1. Name of the product

TIXYCOF FOR CHILDREN SYRUP

2. Qualitative & Quantitative composition

Each 5 ml contains

Diphenhydramine HCL BP 7mg

Sodium Citrate BP 28.5mg

3. Pharmaceutical Dosage Form

Oral Syrup.

4. Clinical particulars

4.1 Therapeutic indications

4.2 Posology and method of administration

Posology

One to two 5ml to be taken every 4 hours

To aid sleep the patient may start with two 5ml at bedtime followed by two 5ml every 6 hours.

Do not take more than 4 doses (1 dose = two 5ml) in 24 hours.

Do not exceed the stated dose.

Method of Administration

Oral

4.3 Contraindications

- Hypersensitivity to any of the ingredients
- Patients on monoamine oxidase inhibitor therapy within previous 14 days.

4.4 Special warnings and precautions for use

- Do not combine with other treatments for coughs and colds.
- TIXYCOF FOR CHILDREN SYRUP Oral Solution should be used with caution in patients withthe following conditions: prostatic hypertrophy, urinary retention, susceptibility to 'closed angle' glaucoma and hepatic disease.
- TIXYCOF FOR CHILDREN SYRUP Oral Solution may cause drowsiness.

- Seek medical advice when suffering from chronic or persistent cough and when also suffering from asthma, and acute asthmatic attack or where cough is accompanied by excessive secretions Keep out of the reach and sight of children.

Excipient Warnings:

Parahydroxybenzoates may cause allergic reactions (possible delayed).

Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

- Additive CNS depressant effects with alcohol and other CNS depressants including barbiturates, hypnotics, opiod analgesics, anxiolytic sedatives and anti-psychotics.
- Additive anti-muscarinic effects with other drugs of similar properties such as atropine and some anti-depressants.
- Not to be taken in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 of stopping treatment as there is a risk of serotonin syndrome.
- Diphenhydramine can inhibit the oxidative metabolism of some drugs.
- Diphenhydramine may enhance the effects of ephedrine.
- Diphenhydramine may mask the response of the skin to allergenic skin tests and also the ototoxic symptoms associated with certain antibiotics.

4.6 Effects on ability to drive and use machines

TIXYCOF FOR CHILDREN SYRUP Oral Solution may cause drowsiness.

4.8 Undesirable effects

The overall percentage of treated patients expected to experience adverse reactions is unknown.

Common side effects include:

- CNS effects such as nervous drowsiness (usually diminishes within a few days), paradoxical stimulation, nervous headache, nervous psychomotor impairment.
- Anti-muscarinic effects such as urinary retention, dry mouth, blurred vision, gastrointestinal disturbances and thickened respiratory tract secretions.

Rare side effects include:

Hypotension, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, palpitation, arrhythmia, hypersensitivity reactions, blood disorders and liver dysfunction.

Organ system Class	Common ADRs, >1/100, < 1/10	Uncommon ADRs, >1/1,000, <1/100	Rare ADRs >1/10,000, <1/1000
Blood Lymphatic System Disorder			Blood Disorders NOS
Cardiac Disorder			Palpitation, arrhythmia
Eye Disorders	Blurred vision		
Gastrointestinal Disorder	Dry mouth, gastrointestinal disturbance		
General Disorder	Paradoxical drug reaction		
Hepatobiliary Disorder			Liver Disorder
Immune System Disorders			Hypersensitivity
Nervous System Disorders	Psychomotor skills impairment, drowsiness, headache		Tremor, convulsions, extrapyramidal disorder, dizziness
Psychiatric Disorders			Confusion, depression, sleep disturbances
Renal and Urinary Disorder	Urinary retention		
Respiratory Disorder	Increased upper airway secretion		
Vascular Disorders			Hypotension

4.9 Overdose

Symptoms of overdosage include those due to diphenhydramine or menthol (drowsiness, dizziness, ataxia, anti-cholinergic effects, pyrexia, headaches, convulsions, hallucinations, excitement and respiratory depression).

Treatment consists of gastric lavage and aspiration. Administration of activated charcoal may help. Other symptomatic and supportive measures should be provided.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Diphenhydramine HCl ATC Code: R06AA52

Pharmacotherapeutic Group: Antihistamines for systemic use, Aminoalkyl ethers

Diphenhydramine is a potent antihistamine and antitussive with concurrent anticholinergic and sedative properties. Experiments have shown that the antitussive action is discrete from H1-rececptor blockade and is located in the brain stem. The duration of activity of diphenhydramine is between 4 and 8 hours. The sedative mechanism for diphenhydramine is thought to result from antagonism of central histamine and cholinergic receptors. The time course for sedation following a 50 mg oral dose was associated with higher plasma concentrations, and was significantly different from placebo during the first three hours following administration. The pharmacodynamics of sedation was correlated with peak concentrations of drug occurring during absorption and the alpha distribution phase.

Sodium Citrate

Sodium citrate has no relevant pharmacodynamic activity other than that caused by its alkalinity (e.g. its gastric acid neutralising capacity).

5.2 Pharmacokinetic properties

Diphenhydramine HCI

Absorption

Diphenhydramine is well absorbed from the gastrointestinal tract, reaching peak plasma concentrations from 47-153 ng/mL between 1.5 and 4 hours after a single 50-mg dose in children. After multiple oral doses of 50 mg diphenhydramine HCl four times during each day to four subjects, minimum diphenhydramine plasma concentrations at steady state on the third day ranged from 57-150 ng/mL.

Distribution

Diphenhydramine is widely distributed throughout the body, including the CNS. The pharmacokinetics of diphenhydramine follows a two-compartment model in which the

distribution or alpha phase is apparent over the first eight to ten hours. The volume of distribution adjusted by body weight is large for diphenhydramine at 14.0 L/kg (38%) for children, 16.0 (32%) for adolescents, and 19.5 (28%) for children. Diphenhydramine is highly protein bound, with free drug concentrations of 24.0 ± 1.9% ng/mL and 14.8 ± 1.5% ng/mL measured in Asian and Caucasian plasma. In children with liver disease, protein binding is lower, although the volume of distribution is comparable to healthy children.

Metabolism

Diphenhydramine undergoes extensive first pass metabolism with an absolute bioavailability of 72% ± 8%. It is extensively metabolized in the liver by demethylation to N-demethyl diphenhydramine (DMDP), and the extent of DMDP measured in plasma is highly correlated with the clearance of diphenhydramine. DMDP is subsequently demethylated to N,Ndidemethyl diphenhydramine. Because only the latter, minor metabolic pathway of N,N-didemethylation appears to be mediated by cytochrome P450 2D6, diphenhydramine disposition in humans is not determined by CYP2D6 activity. Rather, clinical pharmacokinetics data suggest that diphenhydramine may be an inhibitor of CYP2D6 without being extensively metabolized by this cytochrome P450 isozyme. N,Ndidemethyl diphenhydramine is further metabolized by oxidative deamination to diphenylmethoxyacetic acid.

Elimination

Mean beta elimination half-life from 8.5 and 11.5 hours in children have been reported in studies in which blood is sampled up to 24 to 72 hours. The half-life is increased to 13.6 ± 4.2 h in the elderly and to 15.2 ± 1.5 h in children with liver cirrhosis. Little unchanged drug is excreted in the urine. Mean oral clearances for children after a 25- and 50-mg dose are 1041 and 1029 mL/min, respectively, having coefficients of variation of 40% and 35%. Oral clearance is about 50% lower in children. Oral clearance is 691 mL/min (32%) for children ages 2 to 11 years, and is 1251 mL/min (43%) for adolescents' ages 12 to 17 years.

Hepatic dysfunction

After intravenous administration of 0.8 mg/kg diphenhydramine, a prolonged shelf-life was noted in patients with chronic liver disease which correlated with the severity of the disease. However, the mean plasma clearance and apparent volume of distribution were not significantly affected.

Menthol

Absorption

Menthol is highly lipid soluble and, when taken orally, is rapidly absorbed from the small intestine.

Distribution

There is insufficient data on the distribution of menthol.

Metabolism

In humans, menthol is partially metabolized to menthol glucuronide by rapid conjugation. Animal studies in rats have demonstrated that menthol then undergoes extensive enterohepatic recirculation after being cleaved from the glucuronide conjugate and reabsorbed in the small intestine. The reabsorbed menthol is then subsequently metabolized by oxidative processes in the liver. There is support for this model in humans as well because menthol has been shown to be oxidized by CYP2A6 in human liver microsomes.

Elimination

A study in humans has demonstrated that approximately 50% of a menthol dose is excreted in the urine as menthol glucuronide. Other studies in rats have shown that menthol glucuronide is excreted in both the bile and the urine, but with the bile containing the majority of menthol glucuronide and with the urine also containing various oxidation products.

Sodium Citrate

Sodium citrate is systemically absorbed and renally eliminated, causing metabolic alkalosis and urine alkalisation in sufficient doses.

5.3 Preclinical safety data

Mutagenicity

The results of a range of tests suggest that neither diphenhydramine or menthol have mutagenic potential.

Carcinogenicity

There is insufficient information to determine the carcinogenic potential of diphenhydramine or menthol, although such effects have not been associated with these drugs in animal studies.

Teratogenicity

The results of a number of studies suggest that the administration of either diphenhydramine or menthol does not produce any statistically significant teratogenic effects in rats, rabbits and mice.

6. Pharmaceutical particulars

6.1 List of excipients

Sucrose, Cocoa flavour, Glycerol, Propylene Glycol, Sodium Citrate, Nipastat (methylparahydroxybenzoate E218, ethylparahydroxybenzoate E215, propylparahydroxybenzoate E216, butylparahydroxybenzoate), Purified Water.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light. Store in the original package.

6.5 Nature and contents of container

60ml Amber pet Bottles capped with white rop cap.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing authorisation holder

JEHYSON HEALTHCARE LIMITED
Jehyson Crescent, km 78 Lagos
Abeokuta Express way Apomu,
Ewekoro LGA, Ogun State