TITLE OF THE INVENTION

Liquid Formulation for Deferiprone With Palatable Taste

FIELD OF THE INVENTION

The present invention relates to novel taste masked liquid deferiprone compositions for oral administration.

Background of the Invention

Orally administered drugs are provided to the patient in many dosage forms, including solid forms such as capsules, caplets or tablets and liquid forms such as solutions, syrups, emulsions or suspensions. Pharmaceutically active agents administered in solid dosage form are usually intended to be swallowed whole. The disagreeable taste of the drug is generally not of concern when formulating oral solid dosage forms, because the pharmaceutical's taste can be easily masked with an exterior coating.

Children, older persons, and many other persons including disabled or incapacitated patients often have trouble swallowing tablets or capsules. In these situations, it is desirable to provide the drug either in a chewable solid form or a liquid form. For many patients, including pediatric and geriatric patients, a liquid oral dosage form is preferred over a chewable dosage form. A liquid dosage form is especially preferred for this class of patients because of the ease with which it may be swallowed. Additionally, patients may be more inclined to comply with their medication instruction if the dosages are easier to ingest, particularly for products administered in large doses, requiring several tablets at a time.

Some liquid pharmaceutical compositions formulated for use by pediatric or geriatric patients are often prepared by grinding a tablet dosage form into a powder and mixing the powder with a diluent. Such a formulation may cause some of the drug to remain undissolved, thereby affecting the therapeutic dose of drug in the composition. In addition, the powder exposes the unpleasant tasting pharmaceutically active agent, which may result in a lack of compliance due to the unacceptable taste. It is readily understood that such compositions are impractical and may result in underdosing or poor compliance.

A common formulation problem associated with liquid pharmaceutical dosage forms (such as solutions (including syrups or suspensions) is masking the disagreeable taste that a pharmaceutically active agent may often manifest when administered in a liquid dosage form. Many active ingredients, such as antibiotics, possess a strong, unpleasant and bitter taste. Deferiprone particularily has an extremely bitter taste as discussed in the Merck Index. Prior attempts to provide acceptable and palatable liquid deferiprone formulations have been unsuccessful.

Pfertec Limited of London England had previously prepared a liquid deferiprone formulation which was never approved, but was sold as a research drug only to physicians for use in patients on a named patient basis. The taste was unbearably unpleasant. There was no disclosure of the details of the Pfertec liquid deferiprone composition, but taste comparisons, conducted by the applicant, revealed they had failed to produce a palatable product for commercial purposes.

The prior art has shown extensive use of one or a combination of different flavoring methodologies to mask the bitter taste of drugs. For example, a flavor can be selected that complements the taste of the preparation, or a flavor with a longer intensity and stronger taste than the drug can be used. High levels of sweetening agents are often used to overwhelm bitterness with sweetness. The taste buds may also be anesthetized by menthol or mint flavors. These approaches are generally not very effective in masking the taste of a bitter drug, and a flavoring system that works with one drug often does not apply to another drug.

The prior art also indicates that taste masking may be achieved by increasing the viscosity of liquid preparations. Various combinations of viscosity modifiers for taste masking exist in the patent literature. For example, U.S. Pat. No. 5,616,621 provides alleged taste masked liquid preparations by increasing the viscosity with a combination of polyethylene glycol and sodium carboxymethylcellulose; and U.S. Pat. No. 5,658,919 discloses alleged taste masking of an acetaminophen suspension using a suspending system consisting of xanthan gum and a mixture of cellulosic polymers. The increase in viscosity is assumed to limit the contact of the drug with the tongue, presumably by slowing down salivary water uptake into the viscous liquid medicament, which can lead to dilution and dissolution of the taste-offending ingested medication. This approach is only moderately successful in reducing bitterness especially at high drug loading. While bitterness may be reduced at the onset, bitter aftertaste becomes prominent after swallowing because thick preparations are more difficult to wash down thus leaving behind some residual viscous liquid medicament in the mouth after swallowing. This

bitter aftertaste is more prominent with water intake due to the reduction in viscosity and dilution of the residual liquid medicament and subsequent dissolution of the drug in the mouth.

Several other approaches have been pursued to address the unpleasant taste of a drug in a liquid format. U.S. Pat. No. 5,730,997 illustrates the use of a hyperosmotic liquid using a sugar derivative and maltose syrup for taste masking. U.S. Pat. No. 5,154,926 claims reduction of the bitter taste of acetaminophen syrup by using a water-soluble macromolecule with a polyhydric alcohol and/or polymer of a polyhydric alcohol of MW 300–400. U.S. Pat. Nos. 5,763,449 and 5,962,461 teach the use of a combination of povidone, C3–C6 polyol and ammonium glycyrrhizinate for taste masking. EP application No. 1025858A1 discloses relief of bitterness of basic drugs by combining propylene glycol with povidone and/or copolyvidone.

In the case of developing a palatable formulation for a liquid deferiprone product, several approaches were used without success, resulting in a product not much more palatable than the Pfertec product. Thus a series of iterative steps were taken to overcome the difficulty experienced in developing a liquid formulation for deferiprone that has a palatable taste.

It is therefore a primary aspect of the invention to provide a palatable liquid deferiprone formulation using a taste masking composition directed specifically at the offending taste generated by deferiprone.

It is yet another object of this invention to provide a taste masked liquid deferiprone formulation wherein the taste masking composition comprises a taste masking effective amount of sucralose and optionally at least one flavouring agent.

Further and other objects of the invention will become apparent to one skilled in the art when reviewing the following summary of the invention and the more detailed description of the preferred embodiments contained herein.

SUMMARY OF THE INVENTION

The present invention comprises a palatable liquid deferiprone formulation, essentially masking the very bitter and otherwise unpleasant tasting drug deferiprone.

The present invention provides for a novel flavored and taste-masked palatable deferirprone

formulation.

According to a primary aspect of the invention there is provided an oral pharmaceutical liquid formulation comprising deferiprone and a taste masking composition, said taste masking composition comprising an effective amount of a sweetener (such as sucralose) per litre of liquid composition, an effective amount of a thickening and suspension aid, (for example hydroxyethylcellulose), per litre of liquid composition, an effective amount of a humectant (such as glycerin) per litre of liquid composition, and an effective amount of at least one flavoring agent per litre of liquid composition, wherein a final form of said taste-masked pharmaceutical formulation has a substantially non-bitter palatable taste.

In another embodiment of the invention there is provided a taste masked palatable liquid deferiprone formulation wherein the taste masking formulation further comprises a taste masking effective amount of an artificial sweetener and at least one flavoring agent.

Preferably the flavoring agent is selected from the group consisting of natural flavors, natural fruit flavors, artificial flavors, artificial fruit flavors, peppermint, peppermint oils and mixtures thereof. For example only, without limiting the flavor to be incorporated into the formulation, the flavoring agent may be selected from cherry, grape, strawberry, orange-blood, melon, banana and citrus vanilla.

In one embodiment, the composition comprises more than one flavoring agent.

Preferably the sweetener is sucralose. More preferably sucralose is present in an amount of from about 5 grams to about 30 grams per litre of the composition.

In another embodiment the formulation further comprises glycerin. Preferably the amount of glycerin is from about 100 to about 900 grams per litre of the composition.

In yet another embodiment, the formulation further comprises hydroxyethylcellulose. Preferably the amount of hydroxyethylcellulose is from about 0.5 to about 3 grams per litre of the composition..

Preferably said liquid pharmaceutical formulation has a pH from about 2.5 to about 5.

In one embodiment, deferiprone is present at about 20 to about 200 grams per litre of the composition..

In another embodiment the formulation further comprises concentrated hydrochloric acid to preferably adjust the pH thereof and preferably in the range of 2.5 to 5.0.

The sweetening agent may be selected from the group consisting of a high intensity artificial sweetener such as aspartame, sucralose, sacharin or the like.

Preferably said sweetening agent is present at about 0.1 to about 3 percent by weight.

Most preferably deferiprone is present in an amount of about 50 to 200 grams per litre of the composition.

According to yet another aspect of the invention there is provided a palatable liquid pharmaceutical formulation comprising: about 50-200 grams of deferiprone per litre of the formulation, about 15 grams of sucralose per litre of the formulation, about 500 grams of glycerin per litre of the formulation, about 1 gram of hydroxyethylcellulose per litre of the formulation, about 59 grams of concentrated hydrochloric acid per litre of the formulation, about .40 grams of FD&C Yellow No. 6 per litre of the formulation, about 2 grams of artificial cherry flavour per litre of the formulation, about .10 grams of peppermint oil per litre of the formulation and a sufficient amount of purified water to yield 1 litre of the formulation.

In another embodiment said formulations may be used in iron overload conditions of the heart, the mitrochondria or the central nevervous system including the brain.

DETAILED DESCRIPTION OF THE INVENTION

Artificial sweeteners that may be used in the present invention include, and are not limited to, aspartame, saccharin, saccharin sodium, sucralose or mixtures thereof. The taste masking effective amount of an artificial sweetener is that amount whereby the bitter taste of deferiprone is masked and the liquid pharmaceutical formulation is palatable.

Aspartame is used as a table-top sweetener and in beverage and food products and pharmaceutical and vitamin preparations to enhance flavor systems and to mask some unpleasant

taste characteristics. Comparatively, aspartame has approximately 180-200 times the sweetening power of sucrose. The taste masking effective amount of aspartame has a range of from about 0.01 to about 40 grams per 100 mL.

Saccharin is used to enhance flavor systems and to mask some unpleasant taste characteristics and has approximately 500 times the sweetening power of sucrose. The taste masking effective amount of saccharin has a range of from about 0.1 to about 1 gram per 100 mL.

Saccharin sodium is considerably more soluble in water than saccharin, is used more frequently in pharmaceutical formulations and has approximately 300 times the sweetening power of sucrose. The taste masking effective amount of saccharin sodium has a range of from about 0.06 to about 5 grams per 100 mL.

Sucralose is characterized as an intensely sweet, trichlorinated carbohydrate, structurally similar to sucrose, having approximately 600 times the sweetening power of sucrose.

Mixtures of artificial sweeteners, such as a ratio of 10 parts to 1 part, have also been found to have synergistic sweetening properties and improve taste characteristics for some products.

A preferred embodiment of the taste masking formulation comprises a taste masking effective amount of the artificial sweetener sucralose. The amount of sucralose used masks the bitter taste of deferiprone.

Preferably, the taste masking effective amount of sucralose has a range of from about 0.05 to about 2.5 grams per 100 mL. More preferably, the taste masking effective amount of sucralose has a range of from about 0.5 to about 3 grams per 100 mL. Even more preferably, the taste masking effective amount of sucralose is about 1 gram per 100 mL.

The flavoring agent used is of the type and amount desired to enhance the palatability of the particular liquid pharmaceutical formulation to the intended consumer. Flavoring agents that may be used in the present invention include, and are not limited to, natural flavors, natural fruit flavors, artificial flavors, artificial fruit flavors, flavor enhancers or mixtures thereof. Natural flavors, artificial flavors or mixtures thereof include, and are not limited to, mint (such as peppermint or spearmint), and menthol. Natural fruit flavors, artificial fruit flavors or mixtures thereof include, but are not limited to, cherry. For example only, without limiting the flavor to

be incorporated into the formulation, the flavoring agent may be selected from cherry, grape, strawberry, orange-blood, melon, banana and citrus vanilla. Although flavoring agents are generally provided as a minor component of the taste masking composition in amounts effective to provide a palatable flavor to the liquid pharmaceutical formulation, the addition of at least one flavoring agent is preferred, and more preferably, more than one flavoring agents may be employed.

Another embodiment of the taste masking composition further comprises a taste masking effective amount of an artificial sweetener, at least one flavoring agent, an optional sweetening agent and an optional debittering agent or mixtures thereof.

A pH stabilizer such as hydrochloric acid may be optionally added to the taste masked liquid pharmaceutical composition of the present invention to stabilize pH and prevent microbial growth. Hydrochloric acid is advantageously added since a lower pH will prevent microbial growth and add to the stability of the product.

Coloring agents also may be incorporated to provide an appealing color to the taste masked liquid pharmaceutical formulation. Suitable coloring agents are well known to those skilled in the art and are those that are deemed safe for human consumption by relevant governmental regulatory bodies and which avoid chemical incompatibilities with other ingredients.

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given with the understanding that these examples are intended only to be illustrations without serving as a limitation on the scope of the present invention.

Formulation development Rationale of choice of formulation

A deferiprone oral solution was developed to facilitate the administration of the active ingredient to patients with systemic iron overload, such as those with transfusion-dependent thalassemia or those with other disorders who may require an oral iron chelator, such as certain neurodegenerative diseases, who also have difficulty swallowing tablets, particularly when several tablets at a time are required.

Deferiprone oral solution was first developed for a phase I, open label, single-dose, three-way crossover relative bioavailability study of deferiprone tablets as compared to deferiprone solution under fasting and fed conditions in 15 healthy subjects. In the study the bioavailability of three

500mg tablets of deferiprone was compared with that of a 1500mg dose of deferiprone oral solution.

The initial developmental formulation of deferiprone oral solution contained deferiprone, hydrochloric acid, glycerin, saccharin sodium, peppermint oil, bitter blocker type flavour and purified water. Hydroxyethyl cellulose (Type H) was then added to this formulation to increase viscosity allowing for ease of dispensing. This formulation was used in the study.

Subsequently, the saccharin sodium and bitter blocker type flavour used in the oral solution formulation were replaced with sucralose and artificial cherry flavour. This helped improve the product taste. A colouring agent, FD & C Yellow No. 6 was added to the final formulation to improve the appearance of the product. The level of glycerol was decreased slightly. The modified formulation was used to manufacture the clinical batch for the study which was a phase I, randomized, open label, comparative, two-way crossover bioavailability study of deferiprone oral solution and deferiprone tablets under fasting conditions in 42 healthy subjects. The modified formulation was also used to manufacture the stability batches and is proposed for future commercial production.

Table 1 Comparative description of deferiprone oral solution formulations

Ingredient and quality standard	**Composition (g/L)**		
	F1 (Initial developmental formulation)	**F2**	**F3 (proposed for commercial production)**
Deferiprone	100.00	100.00	100.00
Hydrochloric acid NF/EP	50.0	50.0	59.0
Glycerin EP	250.00	600.00	500.00
Hydroxyethyl cellulose Type H	Not used	1.00	1.00
Saccharin Sodium USP	3.00	3.00	Not used
Peppermint Oil	0.100	0.10	0.10
Bitter Blocker Type Flavour	2.00	2.00	Not used

Sucralose NF	Not used	Not used	15.0
Artificial cherry flavour	Not used	Not used	2.00
FD&C Yellow No. 6	Not used	Not used	0.40
Purified Water USP	q.s. to batch size	q.s. to batch size	q.s. to batch size

A phase I, randomized, open label, comparative, two-way crossover bioavailability study of deferiprone oral solution and Ferriprox® (deferiprone) tablets under fasting conditions was undertaken with the following results. The to-be-marketed formulation was used to manufacture the clinical batch for study. Deferiprone oral solution and Ferriprox® (deferiprone) tablets were tested in the study to determine the bioequivalency of the oral solution to the tablets in healthy subjects under fasting conditions. The two formulations were found to be bioequivalent.

In preparing a palatable formulation, it was determined that such could only be achieved via empiric study. Therefore a series of studies were conducted, which led to the establishment of a preferred formulation for treating patients with thalassemia. The most salient of these studies is described below. Subsequently, a formulation using a lower concentration and a different colour was developed to treat patients with iron-related neurodegenerative diseases, which is also considered to be part of the invention described herein.

To determine a formulation that could be used clinically, a series of experiments were conducted using an array of sweeteners and substances that mask the taste of a bitter deferiprone oral solution.

Taste testing:

To decide the most suitable taste and flavor, a series of experiments were conducted with a group of 7 volunteers who were blinded as to the composition of different formulations.

Exercise #1

Six different formulations of Deferiprone oral solution were prepared using different artificial flavors; 1. cherry, 2. Lemon-lime, 3. Grape, 4. strawberry, 5. orange-blood and 6. citrus-vanilla while keeping all other exipients substantially the same as the original formulation presented.

1. The samples were randomized and assigned a sample number of 1-6.

2. Separate plastic spoons were used for each of the samples.
3. A randomized and individualized list of sample testing was supplied.
4. A score sheet for flavor and taste tolerability ranking was supplied.
5. Water was provided for rinsing after each test and the washing spit out into a container.
6. Participants tasted and swallowed a sample of each formulation as per individualized lists.
7. The testing sequence was different for each subject to minimize the influence of order on the results.
8. After each taste, participants rated the product of their choice using a 1-10 scale, 1 being the least acceptable value and 10, the most acceptable.

Exercise #2:

Cherry was the flavor of choice. However, there was a need for further improvement of the palatability of the formulation. A different concentration of sweetener was used and another set of five formulation were prepared, keeping all excipients the same except for different concentrations of sweeteners as listed below:

Formulation #1 Saccharin Sodium 6g/L
Formulation #2 Saccharin Sodium 6g/L + NaCl (0.9%)
Formulation #3 Saccharin Sodium 0.5g/L + Acesulfame K 4.70g/L
Formulation #4 Saccharin Sodium1.5g/L + D-Fructose 180.6g/L
Formulation #5 Saccharin Sodium 3g/L

The preferred formulation was the one with 6g/L concentration of Saccharin, but additional changes were desired as the taste had not been optimized.

Exercise #3

The sweetener was changed to Aspartame. After another round of taste testing the formulation with 10g/L of Aspartame became the most acceptable formulation in terms of taste tolerability, but Aspartame is unstable at pH below 3.4 and this was confirmed by testing the degradation of Aspartame following 2 months storage.

Exercise #4

Now that Saccharin and Aspartame became unsuitable, a different sweetener "Xylitol", was used to prepare another set of four formulations (again keeping all other excipient the same) as listed below:

Formulation #1 Xylitol 30%
Formulation #2 Xylitol 40%
Formulation #3 Xylitol 20% + Saccharin Sodium 0.3%
Formulation #4 Xylitol 30% + Saccharin Sodium 0.3%

The participants concluded that the taste of the formulations with Xylitol was unacceptable. Xylitol even suppressed the Cherry flavor of the formulation.

Exercise #5

Sucralose was used as a 2% solution of Sucralose in 100mg/ml of Deferiprone.

A set of 3 formulations with 0.5%, 1.0% and 2.0% of Sucralose concentrations were prepared. The formulation with 2% sucralose was preferred.

Further studies were conducted with Aspartame using a set of formulations at 0.5%, 1.0%, 1.3%, 1.5% and 1.7% concentration of Aspartame.

In order to make the taste testing results less influenced by the previous formulation, participants were given crackers to chew in between the tests, to neutralize any aftertaste that may influence the taste of other formulations. Again, in order to avoid any interference from the reaction, comments or body language from other participants, testing was conducted separately.

The taste of our solution was much more tolerable than the Pfertec product, a liquid formulation of deferiprone used as an unacceptable reference for comparison. The following charts provide the details of the product development.

PHARMACEUTICAL DEVELOPMENT

NAME: Deferiprone Oral Solution (US/Can)		**LOT NO:**
STRENGTH: 100 mg/mL	**BATCH SIZE:** 1 L	**PRODUCT CODE:**

ITEM	MATERIAL NO.	QTY/L
Deferiprone		100.00g
Glycerin USP	35158	600.00g
Hydrochloric Acid NF/EP	35162	50mL
Hydroxyethyl Cellulose NF Type H	35163	1.00g
Saccharin Sodium USP	35292	3.00g
Peppermint Oil	35264	0.10g
Bitter Blocker type Flavour	207184	2.00g
Artificial Cherry Flavour	35009	2.00g
Purified Water USP/EP	35244	q.s to 1 L

PHARMACEUTICAL DEVELOPMENT

Bulk Formulation Procedure

NAME: Deferiprone Oral Solution (EU)		**LOT NO:**
STRENGTH: 100mg/mL	**BATCH SIZE:**1 L	**PRODUCT CODE:** 1863 (EU)
PACKAGE:		**EXPT.NO:** f3 (12-F2)
DESCRIPTION: A clear slight yellow solution with peppermint and cherry-flavoured aroma		

ITEM	MATERIAL NO.	QTY/L	QTY/ BATCH
Deferiprone		100.00g	100.00g
Glycerin USP	35158	500.00g	500.00g
Hydrochloric Acid NF/EP	35162	50mL	50mL
Hydroxyethyl Cellulose NF Type H	35163	1.00g	1.00g
Sucralose NF	226796	15.00g	15.00g
Art. Cherry Flavour	35009	2.00g	2.00g
Peppermint Oil	35264	0.10g	0.10g

Purified Water USP/EP	35244	q.s to 1 L	q.s to 1 L

Deferiprone oral solution contains the following excipients:

Hydroxyethyl cellulose Type HX EP

This excipient has a dual function in the formulation of deferiprone oral solution, acting as a thickener and as a suspension aid. It is used in oral and topical drug products as an inert ingredient. It is incorporated at 0.1% w/v in this formulation. It dissolves readily in water to give a clear, smooth, non-thixotropic solution. It has excellent compatibility with a large number of ingredients.

Glycerol EP

This excipient performs a dual function in the formulation of deferiprone oral solution, acting as a humectant and as a sweetening agent. As a humectant, glycerol promotes the retention of moisture. As a sweetening agent, it imparts a pleasant flavor in combination with sucralose NF, cherry flavour and peppermint oil. In liquid pharmaceutical formulations, glycerol is added at concentrations above 20% to serve as a preservative agent. In this formulation, it is incorporated at 50% w/v, which adds texture to the product making it easier for the patient to swallow.

Sucralose NF

This excipient acts as a sweetening agent. It is incorporated at 1.5% w/v in this formulation. Sucralose is widely used in the food industry as a non-nutritive, high intensity sweetener about 600 times sweeter than sugar. Sucralose does not break down in the human body; it is non-caloric and does not promote tooth decay.

Artificial cherry flavour

This excipient acts as a flavouring agent; it is incorporated in the formulation at 0.2% w/v. Its presence is to increase palatability of the oral solution.

Hydrochloric acid NF/EP

This excipient acts as an acidifying agent; it is incorporated in the formulation at 5.9% w/v.

Peppermint oil

This excipient acts as a flavouring agent; it is incorporated in the formulation at 0.01% w/v. Its presence is to increase palatability of the oral solution.

FD & C Yellow No. 6

This excipient acts as a colouring agent; it is incorporated in the formulation at 0.04% w/v.

Bulk Formulation Procedure

ITEM	MATERIAL NO.	QTY/L	QTY/ BATCH
Deferiprone		100.00g	100.00g
Glycerin USP	35158	500.00g	500.00g
Hydrochloric Acid NF/EP	35162	50mL	50mL
Hydroxyethyl Cellulose NF Type H	35163	1.00g	1.00g
Sucralose NF	226796	15.00g	15.00g
Art. Cherry Flavour	35009	2.00g	2.00g
Peppermint Oil	35264	0.10g	0.10g
F D & C Yellow No. 6 (#10-21-DA-4415)	35285	0.4g	0.4g
Purified Water USP/EP	35244	q.s to 1 L	q.s to 1 L

PHARMACEUTICAL DEVELOPMENT

Bulk Formulation Procedure

PROCEDURE:

1. In a suitable container take about 30% batch size of Purified Water USP/EP. Start heating and mixing using a propeller mixer until a vortex is formed. While heating and mixing, add slowly Hydroxyethyl Cellulose NF Type H into the container and mix until dissolved (20min.).

   Speed Reading 588 rpm

2. Cool down the above to room temperature. While mixing, add Glycerin USP into the above container and mix until uniform solution is obtained (5min.).

   Speed Reading 653 rpm

3. While mixing add Deferiprone into above and mix until uniform dispersion is obtained (10min.).
   Speed Reading 653 rpm

4. While mixing add Hydrochloric Acid NF/EP into above and mix until a clear solution is obtained (10min.).
   Speed Reading 653 rpm

5. While mixing add Sucralose NF/EP into above and mix until dissolved (12min.).
   Speed Reading 653 rpm

6. While mixing add Peppermint Oil and Art. Cherry Flavour into above and mix (10 min.).
   Speed Reading 653 rpm

7. Dissolve F D & C Yellow No. 6 (#10-21-DA-4415) in 2% batch size of Purified Water USP/EP, and mix using magnetic stirrer.

8. While mixing the solution of step 6, add dye solution from step 7 to step 6.

9. Bring the volume of step 8 solution to the final batch size using Purified Water USP/EP. Mix thoroughly (5 min.).
   Speed Reading 653 rpm

10. Check pH of the final bulk (Range 2.8 - 3.0)

A preservative may or may not be included with the fomulation. In the example that follows methylparaben NF and Propylparaben NF were used to evaluate the value of a preservative in the final formulation. Other appropriate preservatives may be used as well provided they are selected giving due consideration to the impact on the other qualities of the formulation.

PREPARATION OF PRESERVATIVES STOCK SOLUTION:

Dispense 23.9g of Purified water USP/EP in a pre-tare suitable container and heat it to 80°C - 90°C and add 1.00g of Methylparaben NF and 0.10g of Propylparaben NF. Mix thoroughly until dissolved. Use this stock solution in step # 8 as follows: **Note: The weight of stock solution**

should be 25.0g.

Part#	Qty of stock solution to be added	% of Label Claim	Methylparaben NF	Propylparaben NF
1	1.0g	20%	0.04g	0.004g
2	2.0g	40%	0.08g	0.008g
3	3.0g	60%	0.12g	0.012g
4	4.0g	80%	0.16g	0.016g
5	5.0g	100%	0.2g	0.02g

PROCEDURE:

1. In a suitable container take about 30% batch size of Purified Water USP/EP and start heating 80°C - 90°C and mixing using a propeller mixer. While continuing mixing and marinating the temperature add slowly Hydroxyethyl Cellulose NF Type H and mix until dissolved.

2. Cool down the above solution to room temperature.
   While mixing, add Glycerin USP into the above container and mix until uniform solution is obtained.

3. While mixing add Deferiprone into above and mix until uniform dispersion is obtained .

4. While mixing add Hydrochloric Acid NF/EP into above and mix until a clear solution is obtained.

5. While mixing add Sucralose NF/EP into above and mix until dissolved.

6. While mixing add Peppermint Oil and Art. Cherry Flavour into above and mix until uniform.

7. Dissolve F D & C Yellow No. 6(#10-21-DA-4415) in 2% batch size of Purified Water USP/EP, and mix using magnetic stirrer.

8. Divide the above bulk into 5 equal parts by weight. To each part add the proposed quantity of stock solution (see above for quantity of stock solution to be added) to get the label

claims of preservatives. Record as specified.

9. Bring the volume of each part from above step to 200mL with Purified water USP/EP. Mix each part thoroughly until uniform.

10. Check pH of the final bulk (Range 2.8 - 3.0)

The tolerability, safety and efficacy of our liquid formulation of deferiprone were assessed in a multi-national, open label study in 100 iron-overloaded pediatric patients (≤10 years of age) with transfusion-dependent anemias. Deferiprone was given in a special formulation to mask the taste, similar to that described, using a concentration of 100 mg/ml at a total daily dose of 50 mg/kg, divided in 3 doses, for the first 2 weeks and then increased to a total daily dose of 75 mg/kg or 100 mg/kg/day if required. The oral solution was tolerated well by all children and there were no unexpected adverse reaction. In fact, the data suggest that there was lower incidence of gastrointestinal adverse reactions (vomiting; 6% of patients; abdominal pain= 3% and no reports of nausea) than what has been reported with the tablet formulation of deferiprone (nausea= 16% of patients; vomiting= 13%; abdominal pain= 14%) in previous studies.

As many changes can be made to the preferred embodiment of the invention without departing from the scope thereof. It is considered that all matter contained herein be considered as illustrative of the invention but not in a limiting sense.

What is claimed is:

1. An oral pharmaceutical liquid formulation comprising deferiprone and a taste masking composition, said taste masking composition comprising an effective amount of a sweetener (such as sucralose) per litre of liquid formulation, an effective amount of a thickening and suspension aid, (for example hydroxyethylcellulose), per litre of liquid formulation, an effective amount of a humectant (such as glycerin) per litre of liquid formulation, and an effective amount of at least one flavoring agent, wherein a final form of said oral liquid pharmaceutical formulation has a substantially non-bitter and palatable taste.

2. The formulation of claim 1, wherein the flavoring agent is selected from the group consisting of natural flavors, natural fruit flavors, artificial flavors, artificial fruit flavors, peppermint, peppermint oils and mixtures thereof.

3. The formulation of claim 1 comprising more than one flavoring agent.

4. The formulation of claim 1, wherein the sweetener is sucralose.

5. The formulation of claim 1, comprising glycerin.

6. The formulation of claim 4, wherein sucralose is present in an amount of from about 5 grams to about 30 grams per litre of the formulation.

7. The formulation of claim 1 comprising hydroxyethylcellulose.

8. The formulation of claim 1, wherein said liquid pharmaceutical formulation has a pH from about 2.5 to about 5.0.

9. The formulation of claim 1 wherein deferiprone is present at about 20 to about 200 grams per litre of the formulation.

10. The formulation of claim 1, wherein the amount of glycerin is from about 100 to about 900 grams per litre of the formulation.

11. The formulation of claim 1, wherein the amount of hydroxyethylcellulose is from about 0.5 to about 3 grams per litre of the formulation.

12. The formulation of claim 8, further comprising concentrated hydrochloric acid.

13. The formulation of claim 1, wherein said sweetener is selected from the group consisting of a high intensity artificial sweetener.

14. The formulation of claim 1, wherein said sweetener is present at about 0.1 to about 3 percent by weight.

15. The formulation of claim 1, wherein deferiprone is present in an amount of about 50 grams to about 200 grams per litre of the formulation.

16. The formulation of claim 2 wherein the flavoring agent comprises artificial cherry flavor.

17. The formulation of claim 16 wherein peppermint oil is added as an additional flavor.

18. A palatable liquid pharmaceutical formulation comprising: about 50-200 grams of deferiprone per litre of the formulation, about 15 grams of sucralose per litre of the formulation, about 500 grams of glycerin per litre of the formulation, about 1 gram of hydroxyethylcellulose per litre of the formulation, about 59 grams of concentrated hydrochloric acid per litre of the formulation, about 0.40 grams of FD&C Yellow No. 6 per litre of the formulation, about 2 grams of artificial cherry flavour per litre of the formulation, about 0.10 grams of peppermint oil per litre of the formulation and a sufficient amount of purified water to yield 1 litre of the formulation.

19. The formulation of any one of claims 1 to 18, wherein said formulation is used in iron overload conditions of the heart, the mitrochondria or the central nervous system including the brain.