1. NAME OF THE MEDICINAL PRODUCT

Feverex Toto Suspension

1.1 Strength

Each 5ml of the suspension contains 120mg of Paracetamol BP.

1.2 Pharmaceutical Form

Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative declaration

Paracetamol BP

2.2 Quantitative declaration

Each 5ml of the suspension contains 120mg of Paracetamol BP.

3. PHARMACEUTICAL FORM

Oral Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Feverex Toto Suspension is indicated for the relief of painful or feverish conditions such as teething, headache, toothaches, earache, muscular pains, symptoms of cold and flu.

4.2 Posology and Method of Administration

Posology

Dosage:	
Age (Years)	Number of 5ml teaspoonful's
3 months to less than 1 year	Half a spoonful (2.5ml)
1 year to less than 3 years	One spoonful (5ml)
3 years to less than 5 years	One and a half spoonfuls (7.5ml)
5 years to less than 8 years	Two spoonfuls (10ml)
8 years to less than 12 years	Three spoonfuls (15ml)
The dosage may be repeated up to four times daily	

4.3 Method of Administration

For oral administration only

It is important to **shake the bottle** for at least 10 seconds before use

4.4 Contraindications

Feverex Toto Suspension contains paracetamol that promotes the reduction of body temperature during fever. It produces antipyretic by acting on the hypothalamic heat-regulating centre.Paracetamol also produces analgesic by elevation of pain threshold. It unlikely to produce nay of the side effects associated with aspirin based products.

4.5 Special Warnings and Precautions for Use

***Warning*: -** Do not exceed the stated dosage

Precautions: Should be given with care to patients with impaired kidney or liver function. Although Feverex is very effective in managing fever associated with malaria and other infections, it is not a cure and should be used in combination with suitable anti-infectives

4.6 Paediatric Population

According to WHO guidelines, the only available option for pain management in children below 3 months of age is paracetamol; the 10 mg/kg dose every 4–6 hrs should be recommended in this case. For the effective control of pain, paracetamol should be given as a scheduled dose over time, and not administered at need. The correct dose of paracetamol provides effective treatment of pain and fever that is equivalent to that seen with NSAIDs, making it an effective and safer treatment option in this setting. Only paracetamol and ibuprofen appear recommended for reduction of fever in children

4.7 Interaction with other medicinal products and other forms of interaction

• Anticoagulants - the effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.

• Metoclopramide – may increase speed of absorption of paracetamol.

• Domperidone – may increase speed of absorption of paracetamol.

• Colestyramine – may reduce absorption if given within one hour of paracetamol.

• Imatinib - restriction or avoidance of concomitant regular paracetamol use should be taken with imatinib.

4.8 Additional information on special populations

Not Stated

4.9 Paediatric Population

Paediatric metabolism summary: The major route of paracetamol metabolism is via sulphation and glucuronidation. Sulphation is the major route of paracetamol metabolism in children while glucuronidation is the major route in adults. Around 5- 10% of paracetamol is oxidised by cytochrome P (CYP) enzymes (the expression and activity of which varies with age and between individuals) to form N-acetyl-p benzoquinoneimine (NAPQI), a toxic by-product. Normally NAPQI is detoxified by conjugation with glutathione in both adults and children. If the concentration of NAPQI exceeds glutathione levels (eg, after paracetamol overdose), NAPQI binds to hepatocytes causing severe liver damage.

Paediatric pharmacokinetics summary: Drug clearance of paracetamol in children is thought to be lower than in adults, particularly in children age 3 years or less. The lower rate of clearance in children may be due to their lower weight, or their slower metabolism. The maximum analgesic effect of paracetamol in a child appears to occur approximately 1.5 – 2 hours after administration.

4.10 Fertility, pregnancy and lactation

Pregnancy

Epidemiological studies in human pregnancy have shown no effects due to paracetamol used in the recommended dosage. However, paracetamol should be avoided in pregnancy unless considered essential by the physician.

Breast-feeding

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

4.11 Effects on ability to drive and use machines

It does not have any known any effect on the ability to drive and use machines

4.12 Undesirable effects

Adverse effects of Paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia, neutropenia, pancytopenia, leukopenia and agranulocytosis but these were not necessarily causality related to Paracetamol and Very rare cases of serious skin reactions have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard

4.13 Overdose

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

Risk Factors:

If the patient

A, is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs than induce liver enzymes.

Or

B Regularly consumes ethanol in excess of recommended amounts.

Or

C, Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV, starvation, cachexia.

Symptoms

Symptoms of Paracetamol over dosage 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, hemorrhage, hypoglycemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.

Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetyl cysteine may be used up to 24 hours after ingestion of Paracetamol; however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetyl cysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacological Properties

ATC Code: **N02BE01**

Paracetamol:

Paracetamol is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDs, acetaminophen does not inhibit cyclooxygenase in peripheral tissues and, thus, has no peripheral anti-inflammatory affects. While aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site, studies have found that paracetamol indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides. This might explain why paracetamol is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides. Studies also report data suggesting that paracetamol selectively blocks a variant of the COX enzyme that is different from the known variants COX-1 and COX-2. This enzyme is now referred to as COX-3. Its exact mechanism of action is still poorly understood, but future research may provide further insight into how it works. The antipyretic properties of paracetamol are likely due to direct effects on the heat-regulating centres of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation.

5.2 Pharmacokinetic Properties

Oral absorption is rapid and almost complete; it may be decreased if Paracetamol is taken following a high carbohydrate meal.

There is no significant protein binding with doses producing plasma concentrations of below 60mcg (µg)/ml, but may reach moderate levels with high or toxic doses.

Approximately 90 - 95% of a dose is metabolised in the liver, primarily by conjugation with glucuronic acid, sulphuric acid and cysteine. An intermediate metabolite, which may accumulate in over dosage after primary metabolic pathways become saturated, is hepatotoxic and possibly nephrotoxic.

Half life is 1 to 4 hours; does not change with renal failure but may be prolonged in acute over dosage, in some forms of hepatic disease, in the elderly, and in the neonate; may be somewhat shortened in children.

Time to peak concentration, 0.5 - 2 hours; peak plasma concentrations, 5 - 20mcg (µg)/ml (with doses up to 650mg); time to peak effect, 1- 3 hours; duration of action, 3- 4 hours.

Elimination is by the renal route, as metabolites, primarily conjugates, 3% of a dose may be excreted unchanged.

Peak concentration of 10 - 15mcg(µg)/ml have been measured in breast milk, 1 - 2 hours following maternal ingestion of a single 650mg dose. Half life in breast milk is 1.35 - 3.5 hours.

5.3 Preclinical safety data

There is no preclinical safety data of paracetamol and any other ingredients used in the manufacture of Feverex Toto.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Paracetamol Powder BP
- Keltrol Gum (Xanthan Gum)
- Sodium Benzoate
- Sodium Propyl Parabenzoate
- Citric acid, Raspberry Colour (Carmosine Red)
- Raspberry Flavour Oil
- Glycerine BP
- Sorbitol Solution 70%
- Rectified Spirit
- Sugar Syrup

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30^0C.

Keep tightly closed.

6.5 Nature and contents of container

Feverex Toto Suspension is packed in 60ml amber Glass bottles that are labelled, sealed with a cap and placed in unit cartons made of chipboard.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder & Manufacturing Site Addresses

Name: BETA HEALTHCARE INTERNATIONAL LTD

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8. Marketing Authorization Number

5853/02/07

9. Date of First Registration/Renewal of the Registration

Date of first authorization: 02/2007

Date of latest renewal: 07/2018

10. Date of revision of the text

February 2019

11. Dosimetry

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals

Not Applicable