjustment. In a single-dose study, the disposition and metabolite kinetics of 1,000 mg of acetaminophen in patients with renal disease and in healthy volunteers was compared. The fractional urinary recovery of acetaminophen and its conjugates (e.g. glucuronide, sulphate, cysteine, mercapturate) was similar in healthy volunteers and in patients with moderate renal failure. In a 10-day, multi-dose study, the disposition of acetaminophen 3,000 mg daily in healthy volunteers compared with patients with chronic renal failure was evaluated. A slight increase in pre-dose trough acetaminophen levels was noted in patients with renal failure (3.1 μg/mL) compared with controls (1.1 μg/mL), but there was no evidence of accumulation of the glutathione-derived metabolites of acetaminophen (e.g. cysteine, mercapturate).

Although mean daily pre-dose plasma concentrations of sulphate and glucuronide conjugates were higher in patients with chronic renal disease, these conjugates disappeared rapidly when acetaminophen was discontinued. There is no significant risk of acetaminophen toxicity in patients with moderate-to-severe renal failure.

A National Kidney Foundation position paper notes that physicians preferentially recommend acetaminophen to patients with renal failure because of the bleeding complications associated with aspirin in these individuals. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

### Drug Interactions

**Barbiturates, Hydantoins, Sulphinpyrazone**
May decrease therapeutic effect of acetaminophen; concomitant long-term use may increase risk of hepatotoxicity.

**Charcoal**
As an antidote, charcoal can decrease the absorption of acetaminophen when given as soon as possible after overdosage.

**Ethanol (Alcohol)**
Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Healthcare professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

**Lamotrigine**
Acetaminophen may reduce plasma concentration. If an interaction is suspected, adjust the lamotrigine dose accordingly.

**Warfarin**
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding, especially in doses more than 325 mg/day; occasional doses have no significant effect.

Cholestyramine
The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within 1 hour if maximal analgesia is required.

Metoclopramide and Domperidone
The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Chloramphenicol
Increased plasma concentration of chloramphenicol.

Anticonvulsants
Some reports have suggested that patients taking long-term anticonvulsants, who overdose on acetaminophen, may be at increased risk of hepatotoxicity because of the accelerated metabolism of acetaminophen.

Hydantoins
At the usual oral therapeutic doses of acetaminophen and hydantoins, no special dosage adjustment or monitoring is generally required. There is no increased risk from an acetaminophen overdose in patients on chronic hydantoin therapy.

Carbamazepine
At the usual oral therapeutic doses of acetaminophen and carbamazepine, no special dosage adjustment is generally required. It is not known whether there is increased risk from an acetaminophen overdose in patients on chronic carbamazepine therapy.

Diflunisal
Caution should be used with concomitant administration of diflunisal and acetaminophen, and patients should be monitored carefully.

Potential Laboratory Test Interferences
Using the most current analytic systems, acetaminophen does not cause laboratory test interferences. However, there are certain methods with which the possibility of laboratory changes exists, as described below:

Blood Tests
Acetaminophen at recommended doses does not appear to interfere with glucose analysis using currently marketed blood glucose metres. For further detail, it may be advisable to contact the specific laboratory instrumentation manufacturer.

Urine Tests
Acetaminophen in therapeutic doses may interfere with the determination of 5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding acetaminophen ingestion several hours before and during the collection of the urine specimen.

Renal Impairment
Based on available clinical data, acetaminophen can be used in patients with chronic renal disease without dosage adjustment. However, care is advised in the administration of paracetamol to patients with severe renal impairment.

Hepatic Impairment
Care is advised in the administration of paracetamol to patients with severe hepatic impairment.

Pregnancy
Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of the doctor regarding its use.
Lactation

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

Paediatric Use

Refer to DOSAGE AND ADMINISTRATION.

Geriatric Use

No adjustment in labelled dosage is necessary for older patients who require acetaminophen therapy. Those who require therapy for longer than 10 days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary.

Undesirable Effects

Adverse effects of paracetamol are rare. Very rarely, hypersensitivity and anaphylactic reactions, including skin rash may occur.

There have been reports of blood dyscrasias, including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of the disease improved after paracetamol withdrawal. Nephrotoxicity following therapeutic doses of paracetamol is uncommon. Papillary necrosis has been reported after prolonged administration.

Overdosage

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors as given below.

If the patient
a) is on long-term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St. John's wort or other drugs that induce liver enzymes;
or
b) regularly consumes ethanol in excess of recommended amounts;
or
c) is likely to be glutathione-deplete, e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

If more than 150 to 200 mg/kg or an unknown amount was ingested, obtain a plasma acetaminophen level as soon as
possible, but not sooner than 4 hours following ingestion. In children, an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity. In patients referred for plasma acetaminophen levels, gastric emptying with syrup of ipecac or administration of activated charcoal should be considered. If the plasma acetaminophen level can be obtained within 8 hours post-ingestion, initiating acetylcysteine treatment is not necessary until the result is obtained. However, if the estimated time post-ingestion is approaching 8 hours, then acetylcysteine treatment should be initiated immediately. If the acetaminophen level plots above the treatment line on the nomogram, acetylcysteine treatment should be initiated and continued for a full course of therapy. Serious toxicity or fatalities have been extremely infrequent following an acute acetaminophen overdose in young children, possibly because of differences in the way children metabolize acetaminophen.

### Storage And Handling Instructions

Store in a cool, dark place. Keep out of the reach of children. Shake well before each use.

### Packaging Information

FEVANGO DS Suspension: Bottle of 60 ml  
FEVAGO Suspension: Bottle of 60 ml  
FEVAGO Drops: Bottle of 15 ml

_Last updated: January 2014_  
_Last reviewed: January 2014_

FEVAGO Suspension/Drops

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