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(54) Title: PHARMACEUTICAL COMPOSITIONS OF CEFIXIME

(57) Abstract: A pharmaceutical suspension formulation comprising a dose greater than 100 mg/5ml Cefixime and pharmaceutically acceptable excipients.

PHARMACEUTICAL COMPOSITIONS OF CEFIXIME

FIELD OF THE INVENTION

The present invention relates to pharmaceutical suspension formulation comprising a new strength of Cefixime 200 mg/5ml.

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BACKGROUND OF THE INVENTION

Cefixime is a semi synthetic cephalosporin antibiotic for oral administration. It was first disclosed in US Pat No. 4,409,214 by Fujisawa Corporation, Japan.

10 It has a bactericidal action and the mechanism of action is based on inhibition of bacterial cell wall synthesis.

It is indicated for the treatment of infections caused by various gram – positive and gram – negative organisms chiefly uncomplicated urinary tract infections caused by *E. coli* and *P. mirabilis*, otitis media caused by *H. influenza*, *M. catarrhalis* and *S. pyogenes*, acute bronchitis and exacerbations of chronic bronchitis caused by *S. pneumonia* and *H. influenza*. It is also indicated for uncomplicated gonorrhoea caused by *N. gonorrhoea*. It is one of the most prescribed drugs for pediatric use.

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Cefixime as a drug is poorly soluble in water. From the point of view of bioavailability, the preferred form of administration of sparingly soluble medicaments such as beta lactam antibiotics is often an aqueous suspension. Cefixime, given orally, is about 40%-50% absorbed whether administered with or without food.

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Children 12 years of age or younger receive, e.g., about 8 mg of Cefixime/kg of body weight each day. The recommended dose can be administered alternatively all at once or divided into 2 single doses (e.g., about 4 mg of Cefixime/kg of body weight in the morning and evening). An increase in the daily dose to 2.x6 mg of Cefixime/kg of body weight is possible depending on the severity and the location of the infection. Adults and children above 12 years of age may receive 400 mg of

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Cefixime each day. The recommended daily dose may be administered alternatively all at once or divided into 2 single doses (in the morning and evening). The dose should be reduced for patients with distinctly impaired renal function.

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Solid dosage forms such as tablets and capsules have certain disadvantages since they have to disintegrate in the gastrointestinal tract and then the medicament has to dissolve before it can be absorbed, thus leading to slower absorption as compared to that of the suspension dosage form and also the
10 absorption is less than the suspension dosage form leading to bioequivalence issues. Also, certain patient populations such as pediatrics and geriatrics have difficulty in swallowing tablets and capsules, and there is a practical limit to the size, and therefore the dose, that can be swallowed.

15 The oral suspension dosage forms have certain advantages over the above mentioned dosage forms especially in population segments such as pediatrics and geriatrics who have problems in swallowing the solid dosage forms. Further The oral suspension dosage form produces average peak concentrations approximately 25%-50% higher than the conventional tablets. The area under the
20 time versus concentration curve is greater by approximately 10%-25% with the oral suspension than with the conventional tablet after doses of 100 to 400 mg, when tested in normal adult volunteers.

US Pat No. 4,079,138 by American Home Products Corporation describe a
25 permanent suspension with a non-aqueous basis as vehicle for active substances, which are sensitive to hydrolysis.

US Pat No. 5,776,926 by Merck discloses Cefixime compositions in the form of
non-aqueous suspensions.

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Cefixime is currently available in a number of different formulations in various strengths for adult and pediatric patients, for example as tablets comprising 200

mg and 400 mg Cefixime and as oral suspension comprising 100 mg/ 5 ml Cefixime.

5 In some patient population the compliance for the currently available oral suspension is low due to requirement of dosing greater than 100mg in certain disease conditions. Lack of availability of a oral suspension dosage form comprising greater than 100mg/5ml cefixime leads to low compliance rates. This is due to multiple dosing required leading to low compliance rates (e.g.; spillage).

10 There is a need to develop a higher strength oral suspension in unit dose for improving the patient compliance and for reducing the frequency of dosing.

OBJECTS OF THE INVENTION

15 The object of the invention is to provide a suspension dosage form comprising an unit dose greater than 100 mg /5ml and not more than 400mg/5ml of Cefixime and pharmaceutically acceptable excipients.

20 The principal object of the invention is to provide a suspension dosage form consisting essentially an unit dose of 200 mg /5ml of Cefixime and pharmaceutically acceptable excipients.

25 Another object of the invention is to provide a suspension dosage form comprising Cefixime, wherein the said new suspension strength 200 mg/5ml is bioequivalent to suspension 2x100 mg/5ml comprising Cefixime trihydrate marketed under the name of "Suprax[®]".

30 Another object of the present invention is to provide a method of treating acute bacterial otitis media, pharyngitis, tonsillitis, Acute and chronic bronchitis with a oral suspension of cefixime wherein said suspension form consists essentially of an unit dose of 200 mg /5ml of Cefixime and pharmaceutically acceptable excipients.

Yet another object of the invention is to provide a method of uncomplicated urinary tract infections and gonorrhoea with a oral suspension of cefixime wherein said suspension form consists essentially of an unit dose of 200 mg /5ml of
5 Cefixime and pharmaceutically acceptable excipients.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for an oral suspension comprising a unit dose of greater than 100mg/5ml and not more than 400mg/5ml of cefixime.

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In preferred embodiment the present invention provides for an oral, pharmaceutical suspension composition comprising Cefixime 200 mg/5ml

In another embodiment the present invention provides for an oral, pharmaceutical suspension composition comprising Cefixime 200 mg/5ml which is bioequivalent
15 to a suspension dosage form of Cefixime 2x100 mg/5ml marketed under the trade name of Suprax®.

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The term Cefixime as used herein also denotes the various salt forms of Cefixime including the commonly used trihydrate salt form.

The term "oral suspension" includes within its scope but is not limited to compositions selected from the group consisting of pellets for suspension which can be coated or uncoated, granules for suspension, in the form of a unit dose packet (sometimes referred to in the art as a "sachet"), in the form of a
25 suspension made from a unit dose packet, in the form of a powder for oral suspension, in the form of a dose sipping device and in the form of an oral suspension per se (liquid suspension) and combinations of these e.g. coated pellets filled in a dose sipping device or in a sachet. It is noted that when a unit dose packet is constituted, it is probably mainly in the form of a suspension if
30 reconstituted according to directions, although the extent of suspension versus solution depends on a number of factors such as pH.

Preferred oral, pharmaceutical suspension compositions comprising Cefixime are in the form of powder for suspension.

5 The oral, pharmaceutical suspension composition can additionally comprise of at least one excipient depending upon the dosage form e.g. whether as pellets or as granules for suspension and so on. The excipient can be one or more selected from the group consisting of diluents, sweeteners, viscosity enhancing agents, dispersing agents, preservatives, flavoring agents and the like. One excipient can perform more than one function.

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Diluents include, but are not limited to, sucrose, sorbitol, xylitol, dextrose, fructose, malitol, sugar potassium, aspartame, saccharin, saccharin sodium, and mixtures thereof. A preferred diluent of the present invention is sucrose. Diluents can also be used as sweetener.

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Suitable sweeteners include, but are not limited to, natural sweeteners such as sugars e.g. fructose, glucose, sucrose, sugar alcohols such as mannitol, sorbitol or mixtures thereof and artificial sweeteners such as sodium saccharine, sodium cyclamate and aspartame.

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The term "viscosity enhancer," as used herein, refers to an agent or a mixture of agents that increases the thickness of a liquid thereby keeping the active ingredient suspended to allow accurate dosing. Viscosity enhancers include, but are not limited to, xantham gum, guar gum, acacia, alginic acid, sodium alginate, propylene glycol alginate, povidone, carbomer, salts of carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, bentonite, polydextrose, carrageenan, sucrose, sorbitol, xylitol, dextrose, fructose, malitol, gelatin, tragacanth, a polyvinyl alcohol, cetearyl alcohol, colloidal silicon dioxide and mixtures thereof. A preferred
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30 viscosity enhancer of the present invention is xantham gum.

Dispersing agents include, but are not limited to, colloidal silicon dioxide and surfactants, wherein the surfactant is used alone or as an admixture with one or more surfactant. Combinations of colloidal silicon dioxide with one or more surfactants can also be used.

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The term "flavoring agent," as used herein, refers to an agent or a mixture of agents that adds flavor to a mixture. Flavoring agents include, but are not limited to, artificial strawberry flavor, art banana flavor and artificial cream flavor. A preferred flavoring agent of the present invention is strawberry flavor.

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The term "preservative," as used herein, refers to an agent or mixture of agents that is used to protect a composition against antimicrobial (e.g., yeast, mold, bacteria) activity. Preservatives include, but are not limited to, sodium benzoate, benzoic acid, ethylenediaminetetraacetic acid, sorbic acid, benzethonium chloride, benzalkonium chloride, bronopol, butyl paraben, methyl paraben, ethylparaben, propyl paraben, thiomerosol, sodium propionate, chlorhexidine, chlorobutanol, chlorocresol, cresol, imidurea, phenol, phenylmercuric salts, potassium sorbate, propylene glycol, and mixtures thereof. A preferred preservative of the present invention is sodium benzoate.

20

All these excipients can be used at levels well known to the persons skilled in the art. The oral suspension compositions can be prepared by means well known to those skilled in the art.

The application of the invention can be seen by the following, non limiting examples:

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EXAMPLE 1:

Cefixime Suspension 200 mg / 5 ml

Ingredients	Quantity per tablet (mg)
Cefixime equivalent to Cefixime anhydrous	200.00
Xanthan gum	10.00
Sodium Benzoate	10.00
Colloidal silicon dioxide	25.00
Strawberry flavor	25.00
Sucrose	2230.00
Total weight	2500.00

BRIEF MANUFACTURING PROCESS:

- 5 Sift Cefixime and sucrose separately through suitable screen. Also sift other excipients like xanthan gum, colloidal silicon dioxide, sodium benzoate and strawberry flavor. Cefixime and the above excipients are milled with approximately 20% quantity of total sucrose.

- 10 All the excipients along with the drug are loaded in a blender and blended for specified period of time.

BIOEQUIVALENCE STUDY

- 15 A bioequivalence study was carried out using the suspension (Test) comprising Cefixime 200 mg/5ml as prepared in Example 1 against the commercially available oral suspension "Suprax[®]" (Reference) using twenty-five healthy human volunteers.

A 10 ml of the reference product was administered with 5 ml of the test product.

- 20 The bioequivalence data for this study is shown below in Table 1. The study was monitored in terms of the AUC and C_{max} achieved with the test product and reference product. AUCs are plots of serum concentrations of Cefixime along the

ordinate (Y-axis) against time on the abscissa (X-axis). Generally, the values for AUC represent a number of values taken from all the subjects in a population and are, therefore, mean values averaged over the entire population. C_{max}, the observed maximum in a plot of serum level concentration of Cefixime (Y-axis) versus time (X-axis) is likewise an average value. The ratios of the log transformed mean values for C_{max} and AUC for the test and reference product (T/R ratio) is a measure of the bioequivalence between the test and reference product. Values between 80 and 125 % for the 90% Confidence Intervals of these ratios indicate bioequivalence as recommended by the USFDA.

Table 1: Comparative Bioequivalence fasting study data of Cefixime suspension 200 mg/5ml against commercially available suspension formulation "Suprax[®]" 2x100 mg/5ml

n= 25

Pharmacokinetic Parameters	Log Trans-formed T/R Ratio of Least Square Means	90% CI of log Transformed Data
C _{max}	103.5	95.32-112.34
AUC _{0-t}	106.2	96.79-116.56
AUC _{0-inf}	105.7	96.72-115.62

From the results of this study we can conclude that Cefixime suspension 200mg/5ml suspension exhibits bioequivalence to that of the marketed suspension formulation "Suprax[®]" 2x100 mg/5ml.

Thus, this invention provides a pharmaceutical suspension composition comprising Cefixime 200 mg/5ml, which when administered in humans demonstrates an AUC and C_{max} for Cefixime which is substantially equivalent to the AUC and C_{max} obtained with twice the dose of an oral suspension formulation comprising Cefixime trihydrate marketed under the name of "Suprax[®]" is administered to humans.

As used herein, the term "substantially equivalent" means that the two products are bioequivalent within the framework of the guidelines for bioequivalence recommended by the USFDA as already elaborated earlier.

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Thus, this invention also provides for a method of achieving bioequivalence between a new suspension dosage form of Cefixime 200 mg/5ml and a suspension comprising Cefixime 100 mg/5ml.

10 The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

CLAIMS

- 5 1. A suspension dosage form comprising a unit dose greater than 100 mg /5ml and not more than 400mg/5ml of Cefixime and pharmaceutically acceptable excipients.
2. A suspension dosage form consisting essentially an unit dose of 200 mg /5ml of Cefixime and pharmaceutically acceptable excipients.
- 10 3. A suspension dosage form of Claim 2, wherein the pharmaceutically acceptable excipients includes diluents, sweeteners, viscosity enhancing agent, dispersing agents, flavoring agents, preservatives.
4. A suspension dosage form of claim 3, wherein the diluent is sucrose, sorbitol, xylitol, dextrose, fructose, malitol, sugar potassium, aspartame, saccharin, saccharin sodium, and mixtures thereof.
- 15 5. A suspension dosage form of claim 3, wherein the sweetener is fructose, glucose, sucrose, sugar alcohols such as mannitol, sorbitol or mixtures thereof and artificial sweeteners such as sodium saccharine, sodium cyclamate and aspartame.
- 20 6. A suspension dosage form of claim 3, wherein the viscosity enhancing agent is selected from the group comprising xantham gum, guar gum, acacia, alginic acid, sodium alginate, propylene glycol alginate, povidone, carbomer, salts of carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, bentonite, polydextrose, carrageenan, sucrose, sorbitol, 25 xylitol, dextrose, fructose, malitol, gelatin, tragacanth, a polyvinyl alcohol, cetearyl alcohol, colloidal silicon dioxide, and mixtures thereof.
7. A suspension dosage form of claim 3, wherein the dispersing agent is colloidal silicon dioxide.

8. A suspension dosage form of claim 3, wherein the flavoring agent is strawberry flavor, art banana flavor and artificial cream flavor.
9. A suspension dosage form of claim 3, wherein the preservative is selected from the group comprising sodium benzoate, benzoic acid,
5 ethylenediaminetetraacetic acid, sorbic acid, benzethonium chloride, benzalkonium chloride, bronopol, butyl paraben, methyl paraben, ethylparaben, propyl paraben, thiomerosol, sodium propionate, chlorhexidine, chlorobutanol, chlorocresol, cresol, imidurea, phenol, phenylmercuric salts, potassium sorbate, propylene glycol, and mixtures
10 thereof.
10. A suspension dosage form comprising Cefixime 200 mg/5ml is bioequivalent to suspension 2x100 mg/5ml comprising Cefixime trihydrate marketed under the name of "Suprax[®]".
11. A method of treating acute bacterial otitis media, pharyngitis, tonsillitis,
15 Acute and chronic bronchitis with a oral suspension of cefixime wherein said suspension form consists essentially of an unit dose of 200 mg /5ml of Cefixime and pharmaceutically acceptable excipients.
12. A method of treating uncomplicated urinary tract infections and gonorrhea with a oral suspension of cefixime wherein said suspension form consists
20 essentially of an unit dose of 200 mg /5ml of Cefixime and pharmaceutically acceptable excipients.