Please add new Claims 51 to 62 as follows:

51. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for preventing the risk of heart disease in patients having iron overload.

52. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for stabilizing the risk of heart disease in patients having iron overload.

53. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for reducing the risk of heart disease in patients having iron overload.

54. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising an oral dosage form of deferiprone or a physiologically acceptable salt thereof with other excipients.

55. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising daily administration of an amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 150mg/kg to the patient.

56. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 125 mg/kg to the patient.

57. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of 25mg/kg to 75mg/kg to the patient.

58. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered in a manner selected from the group of intravenously, transdermally, rectally, orally, bucally, or aurally.

59. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered orally.

60. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein the dosage form is a sustained release formulation.

61. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone has a cardio preferred/selective function when compared to desferrioxamine or other alternative chelating agents utilized in patients suffering iron overload.

62. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered in addition to desferrioxamine.

REMARKS

Enclosed is a cheque in the amount of $4,888.00 U.S. in payment of the filing fee for the National Phase Entry in the United States. If there should occur an overpayment or an underpayment of fees in respect of this application, the Commissioner is authorized to access Deposit Account Number 08-3255 to make the appropriate adjustments and advised Applicants' Agent.

Attached hereto as Exhibit A is a marked-up version of the changes made to the claims by the present voluntary amendment. The attached pages are entitled **"EXHIBIT A – CLAIMS WITH MARKINGS TO SHOW CHANGES".**

Also attached hereto as Exhibit B are sheets that contains a clean set of all pending claims following entry of this amendment. These sheets are entitled **"EXHIBIT B – CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT VOLUNTARY AMENDMENT"**. All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

If the Examiner has any questions, he/she is respectfully requested to contact Applicants' Agent, Neil H. Hughes at (905) 771-6414 at their convenience.

Respectfully submitted,

Neil H. Hughes, P.Eng.
Registration No. 33,636
Agent for Applicant

NHH:mse
Enclosures

EXHIBIT A

CLAIMS WITH MARKINGS TO SHOW CHANGES

Please cancel claims 3, 4, 5, 6, 7, 14, 15, 16, 17, 19, 20, 21, 27, 28, 29, 34, 36, 38, 40, 42, 44, 46, 48 and 50.

Please amend the claims as follows:

30. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for preventing the risk of heart disease in patients having iron overload.

31. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for stabilizing the risk of heart disease in patients having iron overload.

32. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for reducing the risk of heart disease in patients having iron overload.

33. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising an oral dosage form of deferiprone or a physiologically acceptable salt thereof with other excipients.

35. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising daily administration of an amount of deferiprone or

a physiologically acceptable salt thereof substantially in the range of up to 150mg/kg to the patient.

37. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 125 mg/kg to the patient.

39. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of 25mg/kg to 75mg/kg to the patient.

41. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein deferiprone is administered in a manner selected from the group of intravenously, transdermally, rectally, orally, bucally, or aurally.

43. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein deferiprone is administered orally.

45. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein the dosage form is a sustained release formulation.

47. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein deferiprone has a cardio preferred/selective function when compared to desferrioxamine or other alternative chelating agents utilized in patients suffering iron overload.

49. (Amended) The method of [any of the previous] claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein deferiprone is administered in addition to desferrioxamine.

Please add the following claims:

51. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for preventing the risk of heart disease in patients having iron overload.

52. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for stabilizing the risk of heart disease in patients having iron overload.

53. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for reducing the risk of heart disease in patients having iron overload.

54. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising an oral dosage form of deferiprone or a physiologically acceptable salt thereof with other excipients.

55. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising daily administration of an amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 150mg/kg to the patient.

56. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 125 mg/kg to the patient.

57. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of 25mg/kg to 75mg/kg to the patient.

58. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered in a manner selected from the group of intravenously, transdermally, rectally, orally, bucally, or aurally.

59. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered orally.

60. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein the dosage form is a sustained release formulation.

61. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone has a cardio preferred/selective function when compared to desferrioxamine or other alternative chelating agents utilized in patients suffering iron overload.

62. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered in addition to desferrioxamine.

EXHIBIT B

CLEAN SET OF ALL PENDING CLAIMS
FOLLOWING ENTRY OF THE PRESENT AMENDMENT

1. A method of treating iron induced cardiac disease in a patient with iron overload, such as in thalassemia or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

2. A method of preventing iron induced cardiac disease in a patient with iron overload, such as in thalassemia or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

8. An effective therapeutic amount of deferiprone or a physiologically acceptable salt thereof for the prevention of the risk of heart disease in patients having iron overload, such as in thalassemia or the like, comprising an effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

9. An effective therapeutic amount of deferiprone or a physiologically acceptable salt thereof for the stabilization of the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising an effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

10. An effective therapeutic amount of deferiprone or a physiologically acceptable salt thereof for the reduction of the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising an effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

11. A method of preventing the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

12. A method of stabilizing the risk of heart disease in patients having iron overload , such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

13. A method of reducing the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

18. A therapeutically effective amount of deferiprone or physiologically acceptable salt thereof for the prevention, treatment, or reversal of heart disease in patients having an iron overload condition of the heart comprising an effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially

reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

22. A method of treating/preventing/or reversing heart disease in a patient having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone, or a physiologically acceptable salt thereof in order to preferentially reduce the iron stores in the heart in comparison to less critical organs/tissue in the body.

23. A method of treating/preventing/or reversing heart disease in patients having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

24. A method of treating/preventing/or reversing heart disease in patients having an iron overload condition of the heart comprising a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

25. A method of treatment, prevention, or reversal of heart disease in a patient having an iron overload condition of the heart comprising administering to the

patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof for the direct preferential reduction/removal of iron (for example - intracellular iron) stores in the heart.

26. A method to prevent/treat/reverse the occurrence of iron-induced cardiac disease in patients with an iron overload condition such as thalassemia or the like, comprising administering to said patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof, wherein deferiprone's efficacy is cardio preferential when compared with its ability to lower total iron stores in the body.

30. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for preventing the risk of heart disease in patients having iron overload.

31. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for stabilizing the risk of heart disease in patients having iron overload.

32. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for reducing the risk of heart disease in patients having iron overload.

33. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising an oral dosage form of deferiprone or a physiologically acceptable salt thereof with other excipients.

35. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising daily administration of an amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 150mg/kg to the patient.

37. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 125 mg/kg to the patient.

39. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of 25mg/kg to 75mg/kg to the patient.

41. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein deferiprone is administered in a manner selected from the group of intravenously, transdermally, rectally, orally, bucally, or aurally.

43. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein deferiprone is administered orally.

45. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein the dosage form is a sustained release formulation.

47. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein deferiprone has a cardio preferred/selective function when compared to desferrioxamine or other alternative chelating agents utilized in patients suffering iron overload.

49. The method of claims 1, 2, 11, 12, 13, 22, 23, 24, 25 and 26 wherein deferiprone is administered in addition to desferrioxamine.

51. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for preventing the risk of heart disease in patients having iron overload.

52. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for stabilizing the risk of heart disease in patients having iron overload.

53. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for reducing the risk of heart disease in patients having iron overload.

54. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising an oral dosage form of deferiprone or a physiologically acceptable salt thereof with other excipients.

55. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising daily administration of an amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 150mg/kg to the patient.

56. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 125 mg/kg to the patient.

57. The effective therapeutic amount of claims 8, 9, 10 and 18 further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of 25mg/kg to 75mg/kg to the patient.

58. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered in a manner selected from the group of intravenously, transdermally, rectally, orally, bucally, or aurally.

59. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered orally.

60. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein the dosage form is a sustained release formulation.

61. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone has a cardio preferred/selective function when compared to desferrioxamine or other alternative chelating agents utilized in patients suffering iron overload.

62. The effective therapeutic amount of claims 8, 9, 10 and 18 wherein deferiprone is administered in addition to desferrioxamine.

A NEW USE FOR DEFERIPRONE

FIELD OF INVENTION

The invention relates to the use of deferiprone for the prevention/stabilization/reduction of the risk of heart disease, such as heart failure, in patients having an iron overload condition such as is found in those suffering from for example, thalassemia, hemochromatosis, and myelodysplasia, and corresponding methods of treatment involving deferiprone therefor.

BACKGROUND OF THE INVENTION

Although reference is made in the following discussion to thalassemia specifically, the invention is not intended to be interpreted as limited only to the treatment thereof. Any chronic iron overload condition would benefit from treatment by utilizing the method described herein as well as the other aspects of the invention. For example, those suffering from hemochromatosis and transfused sickle cell anemia would also benefit.

Thalassemia, among other afflictions, must be treated by regular transfusions of red blood cells in order to extend the life of the patient. However, transfusions create a widespread iron overload in the patient. Iron overload is dangerous since the excessive iron can cause toxic degenerative changes in the heart, liver and endocrine organs.

While blood transfusions constitute the major source of increased iron load, having about 1 mg of iron per ml of transfused red blood cells, increased iron absorption from the gastrointestinal tract can be observed in some diseases and also cause iron overload. Typically, only 1 mg of the dietary iron is absorbed per day. However, some conditions such as thalassemia, dyserythropoietic anemias, sideroblastic anemias, and hereditary hemochromatosis are associated with

increased absorption of dietary iron. However, only 1 mg of iron is lost each day through sloughing of cells from skin and mucosal surfaces and the body does not have any organ that can perform the role of regulating the iron excretion in conditions of iron overload. Consequently, increased dietary iron absorption can also lead to iron overload and iron-induced organ toxicity, the most serious of which is heart damage. Thus, even without blood transfusions, conditions such as thalassemia, or hemochromatosis lead to increased body levels of iron, resulting in iron toxicity and eventually heart damage.

Iron chelators are drugs that enhance the iron excretion. Iron overload is most often treated by the use of the iron chelator desferrioxamine. However, because desferrioxamine is not effective when given orally, it has to be given by a parenteral route. To be clinically effective, relatively large amounts of desferrioxamine are required to be infused daily for 8 to 12 hours and this regime has to be maintained for the life span of these patients. Due to the obvious difficulties associated with such a regime, an extensive amount of research has been directed towards the development of alternative iron chelators.

Recently another iron chelator, deferiprone by oral administration, has been used successfully for removal of iron in thalassemia patients who could not comply with desferrioxamine. While patient compliance is greater with deferiprone, it is not more effective than desferrioxamine in generally removing iron from the body. In some patients deferiprone is known to produce agranulocytoisis, which is a sudden decline in white blood cells in the body. Therefore, deferiprone has been approved in Europe for use in patients with thalassemia major for whom desferrioxamine is contraindicated or who demonstrate serious toxicity concerns with desferrioxamine therapy. According to regulatory bodies, desferrioxamine is currently the agent of choice.

Children who have untreated thalassemia generally die in the first decade of life from anemia and septicemia. When palliative transfusions are introduced, children live into their late teens, but eventually succumb to heart failure if iron

overload is not treated. With the introduction of frequent chronic transfusion therapy and the use of subcutaneous desferrioxamine, most children are now surviving into adulthood. However, many still die before 30 years of age, most from heart failure.

Since there is no question that desferrioxamine can eliminate iron from the body, thus reducing the total body iron load, there are 2 possible reasons why there remains a high level of premature cardiac deaths in desferrioxamine treated patients: one is that patients do not take adequate amounts of the injectable chelator, and the other is that, while it removes iron from the liver and possibly the blood, its effect on the heart are secondary, not specific for this organ.

The number of patients who are compliant with this therapy is limited since the use of desferrioxamine normally requires the use of an infusion pump for 8 to 12 hours, 5-7 days a week as long as patients continue to receive regular blood transfusions. This is a rigorous and uncomfortable treatment regime and many patients cannot or will not comply, which results in an increased iron load and iron toxicity in various organs, including the heart.

However, it is apparent that this is not the only reason that thalassemia patients receiving desferrioxamine therapy develop iron-induced heart disease. Three separate techniques are generally employed in the assessment of iron overload: measurement of serum ferritin concentrations; measurement of hepatic iron concentrations by chemical means following a liver biopsy; and assessment of iron concentrations in the liver or heart or other organs by physical devices, such as SQUID (super quantum interference device) and MRI (magnetic imaging resonance). The lack of adequate compliance with injectable desferrioxamine leads to a generalized increased iron overload as revealed by increases in iron concentrations assessed by the above methods, and thus also to increased levels of iron in the heart. However, data now reveal that iron-induced heart disease occurs even in patients who are compliant with desferrioxamine, and even some

of those who do not have high levels of total body iron as assessed by serum ferritin or liver iron concentrations. It has thus become evident that lowering of the total body iron alone is insufficient to protect against iron-induced heart damage.

There exists therefore a long felt need to improve the life expectancy of those patients who normally develop an iron overload condition, for example thalassemia patients, who are at risk of developing or who have developed cardiac disease, and to delay the onset of heart failure in the patient as long as possible. This need also applies to others suffering from conditions of chronic iron overload to for example those secondary to blood transfusions or those associated with increased dietary iron absorption. Applicant is aware of the following technical literature which discusses the clinical use of chelating agents in conditions of chronic iron overload. These references are referred to in the detailed description of the invention.

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There are more than 250 articles in the peer-reviewed literature which refer to deferiprone and 48 of these (at the time of writing) present data on the use of deferiprone in patients with iron overload. The vast majority of these references

demonstrate the safety and efficacy of this drug in treating such patients, particularly those with thalassemia major. However, there is some dispute regarding the efficacy and safety of deferiprone as an oral chelating agent, emanating particularly from one article (Reference 26) and challenged by several authors in a series of letters to the editor (References 52 through 55) . Although there is some debate on the relative abilities of deferiprone, at the commonly used dose of 75 mg/kg/day, to reduce the iron concentration within the liver in comparison with desferrioxamine, used at optimal doses, there is no literature that demonstrates that deferiprone has a greater cardio-protective effect than desferrioxamine, or that it might have such activity beyond its general ability to reduce the total body iron load.

The first report of the use of deferiprone to decrease elevated levels of iron in the body in humans was published in 1987 by Kontoghiorges, the discoverer of the drug (Reference 48). Following a series of positive reports from investigators in several different countries, including England, The Netherlands, Italy, India and Canada, a particularly strong publication appeared in the New England Journal of Medicine in 1995 which reported on the unequivocal long term effectiveness of deferiprone in the reduction of body iron stores, and that it should be offered to patients unwilling or unable to use desferrioxamine This had been reported previously in a scientific meeting in 1994 (reference 11).

Reference 35 by Al-Refaie et al stated that their study leaves no doubt as to deferiprone inducing a negative iron balance in thalassemic patients. However, the reference provides that until there is a determination of the true incidence of toxicity of deferiprone, uncontrolled use of deferiprone should be discouraged.

A serious adverse effect, agranulocytosis (a profound lowering of the white blood cell count to levels that may not protect against infection) had been reported by several authors, including those of reference No. 10 which indicates that two patients treated with deferiprone had developed agranulocytosis. That study concluded that data should be provided to determine the long term safety and

effectiveness of deferiprone, particularly with respect to agranulocytosis. Reference 29 by Cohen et al reported on the results of a large study regarding the safety of deferiprone finding that the development of agranulocytosis was about 1 %, which is less common than previously estimated from smaller studies and case reports.

Reference 21, reported on relatively early evidence in humans for deferiprone induced reduction of iron in the liver and the heart. The reference discusses the importance of an oral iron chelating agent in contrast to the use of desferrioxamine and its painful nightly infusions. An oral chelating agent would therefore be highly desirable as concluded in this report.

However, in a later article in the New England Journal of Medicine Report (1998) by the same lead author (Reference 26), it is reported that deferiprone does not adequately control body iron burden in patients with thalassemia and may even worsen iron-induced hepatic fibrosis. Reference 28, by the same lead author, reports the development of heart failure in a 23 year old patient after treatment with deferiprone. The reference provided that the patient had been treated with desferrioxamine for 15 years until 1993 when treatment with deferiprone commenced. The author of this report suggested that deferiprone may contribute to heart failure and cardiac fibrosis.

Reference 25 by Tondury et al reports on his long term treatment (up to 8 years) of thalassemic patients with deferiprone and he concluded that there was no drug-induced liver fibrosis in his patients, although he felt there was an increase in liver iron concentrations in some of these patients.

Reference 42 by Faa and Crisponi discusses problems related to the development of non-toxic oral iron chelators with particular emphasis on the usefulness and safety of deferiprone.

Iron-induced heart toxicity is thought to be due, at least in part, to the accumulation of iron in the myocytes. Therefore evidence that deferiprone removes iron from the heart would support, although not prove, the hypothesis of a cardioprotective effect for deferiprone. An early study indicated that there was no such effect, at least in a mouse model that was studied by Gale et al (reference 38) who found that none of the compounds studied, being desferrioxamine and deferiprone among others, reduced iron concentrations from the heart in their animal model. However, later, Hershko (reference 12) reported that both desferrioxamine and deferiprone were effective in removing iron from iron-loaded rat neonatal myocytes (heart cells studied *in vitro*). Of particular interest was the finding that, at equimolar concentrations, desferrioxamine removed more iron than deferiprone. The observation was made that both compounds were equally effective in protecting the myocytes against iron-induced damage, even though desferrioxamine removed more iron, at the concentrations used.

The findings of the above *in vitro* study of rat neonatal myocytes were consistent with a study in humans suggesting decreased levels of iron in the heart during deferiprone therapy, but no benefit to heart function has been previously reported in patients. The first report of an apparent reduction in the amount of iron in the heart of a patient with thalassemia, based on magnetic resonance imaging (MRI) data, was reported in 1994 (Reference 11). The second was by the same author a year later (Reference 10). However, since the MRI was considered a semi-quantitative instrument in its ability to measure cardiac iron concentrations, and since the relationship between the level of cardiac iron and iron-induced heart disease was not known, it would have been inappropriate, at that time to have connected these observations with a reduced risk of heart disease. In addition, this author subsequently hypothesized that deferiprone is toxic to the heart (Reference 28).

Another potential contributing factor to the generation of heart disease in conditions of iron overload is "non-transferrin-bound iron" (NTBI), which is

believed to represent iron bound to a heterogeneous group of non-specific and/or non-protein carriers, such as citrate. Current literature suggests that high levels of NTBI may play an important role in the development of heart disease in patients with iron overload and that a reduction in these levels may decrease the risk of developing heart disease (Reference 58).

There are some very recent publications that support the discovery of the cardioprotectant effects of deferiprone, including one published a few months ago by Mumby et al (Reference 59), where the authors state, "Our data suggest that pediatric patients are at greater risk of iron overload during cardiopulmonary bypass, and that some form of iron chelation therapy may be advantageous to decrease oxidative stress." The applicant emphasizes that this suggestion by these authors does not refer to chronic iron loading in conditions such as thalassemia, but rather to a possible acute iron loading situation, of a much less magnitude than in thalassemia, that theoretically may occur during the procedure of cardio pulmonary bypass during heart surgery. Reference 40 by Dr. van der Kraaij et al noted that there may be protection by the administration of the orally active iron chelator deferiprone which may be a promising and easily accessible approach in establishing postischemic cardiac protection in patients. Another paper (Reference 13 by De Franceshchi et al), reports that deferiprone therapy can remove pathological free iron from beta-thalassemic membrane erythrocytes, irrespective of its ability to decrease total body iron. This may be indirectly related to deferiprone's cardioprotective effect as well.

Reference is made to United States Patent No. 4,840,958 by Hider et al which claims a method of treatment of a patient having a toxic concentration of iron in the body comprising administering to said patient by mouth, by bowel or parenterally, an effective amount to reduce said toxic concentration of a 3-hydroxypyrid-4-one compound which in one embodiment is deferiprone. See also at column 6, line 65. Further reference is made to UK Patent 2,118,176 to Hider et al.

Finally, reference 43, by Kaul and Venkataram discusses sustained release tablet formulations for deferiprone which, as would normally be expected by those skilled in the art, include Eudragit (a Trade mark), an acrylic based polymer, and hydroxypropylmethylcelulose.

Thus while a general review of the literature reveals that deferiprone is effective in removing iron from patients who are iron loaded (not withstanding some dissenting views), it is not definitive and clear whether or not such activity would result in decreased iron-induced heart disease and in prolongation of life. Nowhere is there taught the cardio selective/preferred function of deferiprone in relation to desferrioxamine and/or other chelating agents when administered to patients having iron overload.

It is therefore an object of this invention to use deferiprone or a physiologically acceptable salt thereof for treating and/or preventing iron induced cardiac disease or cardiac complications in a patient with iron overload, such as thalassemia or the like.

It is a further object of the invention to provide a method of reversing and or preventing iron induced cardiac disease in a patient with iron overload, such as thalassemia or the like.

Further and other objects of the invention will become apparent to those skilled in the art when considering the following summary of the invention and the detailed description of preferred embodiments related thereto.

SUMMARY OF THE INVENTION

Applicants have now discovered that the use of deferiprone in effective amounts as an iron chelating agent for patients suffering from an iron overload condition such as is found in those suffering from for example, thalassemia,

hemochromatosis, or the like provides for unexpected prevention/stabilization/reduction of the risk of heart disease such as heart failure and iron-induced cardiac complications. We have unexpectedly discovered that deferiprone has a cardio selective/preferred function when compared to desferrioxamine or alternative chelating agents utilized in patients suffering iron overload. We have also determined that certain benefits are realized by the administration of deferiprone in addition to desferrioxamine to patients suffering from iron overload.

Therefore according to one aspect of the invention we have provided a method of treating and or preventing iron induced cardiac disease (such as heart failure, and iron induced cardiac complications) in a patient with iron overload, such as thalassemia or the like, comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat or prevent the iron overload condition (the iron induced cardiac disease) normally associated with thalassemia or the like.

According to another aspect of the invention we have provided a novel use of deferiprone to treat or prevent iron induced cardiac disease such as heart failure and iron-induced cardiac complications in a patient with iron overload such as thalassemia or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat the iron overload condition (the iron induced cardiac disease) normally associated with thalassemia or the like.

According to another aspect of the invention there is provided a novel use of deferiprone or a physiologically acceptable salt thereof for the prevention/stabilization/reduction of the risk of heart disease such as heart failure and iron induced cardiac complications in patients having an iron overload condition associated with thalassemia or the like.

According to another aspect of the invention there is provided an effective therapeutic amount of deferiprone or a physiologically acceptable salt thereof for the prevention/stabilization/reduction of the risk of heart disease such as heart failure and iron induced cardiac complications in patients having an iron overload condition such as thalassemia or the like comprising an effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat the iron overload condition normally associated with thalassemia or the like.

According to another aspect of the invention there is provided a method of preventing/stabilizing/reducing the risk of heart disease such as heart failure and iron induced cardiac complications in patients having an iron overload condition such as thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat the iron overload condition normally associated with thalassemia or the like.

According to another aspect of the invention there is provided a novel use of deferiprone in the manufacture of a pharmaceutical for preventing/stabilizing/reducing the risk of heart disease such as heart failure and iron induced cardiac complications in patients having an iron overload condition such as thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat the iron overload condition normally associated with thalassemia or the like.

Effective amounts of deferiprone for administration according to the invention, not only removes iron from the body, as does desferrioxamine, but also is able to bind with available iron within and/or in contact with vital organs and in so doing decrease iron-induced damage to such vital organs. Applicants have discovered the administration of these effective amounts results, in said patient being less at risk of developing cardiac disease than a patient treated with

desferrioxamine. The mechanism of the apparent cardio-protective effect of deferiprone may be because of its lipophilicity and low molecular weight. Therefore, deferiprone can readily cross cell-membranes and bind intracellular iron. It may be postulated that even at relatively high liver iron concentrations, deferiprone can remove iron directly from myocytes, thus lowering or preventing iron-induced damage. This has never been demonstrated for desferrioxamine.

Even though DFO reduces general iron stores in the body, it is not cardio preferential when given subcutaneously, even for those who can (85%+) comply with the difficult parenteral regimen. Applicant's best understanding is that deferiprone readily crosses membranes and binds intracellular iron. One explanation may involve its lipophilicity, low molecular weight, and neutral charge at a pH of 7.4.

According to yet another aspect of the invention there is provided a novel use of deferiprone for the prevention, treatment, or reversal of heart disease in a patient having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone, or a physiologically acceptable salt thereof in order to preferentially reduce the iron stores in the heart in comparison to less critical organs/tissue in the body.

According to yet another aspect of the invention there is provided a therapeutically effective amount of deferiprone or physiologically acceptable salt thereof for the prevention, treatment, or reversal of heart disease in patients having an iron overload condition of the heart comprising an effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

According to yet another aspect of the invention there is provided a novel use of deferiprone or a physiologically acceptable salt thereof in the manufacture of a pharmaceutical for the prevention, treatment or reversal of heart disease in patients having an iron overload condition of the heart comprising a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

According to yet another aspect of the invention there is provided a novel use of deferiprone for the treatment, prevention, or reversal of heart disease in a patient having an iron overload condition of the heart comprising administering to the patent a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof for the direct preferential reduction/removal of iron (for example - intracellular iron) stores in the heart.

According to yet another aspect of the invention there is provided a novel use of deferiprone to prevent/treat/reverse the occurrence of iron-induced cardiac disease in patients with an iron overload condition such as thalassemia or the like, comprising administering to said patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof, wherein deferiprone's efficacy is cardio preferential when compared with its ability to lower total iron stores in the body.

According to yet another aspect of the invention there is provided a novel method of treating/preventing/or reversing heart disease in a patient having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone, or a physiologically acceptable salt thereof in order to preferentially reduce the iron stores in the heart in comparison to less critical organs/tissue in the body.

According to yet another aspect of the invention there is provided a novel method of treating/preventing/or reversing heart disease in patients having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

According to yet another aspect of the invention there is provided a novel method of treating/preventing/or reversing heart disease in patients having an iron overload condition of the heart comprising a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

According to yet another aspect of the invention there is provided a novel method of treatment, prevention, or reversal of heart disease in a patient having an iron overload condition of the heart comprising administering to the patient

a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof for the direct preferential reduction/removal of iron (for example - intracellular iron) stores in the heart.

According to yet another aspect of the invention there is provided a novel method to prevent/treat/reverse the occurrence of iron-induced cardiac disease in patients with an iron overload condition such as thalassemia or the like, comprising administering to said patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof, wherein deferiprone's efficacy is cardio preferential when compared with its ability to lower total iron stores in the body.

Preferably the uses and methods previously described further comprise the pharmaceutical deferiprone or a physiologically acceptable salt thereof for preventing/stabilizing/reducing the risk of heart disease such as heart failure and iron induced cardiac complications in patients having an iron overload condition such as thalassemia or the like and preferably further comprises an orally administrable dosage form of deferiprone or a physiologically acceptable salt thereof with other excipients as would be understood by persons skilled in the art. Preferably the daily administration of an amount of deferiprone and physiologically acceptable salt thereof is substantially in the range of up to 150mg/kg of body weight of the patient, or alternatively up to 125 mg/kg, or in another embodiment up to 75mg/kg. As is known the implied body weight assumed is a 50-60 kg individual in the case of thalassemia, or otherwise a 70kg individual. In one embodiment the administration of a dosage amount of deferiprone or a physiologically acceptable salt thereof is preferably 25mg/kg administered three times daily.

Preferably deferiprone is administered in a manner selected from the group of intravenously, transdermally, rectally, orally, bucally, or aurally. In a preferred embodiment deferiprone is administered orally. In one embodiment the dosage form is a sustained release formulation preferably made in accordance with the common knowledge of a man skilled in the art. By having a constant level of deferiprone in the body, we protect against the development of heart damage from non-transferrin-bound iron. Although the current formulation provides protection, blood levels fall to very low levels after about 4 hours. Thus a sustained release formulation provides a greater level of protection by providing higher blood levels throughout the dosing period.

Although compositions incorporating a liquid diluent may be used for oral administration, it is preferred to use compositions incorporating a solid carrier, for example a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate which provides a suitable oral dosage form that is stable and does not degrade. Other forms of administration other than by injection or oral administration may also be employed such as for example by the use of suppositories.

Brief Description of the Figures

The invention will now be illustrated with reference to the following Brief Description of the Figures and Detailed Description of Embodiments.

Figure 1 is a flow chart depicting a comparison of the cardiac function of a sample population.

Figure 2 is a Kaplan-Meier Analysis of heart disease free survival over the study period.

Detailed Description of Embodiments

Numerical Reference in this discussion is made to the list of references listed in the background of the invention.

The efficacy of iron chelation by desferrioxamine therapy, in subjects with thalassemia major is known. Daily subcutaneous infusions of desferrioxamine has been shown to ameliorate hepatic, cardiac and endocrinological dysfunction, improve growth and sexual maturation, and prolong survival in iron-overloaded thalassemia major patients. [1,2,3,4,5] However, iron-induced cardiac disease remains a frequent cause of morbidity in patients with thalassemia and is still responsible for 70% of the deaths among those subjects.[6] A sustained reduction in iron load, as measured by the proportion of serum ferritin results below 2500 µg/L, and the ability to comply with daily infusions of desferrioxamine have been reported to be the most important factors in the survival among patients with thalassemia major.[1,7] The age at the start of chelation therapy and the hepatic iron concentration may also affect the development of cardiac disease.[4,6]

Deferiprone, (1,2-dimethyl-3-hydroxypyrid-4-one), is an orally active iron chelator that has been approved for patients with thalassemia major for whom desferrioxamine is contraindicated or who present serious toxicity with desferrioxamine therapy. Results from clinical studies have demonstrated the ability of deferiprone to remove iron from the body.[8,9] It may be relatively selective in removing iron from the heart.[10,11,12] Such activity may be a function of the physicochemical properties of deferiprone, enabling it to cross cardiac cell membranes and remove excess intracellular iron directly[13], as opposed to the more generalized action of desferrioxamine which appears to decrease cardiac iron indirectly by lowering total body iron. On the other hand, concerns have been raised that some bidentate iron chelators may play a role in Fenton reactions under conditions of incomplete iron binding[14], although more recent evidence discounts this likelihood when biologically relevant *in vitro* systems are employed for the study of reactive oxygen species.[15] Thus, while *in vivo*

(animal studies) and *in vitro* studies are helpful, data from clinical studies are necessary to evaluate the long term efficacy of deferiprone in preventing/stabilizing/reducing iron-induced cardiac disease.

Although the long-term efficacy of deferiprone has been evaluated in various clinical trials, no information is available on the long-term efficacy of deferiprone in preventing iron-induced cardiac complications or in prolonging the survival of subjects with thalassemia major.

While a prospective study comparing deferiprone-treated and untreated patients is not possible, due to ethical concerns, meaningful data has been obtained by conducting a retrospective study comparing cardiac disease and survival in deferiprone and desferrioxamine-treated patients. A preliminary analysis by us of the data from one of the centers involved in a long-term trial with deferiprone, enabled us to determine that the use of deferiprone will prevent the occurrence of iron-induced cardiac disease in patients with thalassemia major, and that protection is greater than would be predicted from its ability to lower total body iron alone.

Applicant has explored this matter in depth and herein provides insight on the prevalence and progression of cardiac disease, and on the survival of patients treated with deferiprone for 4 or more years and compares the results with those of patients treated with daily subcutaneous infusions of desferrioxamine over the same period of time. The results of this study are set out below which also draws on the previously listed literature to interpret the findings and place them in perspective.

METHODS

Study Design

The study was a single centre, retrospective analysis of medical records of the occurrence of cardiac disease and of the survival of all subjects with thalassemia major treated with deferiprone or with desferrioxamine at the Centro Microcitemie of the University of Turin since January 1, 1995. The medical records were evaluated of all patients ≥ 5 year-old at the time of the start of the review period and who had the diagnosis of thalassemia major confirmed by laboratory tests (electrophoresis and/or DNA analysis) and clinical criteria (participant's hemoglobin and transfusion dependency). Patients with anemia other than thalassemia major, who were HIV antibody positive, or who had a history of malignancy or required radiation or chemotherapy were not included in this review.

All patients were subjected to the same transfusion regimen aimed at maintaining the pretransfusion hemoglobin levels at 9.5-10.0 g/dL and the mean hemoglobin at 12.0 g/dL. At each episode of red blood cell transfusion, each patient was interviewed and underwent clinical evaluation by a staff physician. The iron overload was determined by monthly assessment of the transfusional-iron input and by quarterly assessment of serum ferritin. Some patients also had an annual assessment of their liver iron concentration, determined by magnetic susceptometry SQUID (Hamburg, Germany) or by biochemical assay of liver biopsy samples.

In addition to the clinical evaluation and laboratory testing, patients underwent periodic cardiac examination and assessment by a cardiologist, which in addition to the physical examination included echocardiogram and 24-hour electrocardiographic Holter monitoring if indicated. Cardiac disease was classified, according to the criteria defined by the New York Heart Association[17], by a cardiologist experienced in heart problems in subjects with hemoglobinopathies and who was unaware of the chelation therapy of the patients. Worsening of the Systolic Function (SF) or the Ejection Fraction (EF) was defined as an abnormal result at the last assessment in patients with a normal result at the first assessment for the study. Improvement was defined as

a normal result at the last assessment for patients with an abnormal result at the first assessment. The first cardiac assessment was considered as the baseline value for each patient. For patients with more than one echocardiograph assessment within a year of the study, the change was based on the mean of the results of that year.

Starting in 1995, a substantial proportion of subjects followed up at the center were treated with deferiprone, in clinical trials or for compassionate therapy. For these patients, deferiprone was given in a dose of 25 mg/kg of body weight, three times per day. The remaining patients had maintained therapy with desferrioxamine (20 to 60 mg/kg/day), given as a subcutaneous infusion for 8 to 12 hour, 4 to 7 days a week except for one patient. Although 2 patients in the desferrioxamine group had their chelation intensified with intravenous chelation during the period of this review, they were not excluded from the analysis.

For patients treated with desferrioxamine compliance with chelation therapy included the following at each transfusional event:

1.0 an individual interview focused on compliance with a non-directive approach,

2.0 the examination of infusion sites,

3.0 the comparison of the number of infusions prescribed to the number of infusions reported by the patient,

4.0 records of the electronic infusor Crono® (Cane S.r.I, Italy) which registers the number of infusions, and

5.0 the pharmacy records of desferrioxamine, syringes and needles dispensed.

For patients treated orally with deferiprone, in addition to the individual interview, the compliance was assessed at each transfusional event by the electronic MEMS® cap (Medication Event Monitoring System, Ardex Ltd, Switzerland) which records the time and date of each opening of a deferiprone

container. Each record of opening of a container was presumed to represent an administered dose. Compliance was also measured by monthly counts of the number of deferiprone tablets dispensed and returned. For patients whose therapy with either chelator was interrupted for more than 4 weeks during the review period, the compliance was not calculated during the interval of interruption, but calculated separately for the various treatment periods.

Blood consumption was calculated annually using a previously standardized method[18] on the basis of the net weight and hematocrit of the blood transfused, and stored in a specific computerized system.

The Institutional Review Board (IRB) of the Turin Regional Health Authority, Italy, reviewed and approved the study protocol. Consent for review of the medical charts was obtained from patients and, for those under the age of 18, from their guardians.

Statistical Analysis

To evaluate the differences at baseline between the two groups of patients that could have an impact on the occurrence of cardiac disease and/or survival, the following clinical and laboratory parameters at the start of the study period were analysed:

1) Gender
2) Age
3) Age at start of chelation therapy
4) Transfusional iron input in the year preceding the study
5) Serum ferritin results at the initiation of the review period
6) Percentage of patients with more than 50% of their serum ferritin results greater than 2,500 µg/L
7) Percentage of patients with HCV antibodies
8) Liver iron concentration during the year preceding the study period

9) Urinary iron excretion results in the year preceding the study
10) Incidence of patients with cardiac disease (NYHA class I to IV) at their first cardiac assessment

The following parameters were used for comparison at termination:

1.0 Kaplan-Meier analysis of heart disease-free survival
2.0 Transfusion iron input
3.0 Mean of all serum ferritin results during the last year of the study
4.0 Percentage of patients with more than 50% of their serum ferritin results greater than 2,500 µg/L during the period of the study
5.0 Compliance with chelation
6.0 Liver iron concentration
7.0 Mean of all urinary iron excretion results in the last year of the study
8.0 Incidence of patients with cardiac disease (NYHA class I to IV) at their last cardiac assessment
9.0 Worsening or improvement of the NYHA classification

Two sample t-tests or Chi-square tests, where appropriate, were used to compare the baseline characteristics of the two treatment groups.

The Kaplan-Meier analysis of heart disease free survival for patients who were disease-free (NYHA class not applicable=0) at the beginning of the review period was performed by using the procedure LIFETEST from SAS (SAS Institute, Cary, NC). The primary comparison of the two groups was based on the log rank test. As not all patients had a cardiac assessment at the beginning of the review period (year 0), the time for development of heart disease was calculated as the time difference between the first available NYHA class of 0 and the first occurrence of a greater than 0 NYHA class. In addition to the Kaplan-Meier analysis, the incidence of patients with a worsening of their NYHA class from the first to the last cardiac assessment was determined for each treatment group. Chi-square test was performed to compare the incidence between the two groups. The incidence

of patients with cardiac disease diagnosed at the first cardiac assessment who showed an improvement of their NYHA class during the study was determined and compared between the two treatment groups by using the Fisher's Exact test.

To evaluate the differences related to chelation therapy between the two groups of subjects, after the start of the study, 2 sample t-tests or Chi-square tests were performed to compare their transfusional iron input, serum ferritin, percentage of subjects with more than 50% of their serum ferritin data greater than 2500 µg/L during the study, compliance with chelation therapy, liver iron concentration and urinary iron excretion.

All statistical tests were two-sided with a type 1 error (α) of 0.05. SAS (version 6.12) was used for conducting all the statistical tests.

Documentation Monitoring

A review of source documentation such as clinical charts, cardiac assessment reports and laboratory slips was made. The monitoring was conducted with 100% source document verification of the critical data cardiac assessments and 10% source document verification for non-critical data (e.g. serum ferritin results). The accepted overall error rate was 0% for critical data and less than or equal to 0.5% for non critical data.

The methodology employed in this study was a retrospective analysis of well-documented data. It is important to provide as much information as possible in retrospective analysis to prevent a selection bias, if any. In keeping with this philosophy, data for all patients that met the inclusion criteria were included. Whenever a parameter was compared in the deferiprone and desferrioxamine groups, the number of subjects which were included in each group was identified. Figure 1 provides a graphical illustration of the main comparative groups.

Results

A total of 126 patients out of the 168 patients with thalassemia major, had been treated with desferrioxamine or deferiprone for 4 or more years at the Centro di Microcitemie since January 1, 1995. Six out of the 168 patients were younger than 5 years-old at the start of the review period and were not evaluated. One patient was excluded since he presented serum antibodies for HIV. Eleven additional patients were also excluded from the study because no information was available on their chelation therapy or cardiac status. The remaining 24 patients were excluded from the analysis for having not been prescribed deferiprone or desferrioxamine for at least 4 years during the review period. One patient treated with deferiprone was maintained in the analysis although he had interrupted therapy for approximately one year during the review period.

All but one of the 126 evaluated patients were regularly chelated with daily subcutaneous infusions of desferrioxamine prior to the start of the period of this review. In 1995, forty-eight of those patients had their chelation therapy switched to deferiprone (oral administration) whereas the remaining 78 were maintained with desferrioxamine. At the time of the start of the review period, hepatic iron concentration was measured by magnetic biosusceptometry SQUID (Hamburg, Germany) in 46 of the patients treated with deferiprone and in 17 of those treated with desferrioxamine. Thirty-seven of the patients switched to deferiprone also had their hepatic iron concentration measured by biochemical assay of liver biopsy samples.

At the start of the study, both treatment groups were similar for age, gender distribution, serum ferritin values, the percentage of patients with the majority of their serum ferritin values greater than 2,500 ug/L and urinary iron excretion results during the 2 years that preceded the study, and for the amount of

transfusional iron input during the previous year. Patients whose therapy was switched to deferiprone, on the average, started chelation therapy with desferrioxamine slightly earlier than patients who were maintained with desferrioxamine. However, the mean hepatic iron concentration in the group switched to deferiprone (1.5 mg/g wet weight) appeared to be higher than that of the desferrioxamine group (1.0 mg/g wet weight) at the time of the switch.

The prevalence of cardiac disease at the first assessment was similar for both groups. Table 1 summarizes the results of the assessments at the start of the study period.

TABLE 1 - Comparison of deferiprone and desferrioxamine-treated patient groups at the start of the study

	Deferiprone (N=48)	Desferrioxamine (N=78)	p
Percentage female	46 (22)	53 (41)	0.463
Mean age ± SD (years)	17.1 ± 3.7	18.8 ± 7.1	0.085
Mean age ± SD at start of chelation therapy with desferrioxamine (years)	4.6 ± 2.7 (48)	6.5 ± 4.7 (76)	0.006
Mean serum ferritin ± SD (µg/L)	2047 ± 943 (48)	1787 ± 1425 (64)	0.248
Percentage of patients with more than 50% of their serum ferritin results > 2,500 µg/L	25 (48)	14 (64)	0.142
Percentage of patients positive for HCV antibodies	87 (46)	75 (68)	0.119
Mean transfusional iron input ± SD (mg Fe/year)	7732 ± 1912 (47)	6960 ± 2213 (46)	0.076
Mean DFO-induced urinary iron excretion ± SD mg Fe/day	15.4 ± 10.5 (46)	15.0 ± 11.0 (53)	0.831
Mean heptic iron concentration ± SD – SQUID*	1.5 ± 0.7 (46)	1.0 ± 0.6 (17)	0.003
Mean hepatic iron concentration ± SD – Biopsy†	8.2 ± 5.6 (37)	Not available	—
Percentage of patients with cardiac disease at first assessment	10 (5)	14 (11)	0.546

*mg Fe/g liver wet weight
†mg Fe/g liver dry weight
(N): number of patients

The mean time of follow-up was 3.9 ± 1.4 years for patients treated with deferiprone and 4.8 ± 0.7 years for patients treated with desferrioxamine, which represents a cumulative total of 216 and 386 patient-years of observation for the deferiprone and desferrioxamine groups respectively. The mean compliance with deferiprone was 89% ± 7% SD (range 66% - 99%), which was similar to that of desferrioxamine at 86% ± 11% (54% - 100%). The average prescribed dose of desferrioxamine during this period was 33.5 ± 4.0 mg/kg of body weight/day (range 20 to 45).

During the review period, patients treated with deferiprone were more heavily transfused than patients treated with desferrioxamine ($p=0.0001$) and also presented higher annual mean serum ferritin values over the first 3 years of follow-up ($p<0.05$). Nevertheless, by the end of the study period, there was no significant difference in the annual mean serum ferritin values between the 2 arms of treatment. The percentage of patients who had more than 50% of their serum ferritin values above the apparent threshold for cardiac disease (2500 µg/L)[7] throughout the review period was similar between the 2 groups. The deferiprone-induced mean annual urinary iron excretion (UIE) was greater than the desferrioxamine-induced urinary iron excretion. No decrease in UIE was observed overtime in either group of patients. Table 2 summarizes the results of the analysis.

TABLE 2 - Comparison of deferiprone and desferrioxamine-treated patient groups during the study period.

	Deferiprone (N = 48)	Desferrioxamine (N = 78)	p
Percentage of compliance with chelation therapy	89 ± 7	86 ± 11	0.024
Mean ± SD overall transfusional iron input (mg Fe/year)	8777 ± 1948	7445 ± 2103	0.000
Mean ± SD overall urinary iron excretion (mg Fe/day)	18.1 ± 13.2	15.5 ± 12.9	0.000
Mean serum ferritin µg/L ± SD at year 4 of the review period	2402 ± 1331	2050 ± 1319	0.153
Percentage (%) of patients with more than 50% of their serum ferritin results > 2,500 µg/L during the review period	33	21	0.139
Mean ± SD hepatic iron concentration – SQUID* during the last year of the review period	2.5 ± 1.2 (24)	1.8 ± 1.0 (15)	0.075
Percentage (ratio) of patients with improvement of cardiac disease diagnosed at first assessment	40 (2/5)	27 (3/11)	1.000
Percentage (ratio) of patients with worsening of the cardiac disease	4 (2/45)	17 (10/59)	0.048

*mg FE/g liver wet weight (N): number of patients

Cardiac Disease

Forty-five patients from the deferiprone group and 59 patients from the desferrioxamine group had at least 2 cardiac assessments during the study period. The mean age at the start of chelation therapy with desferrioxamine of the patients who switched to deferiprone was lower than that of patients maintained on desferrioxamine (4.6 ± 2.6 vs 7.0 ± 5.0 years; p= 0.004). The former group of patients were also younger than the latter (17.2 ± 3.7 vs 20.9 ± 6.1 years; p= 0.0002). On the other hand, the deferiprone group of patients appears to have started the study with a higher heptic iron concentration (1.6 ± 0.7 vs 0.9 ± 0.5 mgFE/g liver wet weight; p= 0.0003) and were more heavily transfused than patients treated

with desferrioxamine during the review period (8759 ± 1975 vs 7622 ± 2450 mgFE/year p=0.0001).

TABLE 3 - Patients who were cardiac disease-free at the first assessment and had cardiac disease diagnosed at a follow-up assessment during the study.

Patient Identification	Chelation Therapy	NYHA class (years after 1st normal assessment)
48	Deferiprone	1 (2)
96	Deferiprone	1 (2)
14	Desferrioxamine	1 (2)
20	Desferrioxamine	1 (4)
40	Desferrioxamine	1 (2)
61	Desferrioxamine	1 (2)
63	Desferrioxamine	1 (2)
76	Desferrioxamine	1 (4)
77	Desferrioxamine	1 (2)
101	Desferrioxamine	1 (2)
122	Desferrioxamine	1 (2)

An improvement of the NYHA cardiac disease classification was observed in 2 of the 5 (40%) deferiprone patients and in 3 of the 11 (27%) desferrioxamine patients with cardiac disease diagnosed at the first assessment. A worsening of the cardiac disease was observed in one of the 11 desferrioxamine-treated patient with previously diagnosed cardiac disease and in none of the 5 deferirpone-treated patients. Newly diagnosed cardiac disease occurred in 2 of the 40 (5%) deferiprone treated patients who were cardiac disease-free at the first assessment and had a second cardiac assessment during the duration of the study. Newly diagnosed cardiac disease occurred in 9 of the 48 (19%) desferrioximine treated patients who were cardiac disease-free at the first assessment and had a second cardiac assessment during the duration of the study (Table 3). Kaplan-Meier analysis indicates a significant difference p = 0.047) in the cardiac disease free survival between the two groups. Overall, a worsening of the cardiac disease was diagnosed in 2 (4%) deferiprone-treated patients and in 10 (17%) desferrioxamine-treated patients (p=0.048). Table 4 provides a summary of the demographics,

chelation history, and iron load of the patients who had a worsening of the cardiac function during the study period.

An abnormal SF at the first ecocardiographic assessment of the study was observed in 4 patients from the deferiprone group and in 8 from the desferrioxamine group. Improvement of the SF was observed in 2 of the 4 deferiprone-patients and in 5 of the 8 desferrioxamine-treated patients. A worsening of the SF at the last assessment was observed in 2 deferiprone-treated patients and in 6 desferrioxamine-patients.

Abnormal EF at the first assessment was observed in 3 patients, 2 treated with deferiprone and the other one with desferrioxamine. All three patients presented a normalization of the EF during chelation therapy. Worsening of the EF was observed in 3 patients , all of them in the desferrioxamine group. Seven deferiprone and 16 desferrioxamine patients had at least two 24-hour Holter assessments during the study period. Arrhythmia requiring medication was diagnosed in the first assessment in 4 patients, all in the desferrioxamine group of patients. No change was observed over time in the Holter assessment in any of the evaluated patients.

Two patients received intensive chelation therapy with intravenous desferrioxamine due to the severity of iron overload during the period of the study. One of them also presented a worsening of the cardiac function during the study.

Survival

No patient treated with either deferiprone or desferrioxamine for 4 or more years died during the study period. Three months after the completion of the study period, a male patient that had been treated with desferrioxamine over the previous 5 years died of congestive heart failure. The patient was a 26 year-old at the beginning of the study period and had started chelation therapy with

desferrioxamine at age 13. During the study period his overall compliance with desferrioxamine was 54% and 89% of his serum ferritin values were greater than 2500 µg/L. No information was available regarding this patient's hepatic iron concentration. The first assessment of his cardiac function for this study was done at year 2 of the review period, when it was classified as class II. The patient's cardiac function was also ascertained as class II at the subsequent cardiac assessment during the study period.

One patient with thalassemia major who had not received either deferiprone or desferrioxamine for 4 or more years during the study period died at the Centro Microcitemie during that period. A 23 year old, female, unable to comply with subcutaneous infusions of desferrioxamine because of severe local reactions presented severe iron overload (mean serum ferritin = 9000 µg/L; HIC by SQUID = 9.6 mgFE/g liver wet weight; NYHA class IV). She developed heart disease and experienced two episodes of congestive heart failure while receiving intensive intravenous chelation therapy with desferrioxamine. On the occasion of the second episode, which was resistant to treatment, therapy with desferrioxamine was permanently discontinued due to infection of the central catheter. Heart failure continued to worsen and one month later, the patient initiated therapy with deferiprone, which was interrupted 19 days later because of pneumonia. There were no signs of neutropenia. The patient died a week later of congestive heart failure.

Discussion

Although effective iron chelation with desferrioxamine has been available for over 25 years, cardiac disease remains a frequent cause of morbidity and is still responsible for 70% of the deaths among patients with transfusion-dependent thalassemia patients.[1,6] Although poor compliance with desferrioxamine is considered a major contributing factor and survival beyond the age of 30 can be less than 20% for those patients unable to comply with more than 4 to 5 infusions of desferrioxamine per week.[1], even patients with good compliance

and relatively low levels of iron in the liver, succumb to iron-induced heart disease.

This retrospective study was the first to examine the specific issue of the development and progression of cardiac disease in subjects with thalassemia major treated with deferiprone for 4 or more years, and to compare it with patients treated with the standard therapy, desferrioxamine, over the same period of time.

Cardiac disease, as defined by the heart functional capacity classification developed by the New York Heart Association, was an end point in this study and it was assessed in all of the thalassemia major patients irrespective of chelating treatment type. Data to establish the diagnosis and progression of cardiac disease were obtained from the medical records of patients, noting in particular, physical examinations, echocardiograms, and 24-hour electrocardiographic Holter assessments.

Prior to the start of the study, patients had been prescribed chelation therapy with subcutaneous infusions of desferrioxamine, on an average of 6.2 days per week. Patients were young, with a mean age <19 in both groups and well chelated, as determined by the mean serum ferritin values, and by the mean hepatic iron concentration assessed in a subgroup of them. Patients whose therapy was switched to deferiprone had started iron chelation therapy with desferrioxamine at an earlier age (4.6 years) than patients who were maintained with desferrioxamine (6.5 years). On the other hand, those assigned to deferiprone treatment appeared to be more heavily iron loaded, as indicated by the transfusional iron input (7732 ± 1912 vs. 6960 ± 2213 mg/Fe/year), serum ferritin concentrations (2047 ± 943 vs. 1787 ± 1425 µg/L) and percentage of patients with more than 50% of their serum ferritin results > 2,500 µg/L (25% vs. 14%), although those differences were not statistically significant. The subgroup of deferiprone-treated patients with at least 2 cardiac assessments also started chelation therapy with desferrioxamine earlier than the subgroup of

desferrioxamine-treated patients (4.6 ± 2.6 vs 7.0 ± 5.0 years) and were younger at the start of the study period (17.2 ± 3.7 vs. 20.9 ± 6.1 years). On the other hand, during the study the sub-group of patients switched to deferiprone were more heavily transfused than patients maintained on desferrioxamine 8759 ± 1975 vs 7622 ± 2450 mg Fe/year).

None of the patients evaluated died during the study period, which may reflect the regular iron chelation treatment for both treatment groups during the study period. One patient with cardiac disease (NYHA class II) from the desferrioxamine arm died of congestive heart failure 3 months after the completion of the study. This patient had started chelation therapy with desferrioxamine at the age of 13 and during the study period had an overall compliance with desferrioxamine of 54%. During the same period of time, 89% of his serum ferritin values were above the 2500 µg/L threshold. No information was available regarding his hepatic iron concentration. A patient that did not participate in this study because she could not comply with subcutaneous infusions of desferrioxamine due to severe local reactions died of iron-induced heart failure during the review period.

All subjects that met the entry criteria were included, even if their first cardiac assessment was completed after the initiation of the study. For those patients who had their first assessment after the start of the study, the only perceivable impact of the later assessment would have been to shorten the effective assessment period. The first cardiac assessment of the study showed that the percentage of patients with cardiac disease was similar for both groups. The last cardiac assessment revealed that the number of patients that had an improvement of the cardiac function during the review period was also similar for both groups. However, a worsening of the cardiac function, occurred more frequently in the desferrioxamine-treated patients than in those who had been switched to deferiprone. Overall a worsening of the cardiac function was diagnosed in 2 (4%) deferiprone-treated patients and in 10 (17%) desferrioxamine-treated patients (p=0.048).

The mean age at the start of the study for the 12 patients who presented a worsening of the cardiac function was 19.5 ± 3.6 years (range 13 to 26) and their mean age at starting of chelation therapy with desferrioxamine was 5.8 ± 2.7 years (range 3 to 12). During the study period, their mean compliance with the chelation regimen was 88% ± 12.7% (range 54% to 99%) and their mean serum ferritin values ranged from 260 to 9947 µg/L. (2277 ± 1379 µg/L). Although 5 of the 12 patients had more than 50% of their serum ferritin values measured to be greater than 2500 ng/mL, before or during the study 3 patients did not present any serum ferritin value greater than this threshold during the review period. The hepatic iron concentrations of those patients with a worsening of the heart function ranged from 0.3 mg to 4.4 mg/Fe/g of liver wet weight (SQUID). The average hepatic iron concentration for those patients was 2.0 mg Fe/g of liver wet weight at the end of the study. There was no difference for any of these assessments between the patients who presented a worsening of the heart function and those who did not. Therefore even though desferrioxamine may reduce total body iron stores, some patients remain unprotected against iron-induced cardiac damage.

These data illustrate that development of cardiac disease in this cohort of transfused thalassemia patients could not have been predicted based upon serum ferritin values or liver iron concentrations. While it may be generally true that the greater the total iron body load, the greater the risk of developing iron-induced cardiac disease, no specific value of iron load was predictive of cardiac disease in those patients. These data support a recent study in 58 transfusion-dependent thalassemia patients where no correlation was observed between hepatic iron concentrations and cardiac function.[19].

Conclusions

The finding of this study is that patients maintained with the desferrioxamine treatment appear to be 4-fold more likely (p=0.048) to develop a worsening of

their cardiac status than those who were treated with deferiprone over the same period of time. The difference does not appear to be related to a lack of compliance during the review period in the desferrioxamine treated group. In fact, only one of the ten desferrioxamine-treated patients who presented a worsening of the heart function had a compliance rate <85%. Similarly, many of these patients were "well-chelated" based upon standard measures of total body iron, illustrating that the cardio-protective mechanism of deferiprone goes beyond simple chelation.

Other factors, such as the cardiac iron load or the presence of non-transferrin-bound iron (NTBI) may also play a role in the development of cardiac disease in patients with iron overload.[20]

In retrospect, results from previous clinical studies have generally suggested without clear conclusions, and not proving, that deferiprone can remove iron from the iron-overloaded heart.[10,11,21] Monitoring of iron deposition in the heart through MRI assessments of 23 patients treated with deferiprone for over one year showed an increase of the T2 relaxation time, consistent with a reduction in cardiac iron, from 26.6 ± 8.4 msec to 30.5 ± 6.7 msec ($p<0.005$) (normal 32 msec).[11] MRI assessments during a randomized trial revealed that after a mean treatment period of 22 months, (range 18 to 23 months) there was a significant improvement in T_2 relaxation time in deferiprone-treated patients, but no change in desferrioxamine-treated patients.[10] These MRI data support the findings of the present study, both for deferiprone and for desferrioxamine.

A recent publication by Hershko et al demonstrated that 100 µM of desferrioxamine or deferiprone exhibited equal cardio-protective effects against iron-induced damage in neonatal rat myocytes.[12] However, these concentrations are not clinically relevant for desferrioxamine. Although a serum concentration of 100 µM for deferiprone can occur with the administration of a single 25 mg/kg dose[22], the serum concentration of desferrioxamine in patients receiving 40 mg/kg/day is usually less than 10 µM.[23]. Since the desferrioxamine

concentrations used in the myocyte study were more than 10-fold the expected serum concentrations, the *in vivo* cardioprotective effect of this chelator would be expected to be less than that of deferiprone, but not four times less protective placing the patient at a 4-fold greater likelihood of developing a worsening of their cardiac status with desferrioxamine.

The mechanism of the apparent cardio-protective effect of deferiprone may be because of its lipophilicity and low molecular weight. Therefore, deferiprone can readily cross cell-membranes and bind intracellular iron.[13] It may be postulated that even at relatively high liver iron concentrations, deferiprone can remove iron directly from myocytes, thus lowering or preventing iron-induced damage. This has never been demonstrated for desferrioxamine.

Another factor may be related to the different pharmacokinetic characteristics of deferiprone and desferrioxamine when these drugs are given at standard doses, as in the present study. For example, deferiprone at 25 mg/kg, produces peak concentrations of approximately 100 μM with serum concentrations declining to about 10 μM in 6 hours, and this pattern is repeated three times daily, seven days a week. On the other hand, desferrioxamine at 40 mg/kg achieves concentrations of only 5-10 μM and only for the duration of the infusion (8-12 hours/day, 5-7 days per week). The long periods of time without the presence of an iron chelator may have a profound effect on the generation of iron-induced activity within myocytes and through non-transferrin bound iron. These explanations provide a potential basis for understanding the difference in response to the two chelators, which, as noted by Grady *at. al.* probably represent compounds with access to different iron pools.[24]

The successful reversal by deferiprone of the iron-induced congestive heart failure in a patient participating in the study provides evidence for the cardio-protective effect of this iron chelator.[31]

Early reports raised concerns about the potential role of some iron chelators in promoting Fenton reactions under conditions of incomplete iron binding.[14] However, a recent publication indicates that under physiological conditions there is virtually no generation of free radical damage and no more than would be expected in the control situation.[15] In addition, the toxicity that was observed with the experimental compound CP94 in gerbils, which was the basis for the hypothesis that some iron chelators may exacerbate iron toxicity, employed a defective animal model. Recently it has been shown that many of these animals have infections, but that in the absence of infection, iron does not induce liver fibrosis[32], leading to the conclusion that the infection of the animals not the use of the chelator under investigation, CP94, was responsible for the fibrosis, and this has been confirmed in a subsequent study using deferiprone in disease-free gerbils.[33]

In summary, due to scarcity of an appropriate animal model for predicting the human response to iron chelators, the results obtained in animal studies should be interpreted and have been interpreted herein with caution. The extensive clinical experience acquired during the long-term use of deferiprone by patients with thalassemia major greatly exceeds the value of the results observed in any short-term animal studies.

Clinical trials of deferiprone demonstrated that a dose of 75mg/kg of body weight/day can control the progression of iron overload in patients with transfusion-dependant thalassemia.[8,25,27-29,31,35] The reduction or stabilization of the patients' body iron load that is achieved with the use of deferiprone would be expected to contribute to some reduction on the incidence of cardiac disease, simply due to a decrease in the overall body iron load. This study has confirmed that conclusion, but the magnitude of protection was much greater than expected when measured against a chelator with equal or greater iron chelating ability, leading to the teaching presented in this study of an even greater protective effect than could be expected from overall iron reduction alone. The results also teach

that the use of deferiprone has a beneficial impact on the prevention of cardiac disease among transfusion-dependant thalassemia patients.

Preferably the dosage form may be a sustained release formulation made in accordance with the common knowledge of a man skilled in the art and the constituents set out in Chart A below. By having a constant level of deferiprone in the body, we protect against the development of heart damage from fluctuating levels of non-transferrin-bound iron. Although the standard formulation provides protection, blood levels fall to very low levels after about 4 hours. Thus a sustained release formulation provides a greater level of protection by providing higher blood levels throughout the dosing period. Chart A illustrates one of the formulations prepared by the applicants as an example of a sustained release formulation of deferiprone, where the active ingredient is 500 mg. Other types of sustained release formulations are possible as well.

CHART A

DEFERIPRONE (L1) TABS AS 500 MG CORE	
Ingredient Name	**Mg Per Tablet**
Hydroxypropyl Cellulose NF	6.0
Hydroxypropyl Methylcellulose USP	1.5
Polyethylene Glycol 8000 NF	4.5
Titanium Dioxide USP	6.0
Purified Water USP	132.0
Sub-Total	150.0
Cores:	
Deferiprone (L1) Tabs as 500 mg Core	600.0
Total (Excluding Water)	618.0

The Assignee completed other studies wherein the largest prospective clinical study ever conducted for an iron chelator was made. One hundred eighty-seven subjects with thalassemia were enrolled in this trial conducted by Drs. A. Cohen, R. Galanello, A. Piga, and V. De Sanctis in 3 centres in Italy and 1 center in the

USA. Similar to what was observed in the patients discussed above in this disclosure, no heart failure occurred in any of the other study centres in patients participating in that study, treated with deferiprone for up to 5 years.

As many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

Table 4 – Demographic, chelation, and iron overload in patients with a worsening of cardiac function during the study period.

Patient Identification No.	Chelation therapy during study period	Age at start of the study	Age at start of chelation therapy with deferoxamine	Compliance with chelation therapy	% Ferritin >2500 ng/mL during the 2 years prior the study	% Ferritin >2500 ng/mL during the study period	HIC prior to study (SQUID*/Biopsy†)	Last HIC at study (SQUID*/Biopsy†)
48	Deferiprone	21	6	80	0	83	0.6/3.8	2.0/NA
96	Deferiprone	17	4	98	25	37	1.9/5.6	2.3/NA
14	Deferoxamine	26	12	86	75	37	NA/NA	1.1/NA
20	Deferoxamine	24	9	89	100	92	NA/NA	4.4/NA
40	Deferoxamine	22	7	96	0	77	0.3/NA	NA/NA
50§	Deferoxamine	20	6	92	0	0	NA/NA	0.5/NA
61	Deferoxamine	19	5	88	0	0	1.4/NA	1.6/NA
63	Deferoxamine	19	4	94	0	3	1.5/NA	1.4/NA
76	Deferoxamine	18	4	54	14	77	NA/NA	2.9/NA
77	Deferoxamine	18	4	93	0	3	NA/NA	1.4/NA
101	Deferoxamine	17	3	99	0	3	NA/NA	1.4/NA
122	Deferoxamine	13	6	95	0	0	1.1/NA	1.0/NA

*mg Fe/g liver wet weight
†mg FE/g liver dry weight
§Cardiac disease diagnosed at the first assessment worsened during study period

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A method of treating iron induced cardiac disease in a patient with iron overload, such as in thalassemia or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

2. A method of preventing iron induced cardiac disease in a patient with iron overload, such as in thalassemia or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

3. For use to treat iron induced cardiac disease in a patient with iron overload , such as in thalassemia or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload..

4. For use to prevent iron induced cardiac disease in a patient with iron overload, such as in thalassemia or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload..

5. The use of deferiprone or a physiologically acceptable salt thereof for the prevention of the risk of heart disease in patients having iron overload, such as in thalassemia or the like.

6. The use of deferiprone or a physiologically acceptable salt thereof for the stabilization of the risk of heart disease in patients having iron overload , such as in thalassemia or the like.

7. The use of deferiprone or a physiologically acceptable salt thereof for the reduction of the risk of heart disease in patients having iron overload, such as in thalassemia or the like.

8. An effective therapeutic amount of deferiprone or a physiologically acceptable salt thereof for the prevention of the risk of heart disease in patients having iron overload, such as in thalassemia or the like, comprising an effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

9. An effective therapeutic amount of deferiprone or a physiologically acceptable salt thereof for the stabilization of the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising an effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

10. An effective therapeutic amount of deferiprone or a physiologically acceptable salt thereof for the reduction of the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising an effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

11. A method of preventing the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

12. A method of stabilizing the risk of heart disease in patients having iron overload , such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

13. A method of reducing the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

14. The use of deferiprone in the manufacture of a pharmaceutical for preventing the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

15. The use of deferiprone in the manufacture of a pharmaceutical for stabilizing the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

16. The use of deferiprone in the manufacture of a pharmaceutical for reducing the risk of heart disease in patients having iron overload, such as in thalassemia or the like comprising the administration of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

17. The use of deferiprone for the prevention, treatment, or reversal of heart disease in a patient having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone, or a physiologically acceptable salt thereof in order to preferentially reduce the iron stores in the heart in comparison to less critical organs/tissue in the body.

18. A therapeutically effective amount of deferiprone or physiologically acceptable salt thereof for the prevention, treatment, or reversal of heart disease in

patients having an iron overload condition of the heart comprising an effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

19. The use of deferiprone or a physiologically acceptable salt thereof in the manufacture of a pharmaceutical for the prevention, treatment or reversal of heart disease in patients having an iron overload condition of the heart comprising a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

20. The use of deferiprone for the treatment, prevention, or reversal of heart disease in a patient having an iron overload condition of the heart comprising administering to the patent a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof for the direct preferential reduction/removal of iron (for example - intracellular iron) stores in the heart.

21. The use of deferiprone to prevent/treat/reverse the occurrence of iron-induced cardiac disease in patients with an iron overload condition such as thalassemia or the like, comprising administering to said patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof, wherein deferiprone's efficacy is cardio preferential when compared with its ability to lower total iron stores in the body.

22. A method of treating/preventing/or reversing heart disease in a patient having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone, or a physiologically acceptable salt thereof in order to preferentially reduce the iron stores in the heart in comparison to less critical organs/tissue in the body.

23. A method of treating/preventing/or reversing heart disease in patients having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

24. A method of treating/preventing/or reversing heart disease in patients having an iron overload condition of the heart comprising a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof to preferentially reduce the iron stores in the heart in comparison to the iron stores in less critical organs/tissue in the body.

25. A method of treatment, prevention, or reversal of heart disease in a patient having an iron overload condition of the heart comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof for the direct preferential reduction/removal of iron (for example - intracellular iron) stores in the heart.

26. A method to prevent/treat/reverse the occurrence of iron-induced cardiac disease in patients with an iron overload condition such as thalassemia or the like,

comprising administering to said patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof, wherein deferiprone's efficacy is cardio preferential when compared with its ability to lower total iron stores in the body.

27. The use of any of the previous claims further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for preventing the risk of heart disease in patients having iron overload.

28. The use of any of the previous claims further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for stabilizing the risk of heart disease in patients having iron overload.

29. The use of any of the previous claims further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for reducing the risk of heart disease in patients having iron overload.

30. The method of any of the previous claims further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for preventing the risk of heart disease in patients having iron overload.

31. The method of any of the previous claims further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for stabilizing the risk of heart disease in patients having iron overload.

32. The method of any of the previous claims further comprising the active ingredient deferiprone or a physiologically acceptable salt thereof for reducing the risk of heart disease in patients having iron overload.

33. The method of any previous claim further comprising an oral dosage form of deferiprone or a physiologically acceptable salt thereof with other excipients.

34. The use of any previous claim further comprising an oral dosage form of deferiprone or a physiologically acceptable salt thereof with other excipients.

35. The method of any previous claim further comprising daily administration of an amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 150mg/kg to the patient.

36. The use of any previous claim further comprising daily administration of an amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 150mg/kg to the patient.

37. The method of any previous claim further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 125 mg/kg to the patient.

38. The use of any previous claim further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of up to 125 mg/kg to the patient.

39. The method of any previous claim further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of 25mg/kg to 75mg/kg to the patient.

40. The use of any previous claim further comprising administration of a daily dosage amount of deferiprone or a physiologically acceptable salt thereof substantially in the range of 25mg/kg to 75mg/kg to the patient.

41. The method of any previous claim wherein deferiprone is administered in a manner selected from the group of intravenously, transdermally, rectally, orally, bucally, or aurally.

42. The use of any previous claim wherein deferiprone is administered in a manner selected from the group of intravenously, transdermally, rectally, orally, bucally, or aurally.

43. The method of any previous claim wherein deferiprone is administered orally.

44. The use of any previous claim wherein deferiprone is administered orally.

45. The method of any previous claim wherein the dosage form is a sustained release formulation.

46. The use of any previous claim wherein the dosage form is a sustained release formulation.

47. The method of any previous claim wherein deferiprone has a cardio preferred/selective function when compared to desferrioxamine or other alternative chelating agents utilized in patients suffering iron overload.

48. The use of any previous claim wherein deferiprone has a cardio preferred/selective function when compared to desferrioxamine or other alternative chelating agents utilized in patients suffering iron overload.

49. The method of any previous claim wherein deferiprone is administered in addition to desferrioxamine.

50. The use of any previous claim wherein deferiprone is administered in addition to desferrioxamine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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10 January 2002 (10.01.2002)

PCT

(10) International Publication Number
WO 02/02114 A1

(51) International Patent Classification[7]: A61K 31/44, 31/16, A61P 9/00

(21) International Application Number: PCT/CA01/00956

(22) International Filing Date: 28 June 2001 (28.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2,313,270 30 June 2000 (30.06.2000) CA

(71) Applicant *(for all designated States except US)*: **APOTEX INC.** [CA/CA]; 150 Signet Drive, Weston, Ontario M9L 1T9 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SPINO, Michael** [CA/CA]; 980 Duncannon Drive, Pickering, Ontario L1X 2P3 (CA). **PIGA, Antonia** [IT/IT]; Strada Torino 15B, I-10024 Moncalieri (IT).

(74) Agent: **IVOR, M., Hugues**; Suite 200, 175 Commerce Valley Drive West, Thornhill, Ontario L3T 7P6 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/02114 A1

(54) Title: A NEW USE FOR DEFERIPRONE

(57) Abstract: A method of treating iron induced cardiac disease in a patient with iron overload, such as in thalassemia or the like comprising administering to the patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to treat iron induced cardiac disease normally associated with iron overload.

CARDIAC FUNCTION IN PATIENTS WITH THALASSEMIA MAJOR TREATED WITH DEFERIPRONE OR DEFEROXAMINE

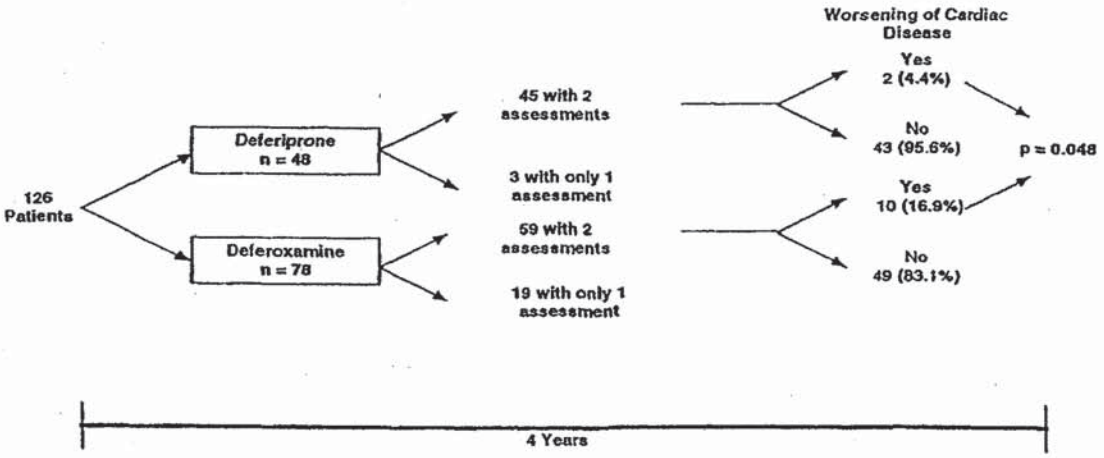
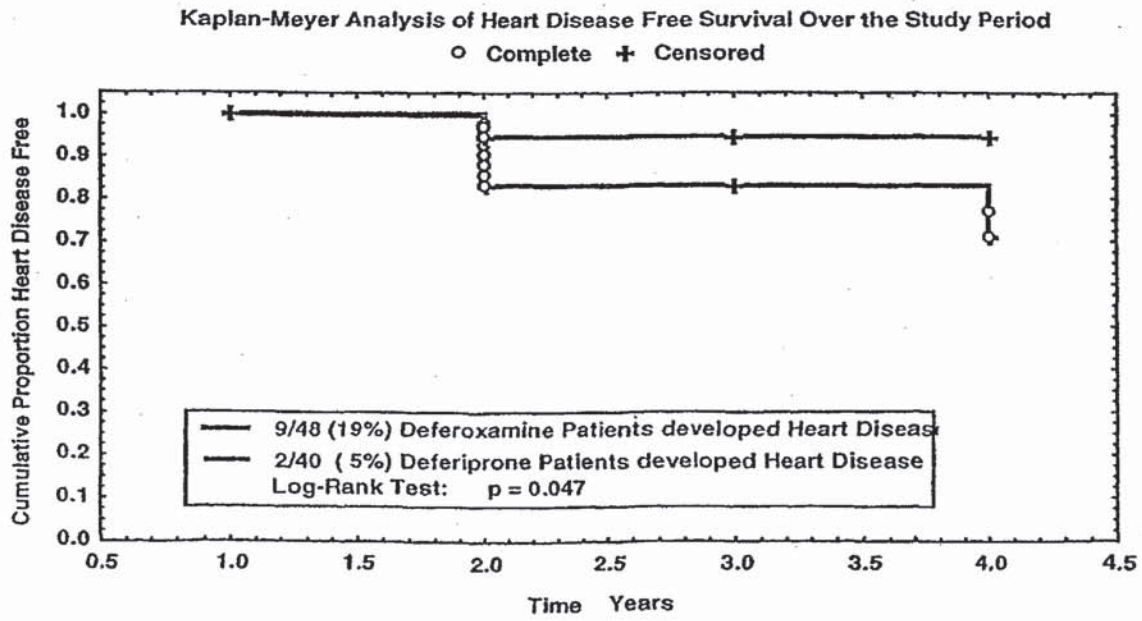


Figure 1.

Figure 2.



PTO/SB/01 (10-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	PC-1834033
First Named Inventor	MICHAEL SPINO
COMPLETE IF KNOWN	
Application Number	10/311,814
Filing Date	
Art Unit	
Examiner Name	

As the below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original and first inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

A NEW USE FOR DEFERIPRONE

(Title of the Invention)

the specification of which

☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) 06/28/2001 as United States Application Number or PCT International

Application Number PCT/CA01/00956 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

10311814.040403

PTO/SB/01 (10-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION — Utility or Design Patent Application

Direct all correspondence to: [X] Customer Number or Bar Code Label 23607 OR [ ] Correspondence address below

Name

Address

City | State | ZIP

Country | Telephone | Fax

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR: [ ] A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]): MICHAEL
Family Name or Surname: SPINO

Inventor's Signature: M Spino
Date: March 26/03

Residence: City: PICKERING
State: ONTARIO
Country: CANADA AX
Citizenship: CA

Mailing Address: AJ 948 ~~980~~ DUNCANNON DRIVE

City: PICKERING
State: ONTARIO
ZIP: L1X 2P3
Country: CANADA

NAME OF SECOND INVENTOR: [ ] A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]): ANTONIO
Family Name or Surname: PIGA

Inventor's Signature
Date

Residence: City: MONCALIERI
State:
Country: ITALY
Citizenship: IT

Mailing Address: STRADA TORINO 15B

City: MONCALIERI
State:
ZIP: I-10024
Country: ITALY

[ ] Additional inventors are being named on the ____supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

10311814.040403

PTO/SB/01 (10-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	PC-1834033
First Named Inventor	MICHAEL SPINO
COMPLETE IF KNOWN	
Application Number	10/311,814
Filing Date	
Art Unit	
Examiner Name	

As the below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original and first inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

A NEW USE FOR DEFERIPRONE

(Title of the Invention)

the specification of which

☒ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) 06/28/2001 as United States Application Number or PCT International

Application Number PCT/CA01/00956 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

Burden Hour Statement: This form is estimated to take 21 minutes to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

10311814.040403

PTO/SB/01 (10-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION — Utility or Design Patent Application

Direct all correspondence to: [X] Customer Number or Bar Code Label 23607 OR [ ] Correspondence address below

Name

Address

City | State | ZIP

Country | Telephone | Fax

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR : [ ] A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]): MICHAEL
Family Name or Surname: SPINO

Inventor's Signature | Date

Residence: City: PICKERING | State: ONTARIO | Country: CANADA | Citizenship: CA

Mailing Address: 980 DUNCANNON DRIVE

City: PICKERING | State: ONTARIO | ZIP: L1X 2P3 | Country: CANADA

NAME OF SECOND INVENTOR: [ ] A petition has been filed for this unsigned inventor

2-d

Given Name (first and middle [if any]): ANTONIO
Family Name or Surname: PIGA

Inventor's Signature | Date: 25-03-03

Residence: City: MONCALIERI | State | Country: ITALY | Citizenship: IT

Mailing Address: STRADA TORINO 15B

City: MONCALIERI | State | ZIP: I-10024 | Country: ITALY

[ ] Additional inventors are being named on the ____supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

[Page 2 of 2]

APR 0 4 2003
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Barrister & Solicitor
Patent & Trade Mark Agents
Canada, United States

DT[illegible]ec'd PCT/PTO 0 4 APR 2003

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Ivor M. Hughes
Rick Tuzi
Patent Agents
Neil H. Hughes, P.Eng.
Marcelo K. Sarkis, P.Eng.
Wm. Kitt Sinden

#3

Our Ref.: PT-1834033

April 3, 2003

VIA COURIER

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 South Clark Place
Crystal Plaza 2, Room 1B03
Arlington, Virginia U.S.A. 22202

Dear Sir:

Re: United States Patent Application Serial No. 10/311,814
of Apotex Inc.
for A NEW USE FOR DEFERIPONE
CUSTOMER NO. 23607
Due Date: April 10, 2003

Further to the Notification of Missing Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office (DO/EO/US) dated February 10, 2003, a copy of which is enclosed herewith, Applicant encloses two separate Oath or Declarations of the inventors, in compliance with 37 CFR 1.497(a) and (b) regarding the above-mentioned matter. The enclosed documents have been executed by the inventors, Michael Spino and Antonio Piga.

Should there be any fees required with regard to the above-identified application the Commissioner is authorized to credit the surplus or take the deficit from Applicant's Agent's Deposit Account No. 08-3255 and advise Applicants' Agent.

Also enclosed herewith is a stamped, self-addressed verification card which we request that you kindly acknowledge and return to this office at the earliest opportunity.

We thank the Commissioner for his cooperation in this regard and look forward to receiving filing data in this matter.

Respectfully submitted,

Neil H. Hughes, P.Eng.
Registration No. 33,636
Agent for Applicant

NHH:mse
Enclosures

175 Commerce Valley Dr. W., Suite 200, Thornhill, Ontario, Canada L3T 7P6 Phone: 905 771-6414 Fax: 905 771-6420
website: www.ivormhughes.com email: mail@ivormhughes.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents, Box PCT
United States Patent and Trademark Office
Washington, D.C. 20231
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/311,814	Michael Spino	PC-1834033

INTERNATIONAL APPLICATION NO.	
PCT/CA01/00956	
I.A. FILING DATE	PRIORITY DATE
06/28/2001	06/30/2000

23607
IVOR M. HUGHES, BARRISTER & SOLICITOR,
PATENT & TRADEMARK AGENTS
175 COMMERCE VALLEY DRIVE WEST
SUITE 200
THORNHILL, ON L3T 7P6
CANADA

CONFIRMATION NO. 2281

371 FORMALITIES LETTER

Date Mailed: 02/10/2003

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as an Elected Office (37 CFR 1.495):

- U.S. Basic National Fees
- Priority Document
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Oath or Declaration
- Preliminary Amendments
- Request for Immediate Examination

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date. The current oath or declaration does not comply with 37 CFR 1.497(a) and (b) in that it:
  - is not executed in accordance with either 37 CFR 1.66 or 37 CFR 1.68.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTH FROM THE DATE OF THIS NOTICE OR BY 22 or 32 MONTHS (where 37 CFR 1.495 applies) FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

*A copy of this notice **MUST** be returned with the response.*

PAULETTE R KIDWELL

Telephone: (703) 305-3656

PART 1 - ATTORNEY/APPLICANT COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/311,814	PCT/CA01/00956	PC-1834033

FORM PCT/DO/EO/905 (371 Formalities Notice)

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents, Box PCT
United States Patent and Trademark Office
Washington, D.C. 20231
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/311,814	Michael Spino	PC-1834033

INTERNATIONAL APPLICATION NO.	
PCT/CA01/00956	
I.A. FILING DATE	PRIORITY DATE
06/28/2001	06/30/2000

23607
IVOR M. HUGHES, BARRISTER & SOLICITOR,
PATENT & TRADEMARK AGENTS
175 COMMERCE VALLEY DRIVE WEST
SUITE 200
THORNHILL, ON L3T 7P6
CANADA

CONFIRMATION NO. 2281

371 ACCEPTANCE LETTER

OC000000009896798

Date Mailed: 04/25/2003

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

04/04/2003	04/04/2003
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF RECEIPT OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 12/20/2002
- Copy of the International Search Report filed on 12/20/2002
- Copy of IPE Report filed on 12/20/2002
- Preliminary Amendments filed on 12/20/2002
- Oath or Declaration filed on 04/04/2003
- Request for Immediate Examination filed on 12/20/2002
- Copy of references cited in ISR filed on 12/20/2002
- U.S. Basic National Fees filed on 12/20/2002

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

PAULETTE R KIDWELL
Telephone: (703) 305-3656

PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

SEARCH NOTES

10/31/814

STN SEATCH:
USPATFULL, MEDLINE,
CAPLUS

```
Welcome to STN International!  Enter x:x

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09  CA/CAplus records now contain indexing from 1907 to the
                  present
 NEWS  4  DEC 08  INPADOC: Legal Status data reloaded
 NEWS  5  SEP 29  DISSABS now available on STN
 NEWS  6  OCT 10  PCTFULL: Two new display fields added
 NEWS  7  OCT 21  BIOSIS file reloaded and enhanced
 NEWS  8  OCT 28  BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS  9  NOV 24  MSDS-CCOHS file reloaded
 NEWS 10  DEC 08  CABA reloaded with left truncation
 NEWS 11  DEC 08  IMS file names changed
 NEWS 12  DEC 09  Experimental property data collected by CAS now available
                  in REGISTRY
 NEWS 13  DEC 09  STN Entry Date available for display in REGISTRY and CA/CAplus
 NEWS 14  DEC 17  DGENE: Two new display fields added
 NEWS 15  DEC 18  BIOTECHNO no longer updated
 NEWS 16  DEC 19  CROPU no longer updated; subscriber discount no longer
                  available
 NEWS 17  DEC 22  Additional INPI reactions and pre-1907 documents added to CAS
                  databases
 NEWS 18  DEC 22  IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
 NEWS 19  DEC 22  ABI-INFORM now available on STN
 NEWS 20  JAN 27  Source of Registration (SR) information in REGISTRY updated
                  and searchable
 NEWS 21  JAN 27  A new search aid, the Company Name Thesaurus, available in
                  CA/CAplus

 NEWS EXPRESS  DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003
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FILE 'HOME' ENTERED AT 11:01:10 ON 02 FEB 2004

=> fil uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
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FULL ESTIMATED COST                                    0.21       0.21

FILE 'USPATFULL' ENTERED AT 11:01:20 ON 02 FEB 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 29 Jan 2004 (20040129/PD)
FILE LAST UPDATED: 29 Jan 2004 (20040129/ED)
HIGHEST GRANTED PATENT NUMBER: US6684403
HIGHEST APPLICATION PUBLICATION NUMBER: US2004019947
CA INDEXING IS CURRENT THROUGH 29 Jan 2004 (20040129/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 29 Jan 2004 (20040129/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2003

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

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>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from     <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s DEFERIPRONE/ti,ab
             1 DEFERIPRONE/TI
             1 DEFERIPRONE/AB
L1           1 DEFERIPRONE/TI,AB

=> d l1

L1   ANSWER 1 OF 1  USPATFULL on STN
AN     2003:226421  USPATFULL
TI     Use for deferiprone
IN     Spino, Michael, Pickering, CANADA
       Piga, Antonio, Moncalieri, ITALY
PI     US 2003158234       A1   20030821
AI     US 2003-311814      A1   20030404 (10)
       WO 2001-CA956            20010628
PRAI   CA 2000-2313270     20000630
DT     Utility
FS     APPLICATION
LN.CNT 1709
INCL   INCLM: 514/348.000
NCL    NCLM:  514/348.000
IC     [7]
       ICM: A61K031-44
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> s DEFERIPRONE
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L2          39 DEFERIPRONE

=> s DEFERIPRONE/clm
L3           2 DEFERIPRONE/CLM

=> d l3 1-2

L3   ANSWER 1 OF 2  USPATFULL on STN
AN     2003:270753  USPATFULL
TI     Modified release minerals
IN     Hermelin, Marc S., St. Louis, MO, UNITED STATES
       Grimshaw, Michael, St. Louis, MO, UNITED STATES
PI     US 2003190355      A1   20031009
AI     US 2002-115892     A1   20020405 (10)
DT     Utility
FS     APPLICATION
LN.CNT 1145
INCL   INCLM: 424/468.000
NCL    NCLM:  424/468.000
IC     [7]
       ICM: A61K009-22
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3   ANSWER 2 OF 2  USPATFULL on STN
AN     2003:226421  USPATFULL
TI     Use for deferiprone
IN     Spino, Michael, Pickering, CANADA
       Piga, Antonio, Moncalieri, ITALY
PI     US 2003158234      A1   20030821
AI     US 2003-311814     A1   20030404 (10)
       WO 2001-CA956           20010628
PRAI   CA 2000-2313270     20000630
DT     Utility
FS     APPLICATION
LN.CNT 1709
INCL   INCLM: 514/348.000
NCL    NCLM:  514/348.000
IC     [7]
       ICM: A61K031-44
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> s l2 and thallasemia
            21 THALLASEMIA
L4           0 L2 AND THALLASEMIA

=> s l2 and thalassemia
          1396 THALASSEMIA
L5          14 L2 AND THALASSEMIA

=> s l5 and cardiac?
         45622 CARDIAC?
L6           4 L5 AND CARDIAC?

=> d l6 1-4

L6   ANSWER 1 OF 4  USPATFULL on STN
AN     2003:312626  USPATFULL
TI     Enhancement of iron chelation therapy
IN     Theil, Elizabeth, San Francisco, CA, UNITED STATES
PA     Children's Hospital & Research Center at Oakland, Oakland, CA, UNITED
       STATES, 94609-1809 (U.S. corporation)
PI     US 2003220230      A1   20031127
AI     US 2003-389424     A1   20030313 (10)
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PRAI US 2002-365094P 20020314 (60)
DT Utility
FS APPLICATION
LN.CNT 1442
INCL INCLM: 514/006.000
INCLS: 424/070.100
NCL NCLM: 514/006.000
NCLS: 424/070.100
IC [7]
ICM: A61K038-40
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 2 OF 4 USPATFULL on STN
AN 2003:226421 USPATFULL
TI Use for **deferiprone**
IN Spino, Michael, Pickering, CANADA
Piga, Antonio, Moncalieri, ITALY
PI US 2003158234 A1 20030821
AI US 2003-311814 A1 20030404 (10)
WO 2001-CA956 20010628
PRAI CA 2000-2313270 20000630
DT Utility
FS APPLICATION
LN.CNT 1709
INCL INCLM: 514/348.000
NCL NCLM: 514/348.000
IC [7]
ICM: A61K031-44
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 3 OF 4 USPATFULL on STN
AN 2003:20255 USPATFULL
TI Method of treating iron overload with acetaminophen
IN Walker, Jr., Ernest M., Huntington, WV, United States
PA Marshall University Research Corporation, Huntington, WV, United States (U.S. corporation)
PI US 6509380 B1 20030121
AI US 2001-14783 20011214 (10)
DT Utility
FS GRANTED
LN.CNT 1157
INCL INCLM: 514/629.000
INCLS: 514/568.000; 514/575.000; 514/922.000; 514/630.000
NCL NCLM: 514/629.000
NCLS: 514/568.000; 514/575.000; 514/630.000; 514/922.000
IC [7]
ICM: A61K031-16
EXF 514/568; 514/575; 514/629; 514/630; 514/922
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 4 OF 4 USPATFULL on STN
AN 2001:45440 USPATFULL
TI Noninvasive room temperature instrument to measure magnetic susceptibility variations in body tissue
IN Kumar, Sankaran, San Marcos, CA, United States
Avrin, William F., San Diego, CA, United States
PA Quantum Magnetics, Inc., San Diego, CA, United States (U.S. corporation)
PI US 6208884 B1 20010327
AI US 1998-135890 19980818 (9)
RLI Continuation-in-part of Ser. No. US 1996-670393, filed on 25 Jun 1996, now patented, Pat. No. US 5842986
DT Utility
FS Granted
LN.CNT 1121

INCL INCLM: 600/409.000
INCLS: 324/260.000; 324/207.210
NCL NCLM: 600/409.000
NCLS: 324/207.210; 324/260.000
IC [7]
ICM: A61B005-05
EXF 600/407; 600/409; 600/410; 324/260; 324/261; 324/207.11; 324/207.12; 324/207.13; 324/207.14; 324/207.15; 324/207.16; 324/207.17; 324/207.18; 324/207.19; 324/207.21

=> d 3 hit

L6 ANSWER 3 OF 4 USPATFULL on STN

SUMM The present invention relates to methods for reducing iron levels and/or levels of other toxic metals or elements in mammals. In a particular aspect, the present invention relates to methods for reducing free iron ion levels and/or excess and toxic levels of other elements in mammals, and to the removal of excess iron or excesses of other metals/elements stored in the organs by administration of acetaminophen and/or structural or chemical analogues or derivatives thereof. These compounds may scavenge excess iron or free iron ions in hosts undergoing anthracycline chemotherapy, as well as hosts suffering from iron overload or non-iron overload diseases and/or conditions, such as hereditary hemochromatosis, blood-transfusion related anemias and hemolytic anemias such as **thalassemia**, hemodialysis, stroke, and rheumatoid arthritis. Acetaminophen is particularly preferred in this regard. In a further aspect, the present invention relates to compositions and formulations useful in the methods disclosed herein.

SUMM In particular, hemochromatosis is a disease of excessive iron storage leading to tissue damage and fibrosis. Both genetic, or hereditary, hemochromatosis, which can affect 1 in 500 of some populations, and the form of this disease which occurs as a secondary consequence of the hemoglobinopathy, homozygous .beta.-**thalassemia**, with 40 million carriers worldwide, have a common pathology. The cardiotoxicity and hepatoxicity, which occurs with this disease, have never been produced experimentally in other species. Hemochromatosis of the liver in man is caused when the iron burden exceeds a threshold in the region of 22 .mu.mol/g liver dry weight.

SUMM Hereditary hemochromatosis involves an increased rate of iron absorption from the gut with subsequent progressive storage of iron in soft organs of the body. Excessive iron storage eventually produces pituitary, pancreatic, **cardiac**, spleen, epidermal, and liver and/or hepatic failure or cancer. Damage to these organs may be characterized by elevated liver enzyme values and hepatomegaly often with cirrhosis which may develop into hepatocellular carcinoma, splenomegaly, pancreatic fibrosis leading to diabetes mellitus, hyperpigmentation of the skin, pituitary insufficiency, hypogonadism, occasional hypothyroidism, **cardiac** abnormalities such as arrythmias and/or congestive heart failure, and arthritis/arthropathy. Early diagnosis can prevent these excess iron-induced problems. Iron overload owing to HLA-linked hereditary hemochromatosis can be distinguished from other causes of hemochromatosis by liver biopsies and interpretations.

SUMM Iron overload as seen in hereditary hemochromatosis patients enhances suppressor T-cell (CD8) numbers and activity, decreases the proliferative capacity, numbers, and activity of helper T cells (CD4) with changes in CD8/CD4 ratios, impairs the generation of cytotoxic T cells, and alters immunoglobulin secretion when compared to treated hereditary hemochromatosis patients or controls. A correlation has recently been found between low CD8+ lymphocyte numbers, liver damage associated with HCV positivity, and severity of iron overload in beta-

thalassemia major patients. Iron overload, with its associated increases of serum iron levels and transferring saturation, may cause a poor response to interferon therapy. Iron overload with hyperferremia is associated with suppressed functions of the complement system (classic or alternative types).

SUMM Presently, the only drug which has been approved by the FDA for treating hemochromatosis is Desferal.RTM. (DF). Unfortunately, Desferal.RTM. must be administered parenterally in treating iron overload in patients and is sometimes associated with severe hypotension, shock, urticaria, ocular toxicity including visual dysfunction, auditory nephrotoxicity with hearing loss, and other drug-induced adverse effects. L1 (**deferiprone**, 1,2-dimethyl-3-hydroxypyridin-4-one), an orally effective iron chelator, is available for patients with **thalassemia** major, who are unable or unwilling to receive deferoxamine, but L1 has not been approved as an oral iron chelator due to its toxic effects (Kontoghiorghes G J. Toxicol Letters 1995;80:1-18).

SUMM The presence of elevated iron levels in a subject is associated with a wide range of disease states and/or indications, such as, for example, **thalassemia**, sickle cell anemia, repeated blood transfusions, hereditary hemochromatosis, secondary hemochromatosis, hereditary spherocytosis, hemodialysis, dietary iron uptake, iatrogenic iron uptake, intramuscular iron dextran, hemolytic disease of the newborn, and the like.

SUMM Secondary hemochromatosis, or hemosiderosis, typically occurs in mammals with conditions causing the accelerated destruction of red blood cells, such as hemolytic anemias, sickle cell anemia, and thalassemias. Treatment of these conditions may require frequent transfusions of red blood cells, which in turn may be destroyed to release even more iron into the body to be stored in target organs. These multiple transfusions result in the accelerated destruction of red blood cells in individuals with hemolytic anemia, sickle cell anemia, and **thalassemia**. This secondary hemochromatosis is slightly different from hereditary hemochromatosis. Chelating agents are commonly used to treat secondary hemochromatosis.

DETD EKG findings revealed premature ventricular complexes in four of 10 iron-overloaded gerbils (40%) but not in animals from the other three groups. Eight of 20 iron-overloaded gerbils died within 5 months after iron overloading, most likely due to **cardiac** and/or liver failure. No deaths occurred in the treatment or control groups. Autopsies, coupled with weight data and histological evaluations suggested that the treatment agent effectively combats iron-induced **cardiac** and hepatic hypertrophy, as judged from treatment-induced reductions in heart weights, heart/total body weight ratios, liver weights, and liver/total body weight ratios.

DETD Treatment greatly reduced accumulations of iron in the bone marrow, proximal renal tubules, heart, and in numerous other organs and tissues, but less than in the livers. Inductively coupled plasma-atomic emission livers. Inductively coupled plasma-atomic emission spectrometry (ICP-AES) tissue iron measurements revealed that treatment reduced **cardiac** iron over 40% (almost entirely from cardiomyocytes, less from **cardiac** macrophages) ($P<0.005$), but the 17% reduction in liver iron was not statistically significant from values in untreated, iron-overloaded animals.

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=> fil reg
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY     SESSION
FULL ESTIMATED COST                           27.61       27.82
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DICTIONARY FILE UPDATES:  30 JAN 2004  HIGHEST RN 644468-14-4

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=> s deferiprone/cn
L7            1 DEFERIPRONE/CN

=> fil medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 4.85      32.67

FILE 'MEDLINE' ENTERED AT 11:10:55 ON 02 FEB 2004

 FILE LAST UPDATED: 31 JAN 2004 (20040131/UP).  FILE COVERS 1958 TO DATE.

 On December 14, 2003, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description
 on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l7
L8          323 L7

=> s l7 and cardiac
            323 L7
         285919 CARDIAC
L9           14 L7 AND CARDIAC

=> s l8 and cardiac
         285919 CARDIAC
L10          14 L8 AND CARDIAC

=> d l10 1-14

L10  ANSWER 1 OF 14      MEDLINE on STN
AN   2003233848      MEDLINE
DN   22640942    PubMed ID: 12756022
TI   Safety monitoring of cardiac and hepatic systems in
```

beta-thalassemia patients with chelating treatment in Taiwan.
AU Peng Ching-Tien; Chow Kuan-Chih; Chen Jeon-Hor; Chiang Yi-Ping; Lin Tze-Yi; Tsai Chang-Hai
CS Department of Paediatrics, China Medical College Hospital and Institute of Medical Sciences, China Medical College, Taichung, Taiwan.. t6218@hpd.cmch.org.tw
SO EUROPEAN JOURNAL OF HAEMATOLOGY, (2003 Jun) 70 (6) 392-7.
Journal code: 8703985. ISSN: 0902-4441.
CY Denmark
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20030521
Last Updated on STN: 20030710
Entered Medline: 20030709

L10 ANSWER 2 OF 14 MEDLINE on STN
AN 2003224074 MEDLINE
DN 22630633 PubMed ID: 12745268
TI Comparative effects of deferiprone and deferoxamine on survival and **cardiac** disease in patients with thalassemia major: a retrospective analysis.
CM Comment in: Haematologica. 2003 May;88(5):481-2
AU Piga Antoni; Gaglioti Carmen; Fogliacco Eugenia; Tricta Fernando
CS Department of Pediatric Hematology, University of Turin, Italy.. antonio.piga@unito.it
SO HAEMATOLOGICA, (2003 May) 88 (5) 489-96.
Journal code: 0417435. ISSN: 1592-8721.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20030515
Last Updated on STN: 20030608
Entered Medline: 20030606

L10 ANSWER 3 OF 14 MEDLINE on STN
AN 2003224070 MEDLINE
DN 22630629 PubMed ID: 12745264
TI Treatment of **cardiac** iron overload in thalassemia major.
CM Comment on: Haematologica. 2003 May;88(5):489-96
AU Westwood Mark; Anderson Lisa J; Pennell Dudley J
SO HAEMATOLOGICA, (2003 May) 88 (5) 481-2.
Journal code: 0417435. ISSN: 1592-8721.
CY Italy
DT Commentary
Editorial
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20030515
Last Updated on STN: 20030608
Entered Medline: 20030606

L10 ANSWER 4 OF 14 MEDLINE on STN
AN 2002477992 MEDLINE
DN 22227033 PubMed ID: 12241655
TI Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia.
CM Comment in: Lancet. 2002 Aug 17;360(9332):501-2

Comment in: Lancet. 2003 Jan 11;361(9352):182-3; author reply 183-4
Comment in: Lancet. 2003 Jan 11;361(9352):182; author reply 183-4
Comment in: Lancet. 2003 Jan 11;361(9352):183; author reply 183-4
Comment in: Lancet. 2003 Jan 11;361(9352):184
AU Anderson Lisa J; Wonke Beatrix; Prescott Emma; Holden Sally; Walker J Malcolm; Pennell Dudley J
CS Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, London SW3 6NP, UK.
SO LANCET, (2002 Aug 17) 360 (9332) 516-20.
Journal code: 2985213R. ISSN: 0140-6736.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200210
ED Entered STN: 20020921
Last Updated on STN: 20030129
Entered Medline: 20021007

L10 ANSWER 5 OF 14 MEDLINE on STN
AN 2002380861 MEDLINE
DN 22122490 PubMed ID: 12127956
TI Orally active iron chelators.
AU Merson L; Olivier N
CS Toronto General Hospital, 200 St Elizabeth Street, CW-3-338, 101 College Street M5G 2C4, Toronto, Canada.. laura.merson@uhn.on.ca
SO BLOOD REVIEWS, (2002 Jun) 16 (2) 127-34. Ref: 77
Journal code: 8708558. ISSN: 0268-960X.
CY Scotland: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20020720
Last Updated on STN: 20030713
Entered Medline: 20030711

L10 ANSWER 6 OF 14 MEDLINE on STN
AN 2002365029 MEDLINE
DN 22102880 PubMed ID: 12106822
TI Deferiprone protects against doxorubicin-induced myocyte cytotoxicity.
AU Barnabe Norman; Zastre Jason A; Venkataram Suresh; Hasinoff Brian B
CS Faculty of Pharmacy, University of Manitoba, Winnipeg, MB, Canada.
SO FREE RADICAL BIOLOGY AND MEDICINE, (2002 Jul 15) 33 (2) 266-75.
Journal code: 8709159. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 20020712
Last Updated on STN: 20030111
Entered Medline: 20030110

L10 ANSWER 7 OF 14 MEDLINE on STN
AN 1998355341 MEDLINE
DN 98355341 PubMed ID: 9700174
TI Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major.
CM Comment in: N Engl J Med. 1998 Aug 13;339(7):468-9
Comment in: N Engl J Med. 1998 Dec 3;339(23):1710-1; author reply 1713-4
Comment in: N Engl J Med. 1998 Dec 3;339(23):1710; author reply 1713-4

Comment in: N Engl J Med. 1998 Dec 3;339(23):1711-2; author reply 1713-4
Comment in: N Engl J Med. 1998 Dec 3;339(23):1712-3; author reply 1713-4
Comment in: N Engl J Med. 1998 Dec 3;339(23):1712; author reply 1713-4
Comment in: N Engl J Med. 1998 Dec 3;339(23):1712; author reply 1713-4
AU Olivieri N F; Brittenham G M; McLaren C E; Templeton D M; Cameron R G; McClelland R A; Burt A D; Fleming K A
CS Department of Medicine, University of Toronto, ON, Canada.
NC DK49108 (NIDDK)
HL58203 (NHLBI)
HL61219 (NHLBI)
SO NEW ENGLAND JOURNAL OF MEDICINE, (1998 Aug 13) 339 (7) 417-23.
Journal code: 0255562. ISSN: 0028-4793.
CY United States
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199808
ED Entered STN: 19980820
Last Updated on STN: 20000303
Entered Medline: 19980813

L10 ANSWER 8 OF 14 MEDLINE on STN
AN 1998091674 MEDLINE
DN 98091674 PubMed ID: 9429839
TI A risk-benefit assessment of iron-chelation therapy.
AU Porter J B
CS Department of Haematology, University College London, England..
j.porter@ucl.ac.uk
SO DRUG SAFETY, (1997 Dec) 17 (6) 407-21. Ref: 102
Journal code: 9002928. ISSN: 0114-5916.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980211

L10 ANSWER 9 OF 14 MEDLINE on STN
AN 1998077542 MEDLINE
DN 98077542 PubMed ID: 9414297
TI Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients.
AU Hoffbrand A V; AL-Refaie F; Davis B; Siritanakatkul N; Jackson B F; Cochrane J; Prescott E; Wonke B
CS Department of Hematology, The Royal Free Hospital School of Medicine, London, UK.
SO BLOOD, (1998 Jan 1) 91 (1) 295-300.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199802
ED Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980202

L10 ANSWER 10 OF 14 MEDLINE on STN
AN 1998011255 MEDLINE
DN 98011255 PubMed ID: 9350180
TI Iron chelation therapy.
AU Hoffbrand A V; Wonke B
CS Department of Haematology, Royal Free Hospital and School of Medicine, London, UK.
SO JOURNAL OF INTERNAL MEDICINE. SUPPLEMENT, (1997) 740 37-41. Ref: 30
Journal code: 8912975. ISSN: 0955-7873.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971119

L10 ANSWER 11 OF 14 MEDLINE on STN
AN 97119120 MEDLINE
DN 97119120 PubMed ID: 8959943
TI Long-term treatment of transfusional iron overload with the oral iron chelator deferiprone (L1): a Dutch multicenter trial.
AU Kersten M J; Lange R; Smeets M E; Vreugdenhil G; Roozendaal K J; Lameijer W; Goudsmit R
CS Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands.
SO ANNALS OF HEMATOLOGY, (1996 Nov) 73 (5) 247-52.
Journal code: 9107334. ISSN: 0939-5555.
CY GERMANY: Germany, Federal Republic of
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19970102

L10 ANSWER 12 OF 14 MEDLINE on STN
AN 92265931 MEDLINE
DN 92265931 PubMed ID: 1586721
TI Reduction of tissue iron stores and normalization of serum ferritin during treatment with the oral iron chelator L1 in thalassemia intermedia.
AU Olivieri N F; Koren G; Matsui D; Liu P P; Blendis L; Cameron R; McClelland R A; Templeton D M
CS Division of Haematology/Oncology, Hospital for Sick Children, Toronto, Canada.
SO BLOOD, (1992 May 15) 79 (10) 2741-8.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199206
ED Entered STN: 19920710
Last Updated on STN: 19980206
Entered Medline: 19920619

L10 ANSWER 13 OF 14 MEDLINE on STN
AN 91242340 MEDLINE
DN 91242340 PubMed ID: 2094334
TI Long-term trial with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1). II. Clinical observations.
AU Bartlett A N; Hoffbrand A V; Kontoghiorghes G J
CS Department of Haematology, Royal Free Hospital, School of Medicine, London.
SO BRITISH JOURNAL OF HAEMATOLOGY, (1990 Oct) 76 (2) 301-4.
Journal code: 0372544. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199107
ED Entered STN: 19910719
Last Updated on STN: 19980206
Entered Medline: 19910702

L10 ANSWER 14 OF 14 MEDLINE on STN
AN 89288600 MEDLINE
DN 89288600 PubMed ID: 2736747
TI Prevention of postischemic **cardiac** injury by the orally active iron chelator 1,2-dimethyl-3-hydroxy-4-pyridone (L1) and the antioxidant (+)-cyanidanol-3.
AU van der Kraaij A M; van Eijk H G; Koster J F
CS Department of Biochemistry, Erasmus University Rotterdam, The Netherlands.
SO CIRCULATION, (1989 Jul) 80 (1) 158-64.
Journal code: 0147763. ISSN: 0009-7322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198908
ED Entered STN: 19900309
Last Updated on STN: 19980206
Entered Medline: 19890804

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=> d l7

L7   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   30652-11-0  REGISTRY
CN   4(1H)-Pyridinone, 3-hydroxy-1,2-dimethyl- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   4(1H)-Pyridone, 3-hydroxy-1,2-dimethyl- (8CI)
OTHER NAMES:
CN   1,2-Dimethyl-3-hydroxy-4(1H)-pyridinone
CN   1,2-Dimethyl-3-hydroxy-4-pyridone
CN   1,2-Dimethyl-3-hydroxypyridin-4-one
CN   1,2-Dimethyl-3-hydroxypyridine-4-one
CN   3-Hydroxy-1,2-dimethyl-4(1H)-pyridinone
CN   3-Hydroxy-1,2-dimethyl-4-pyridinone
CN   3-Hydroxy-1,2-dimethyl-4-pyridone
CN   CGP 37391
CN   CP 20
CN   CP 20 (chelating agent)
CN   Deferione
CN   Deferiprone
CN   Ferriprox
CN   L 1
CN   L 1 (chelating agent)
FS   3D CONCORD
MF   C7 H9 N O2
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS,
       CHEMINFORMRX, CIN, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, IMSDRUGNEWS,
       IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*,
       SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
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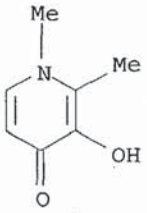


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             375 REFERENCES IN FILE CA (1907 TO DATE)
              21 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             376 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       2.19      43.70

FILE 'CAPLUS' ENTERED AT 11:20:18 ON 02 FEB 2004
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FILE COVERS 1907 - 2 Feb 2004 VOL 140 ISS 6
FILE LAST UPDATED: 1 Feb 2004 (20040201/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l7
L11 376 L7

=> s l11 and cardiac
97823 CARDIAC
L12 13 L11 AND CARDIAC

=> d l12 1-13

L12 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:737570 CAPLUS
DN 139:255356
TI Preventing and/or treating vascular disease, cardiomyopathy and/or associated heart failure
IN Cooper, Garth James Smith; Baker, Richard John
PA Protemix Corporation Limited, N. Z.
SO PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003075910	A1	20030918	WO 2003-NZ43	20030310

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI NZ 2002-517722 A 20020308
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:574082 CAPLUS
DN 139:207453
TI Comparative effects of deferiprone and deferoxamine on survival and **cardiac** disease in patients with thalassemia major: a retrospective analysis
AU Piga, Antonio; Gaglioti, Carmen; Fogliacco, Eugenia; Tricta, Fernando
CS Department of Pediatric Hematology, University of Turin, Italy
SO Haematologica (2003), 88(5), 489-496

CODEN: HAEMAX; ISSN: 0390-6078
PB Ferrata Storti Foundation
DT Journal
LA English
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:535959 CAPLUS
DN 139:173535
TI Safety monitoring of **cardiac** and hepatic systems in .beta.-thalassemia patients with chelating treatment in Taiwan
AU Peng, Ching-Tien; Chow, Kuan-Chih; Chen, Jeon-Hor; Chiang, Yi-Ping; Lin, Tze-Yi; Tsai, Chang-Hai
CS Department of Paediatrics, China Medical College Hospital and Institute of Medical Sciences, China Medical College, Taichung, Taiwan
SO European Journal of Haematology (2003), 70(6), 392-397
CODEN: EJHAEC; ISSN: 0902-4441
PB Blackwell Munksgaard
DT Journal
LA English
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:513562 CAPLUS
DN 139:190458
TI Role of deferiprone in chelation therapy for transfusional iron overload
AU Hoffbrand, A. Victor; Cohen, Alan; Hershko, Chaim
CS Department of Haematology, Royal Free Hospital, London, UK
SO Blood (2003), 102(1), 17-24
CODEN: BLOOAW; ISSN: 0006-4971
PB American Society of Hematology
DT Journal; General Review
LA English
RE.CNT 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:643763 CAPLUS
DN 138:198367
TI Deferiprone protects against doxorubicin-induced myocyte cytotoxicity
AU Barnabe, Norman; Zastre, Jason A.; Venkataram, Suresh; Hasinoff, Brian B.
CS Faculty of Pharmacy, University of Manitoba, Winnipeg, MB, Can.
SO Free Radical Biology & Medicine (2002), 33(2), 266-275
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier Science Inc.
DT Journal
LA English
RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:633604 CAPLUS
DN 138:248220
TI Oral deferiprone vs. subcutaneous desferrioxamine effects on myocardial iron concentrations and ventricular function in beta-thalassemia
AU Anderson, Lisa J.; Wonke, Beatrix; Prescott, Emma; Holden, Sally; Walker, J. Malcolm; Pennell, Dudley J.
CS Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, London, SW3 6NP, UK
SO Lancet (2002), 360(9332), 516-520
CODEN: LANCAO; ISSN: 0140-6736
PB Lancet Publishing Group

DT Journal
LA English
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:31255 CAPLUS
DN 136:79767
TI Deferiprone for treatment of iron-induced **cardiac** disease
IN Spino, Michael; Piga, Antonia
PA Apotex Inc., Can.
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002002114	A1	20020110	WO 2001-CA956	20010628
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CN 1331971	A	20020123	CN 2001-121242	20010326
	EP 1294379	A1	20030326	EP 2001-949158	20010628
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001012280	A	20030513	BR 2001-12280	20010628
	ZA 2001009322	A	20021021	ZA 2001-9322	20011113
	US 2003158234	A1	20030821	US 2003-311814	20030404
PRAI	CA 2000-2313270	A	20000630		
	WO 2001-CA956	W	20010628		

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:150010 CAPLUS
DN 131:662
TI Cardioprotective effect of .alpha.-tocopherol, ascorbate, deferoxamine, and deferiprone: mitochondrial function in cultured, iron-loaded heart cells
AU Link, Gabriela; Konijn, Abraham M.; Hershko, Chaim
CS Department of Human Nutrition and Metabolism, Hebrew University Faculty of Medicine, Jerusalem, Israel
SO Journal of Laboratory and Clinical Medicine (1999), 133(2), 179-188
CODEN: JLCMAK; ISSN: 0022-2143
PB Mosby, Inc.
DT Journal
LA English
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:571361 CAPLUS
DN 129:325881
TI Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major
AU Olivieri, Nancy F.; Brittenham, Gary M.; McLaren, Christine E.; Templeton, Douglas M.; Cameron, Ross G.; McClelland, Robert A.; Burt, Alastair D.;

Fleming, Kenneth A.
CS the Departments of Medicine and Pediatrics (N.F.O.), University of Toronto, Toronto, Can.
SO New England Journal of Medicine (1998), 339(7), 417-423
CODEN: NEJMAG; ISSN: 0028-4793
PB Massachusetts Medical Society
DT Journal
LA English
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:19761 CAPLUS
DN 128:149101
TI A risk-benefit assessment of iron-chelation therapy
AU Porter, John B.
CS Department of Haematology, University College London, London, UK
SO Drug Safety (1997), 17(6), 407-421
CODEN: DRSAEA; ISSN: 0114-5916
PB Adis International Ltd.
DT Journal; General Review
LA English
RE.CNT 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:6901 CAPLUS
DN 128:162827
TI Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients
AU Hoffbrand, A. Victor; Al-Rafaie, Faris; Davis, Bernard; Siritanakakul. Noppadol; Jackson, Beverly F. A.; Cochrane, John; Prescott, Emma; Wonke, Beatrix
CS Department of Hematology, Royal Free Hospital School of Medicine, London, UK
SO Blood (1998), 91(1), 295-300
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:15369 CAPLUS
DN 116:15369
TI Comparison of the subacute toxicity and efficacy of 3-hydroxypyridin-4-one iron chelators in overloaded and nonoverloaded mice
AU Porter, J. B.; Hoyes, K. P.; Abeysinghe, R. D.; Brooks, P. n.; Huehns, E. R.; Hider, R. C.
CS Dep. Clin. Haematol., Middlesex Sch. Med., London, WC1E 6HX, UK
SO Blood (1991), 78(10), 2727-34
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English

L12 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:490096 CAPLUS
DN 111:90096
TI Prevention of postischemic **cardiac** injury by the orally active iron chelator 1,2-dimethyl-3-hydroxy-4-pyridone (L1) and the antioxidant (+)-cyanidanol-3
AU Van der Kraaij, Antonius M. M.; Van Eijk, Henk G.; Koster, Johan F.
CS Dep. Biochem., Erasmus Univ. Rotterdam, Rotterdam, Neth.

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SO   Circulation (1989), 80(1), 158-64
     CODEN: CIRCAZ; ISSN: 0009-7322
DT   Journal
LA   English


=> d his

     (FILE 'HOME' ENTERED AT 11:01:10 ON 02 FEB 2004)

     FILE 'USPATFULL' ENTERED AT 11:01:20 ON 02 FEB 2004
L1            1 S DEFERIPRONE/TI,AB
L2           39 S DEFERIPRONE
L3            2 S DEFERIPRONE/CLM
L4            0 S L2 AND THALLASEMIA
L5           14 S L2 AND THALASSEMIA
L6            4 S L5 AND CARDIAC?

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L7            1 S DEFERIPRONE/CN

     FILE 'MEDLINE' ENTERED AT 11:10:55 ON 02 FEB 2004
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L9           14 S L7 AND CARDIAC
L10          14 S L8 AND CARDIAC

     FILE 'REGISTRY' ENTERED AT 11:19:29 ON 02 FEB 2004

     FILE 'CAPLUS' ENTERED AT 11:20:18 ON 02 FEB 2004
L11         376 S L7
L12          13 S L11 AND CARDIAC

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Interview Search Notes
10/311,814

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SO   Circulation (1989), 80(1), 158-64
     CODEN: CIRCAZ; ISSN: 0009-7322
DT   Journal
LA   English


=> d his

     (FILE 'HOME' ENTERED AT 11:01:10 ON 02 FEB 2004)

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L5           14 S L2 AND THALASSEMIA
L6            4 S L5 AND CARDIAC?

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L7            1 S DEFERIPRONE/CN

     FILE 'MEDLINE' ENTERED AT 11:10:55 ON 02 FEB 2004
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L9           14 S L7 AND CARDIAC
L10          14 S L8 AND CARDIAC

     FILE 'REGISTRY' ENTERED AT 11:19:29 ON 02 FEB 2004

     FILE 'CAPLUS' ENTERED AT 11:20:18 ON 02 FEB 2004
L11         376 S L7
L12          13 S L11 AND CARDIAC

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/311,814	04/04/2003	Michael Spino	PC-1834033	2281

23607 7590 02/17/2004

IVOR M. HUGHES, BARRISTER & SOLICITOR,
PATENT & TRADEMARK AGENTS
175 COMMERCE VALLEY DRIVE WEST
SUITE 200
THORNHILL, ON L3T 7P6
CANADA

EXAMINER	
HENLEY III, RAYMOND J	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/311,814	SPINO ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-13,18,22-26,30-33,35,37,39,41,43,45,47,49 and 51-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8-13,18,22-26,30-33,35,37,39,41,43,45,47,49 and 51-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1,2,8-13,18,22-26,30-33,35,37,39,41,43,45,47,49 and 51-62 ARE PRESENTED FOR EXAMINATION

Applicants' Preliminary Amendment filed April 4, 2003 has been received and entered into the application. Accordingly, claims 3-6, 14-17, 19-21, 27-29, 34, 36, 38, 40, 42, 44, 46 and 48 have been canceled; claims 30-33, 35, 37, 39, 41, 43, 45, 47 and 49 have been amended and claims 51-62 have been added.

Specification

The abstract of the disclosure is objected to because it does not appear on a separate page without extraneous subject matter present. Correction is required. See MPEP § 608.01(b).

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/CA01/00956, filed June 28, 2001. Reference to this prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application for the benefit of not only its filing date, but also the foreign reference also identified by applicants.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-10 and 18 are directed to "effective amounts" (line 1) and yet define this "effective amount" in terms of another recitation of an "effective amount" within the body of the claim. If applicants are intending to claim a composition, then the claims should read "A pharmaceutical composition comprising…an effective amount of…" (or similar language) so it is clear as to which statutory class of invention applicants intend.

Regarding claims 1, 2, 8-13 and 25, the phrase "such as in thalassemia or the like" and "(for example-intracellular iron)"[claim 25] renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Also, the qualitative meaning of the expression "or the like" does not make clear the intended manner in which other conditions are "like" thalassemia. Finally, the parenthesis employed in claim 25 further make it unclear whether the limitation contained in the parentheses are part of the claimed invention.

In claims 30-32, the entire content is unclear because in the claims from which these claims depend, deferiprone is already recited as an active ingredient rendering a limitation of "further comprising…" superfluous and confusing. Claims 51-53 are similarly confusing.

In claim 33, the claim should not read as "further comprising an oral dosage form of deferiprone.." because deferiprone is already present in the claims from which claim 33 depends. Rather, the claim should read as "The method of claim…wherein deferiprone is present in an oral dosage form" or similar language. In a similar manner, claim 54 should be amended in terms of the composition of the independent claims.

Similarly, if applicants have intended claims 35, 37 and 39 to further limit the frequency of administration or dosage amount, such has not been accomplished through the use of the

expression "further…" because applicants are not adding an additional limitation. Language such as "The method of claim…wherein the administration is daily" should be employed.

Claim 45 is considered indefinite because the expression "the dosage form" does not have antecedent basis in the claims from which is depends.

Claim 54 is considered indefinite because it appears that applicants are intending to further limit the form in which deferiprone is present in the independent claims. The expression "further comprising…" does not accomplish this as such connotes the presence of an additional feature. Language such as "The…of claim….wherein deferiprone is present as an oral dosage form" should be employed.

Claims 55-59 and 62 are indefinite because they contain the dynamic limitation "daily administration". The claims from which they depend, however, are static dosage amounts and are not further limited by method steps of administration. Also, in claims 55-57, the unit of measurement "mg/kg to the patient" is improper because measurements of ingredients contained in the "composition" should relate to the composition, i.e., per unit volume or weight of the composition, and not to a feature, i.e., a patient, that is not apart of the "composition" and which is variable, i.e., weight of the patient is variable.

Claim 60 is considered indefinite because the expression "the dosage form" does not have antecedent basis in the claims from which is depends.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 9, 10, 18, 51-59 are rejected under 35 U.S.C. 102(b) as being anticipated by any one of Olivieri et al., Hoffbrand et al. (Examiner cit. Ref. "U") or Hoffbrand et al. (Examiner cit. Ref. "V") who each teach an effective therapeutic amount of deferiprone at a dosage of 75mg/kg/day.

The functional recitations intended use in the present claims which do not appear in the reference fail to impart patentable moment to the claimed subject matter because such recitations do not add any physical or otherwise material to the dose presently claimed that is not taught in the references.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 8-13, 18, 22-26, 30-33, 35, 37, 39, 41, 43, 45, 47, 49 and 51-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai (U.S. Patent No. 5,922,761) who teaches methods for the reduction of free iron levels in subject in which a dithiocarbamate containing composition iron chelator is administered so as to treat subjects afflicted with iron overload and non-iron overload diseases and conditions such as thalassemia and cardiac conditions including myocarditis, heart failure and heart disease. See the abstract and column 7, lines 49 and 51.

The difference between the above and the claimed subject matter lies in that Lai does not teach deferiprone compositions to replace the dithiocarbamate containing compositions and further does not teach the presently claimed deferiprone dosage amounts, forms or routes of administration. Also, the additional use of desferrioxamine is not taught.

However, to the skilled artisan, the claimed subject matter would have been obvious because at col. 2, line 64 – col. 3, line 9 and col. 3, lines 23-33, Lai teaches that deferiprone is an effective iron chelator which would have motivated the skilled artisan to employ it for the purposes taught for the dithiocarbamate-containing compositions. Also, the additional use of desferrioxamine would have been obvious because Lai teaches desferrioxamine for the same purpose and it has been held that it is considered prima facie obvious to have combined two or more ingredients each of which was known to be useful for the same purpose in order to form a third composition that is useful for the very same purpose. The idea for combining them flows logically from their have been used separately. See In re Kerkhoven 205 U.S.P.Q. 1069 (CCPA 1980) and the cases cited therein. The skilled artisan would have been motivated to combine such ingredients in order to achieve at least additive results and to provide the individual being treated with the most convenient, effective therapy possible.

The Examiner notes that the use of deferiprone is not a preferred embodiment, however, such a teaching nevertheless supports the above conclusion of obviousness. See MPEP:

2123 Rejection Over Prior Art's Broad Disclosure Instead of Preferred Embodiments

PATENTS ARE RELEVANT AS PRIOR ART FOR ALL THEY CONTAIN

"The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).

A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.").

NONPREFERRED EMBODIMENTS CONSTI-TUTE PRIOR ART

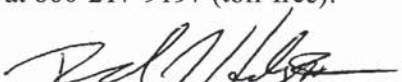
Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (The invention was directed to an epoxy impregnated fiber-reinforced printed circuit material. The applied prior art reference taught a printed circuit material similar to that of the claims but impregnated with polyester-imide resin instead of epoxy. The reference, however, disclosed that epoxy was known for this use, but that epoxy impregnated circuit boards have "relatively acceptable dimensional stability" and "some degree of flexibility," but are inferior to circuit boards impregnated with polyester-imide resins. The court upheld the rejection concluding that applicant's argument that the reference teaches away from using epoxy was insufficient to overcome the rejection since "Gurley asserted no discovery beyond what was known in the art." 27 F.3d at 554, 31 USPQ2d at 1132.).

Accordingly, for the above reasons, the claims are deemed to be properly rejected and none are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Henley whose telephone number is (571)272-0575 The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on 703-308-4725. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Raymond J. Henley III
Primary Examiner
Art Unit 1614

Feb. 3, 2004

Notice of References Cited	Application/Control No. 10/311,814	Applicant(s)/Patent Under Reexamination SPINO ET AL.	
	Examiner Raymond J. Henley III	Art Unit 1614	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-5,922,761	07-1999	Lai, Ching-San	514/476
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
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	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	MEDLINE ABSTRACT, PubMed ID: 9350180, Hoffbrand, et al. , Journ. International Med. Suppl, (1997) 740 37-41.
	V	MEDLINE ABSTRACT, PubMed ID: 9414297, Hoffbrand et al., Blood, (1998 Jan. 1), 91(1), 295-300.
	W	MEDLINE ABSTRACT, PubMed ID: 158721, Olivieri et al., Blood, (1992 May 15), 79 (10), 2741-8.
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims

Application No.	Applicant(s)
10/311,814	SPINO ET AL.
Examiner	**Art Unit**
Raymond J. Henley III	1614

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
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Claim		Date									
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Search Notes

Application No.	Applicant(s)	
10/311,814	SPINO ET AL.	
Examiner	**Art Unit**	
Raymond J. Henley III	1614	

SEARCHED

Class	Subclass	Date	Examiner
514	348	2/2/2004	RJH
↓	(all)	↓	↓

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR
STN Search: CAPLUS, USPATFULL, MEDLINE	2/2/2004	RJH
Palm Inventor Name Search: - Michael Spino - Antonio Piga	↓	↓

IN THE UNITED STATES PATENT OFFICE

Application Serial No. 10/311,814

Our Ref.: PC-1834033
CUSTOMER NO. 23607

Applicant: Apotex Inc.

Agent: Neil H. Hughes, P.Eng.
c/o Ivor M. Hughes
Barrister & Solicitor
Patent & Trade Mark Agents
Suite 200
175 Commerce Valley Dr. W.
Thornhill, Ontario
Canada L3T 7P6

Title: A NEW USE FOR DEFERIPRONE

Inventors: Michael Spino and Antonio Piga

Examiner: Raymond J. Henley III

Group Art Unit: 1614 **Due Date: May 17, 2004**

RESPONSE TO OFFICIAL ACTION OF FEBRUARY 17, 2004

July 28, 2004

VIA COURIER

The Commissioner of Patents
UNITED STATES PATENT OFFICE
220 20th Street S.
Crystal Plaza Two, Lobby, Room 1B03
Arlington, Virginia 22202

Dear Sir:

In response to the outstanding Official Action dated February 17, 2004 and due for response May 17, 2004, Applicant encloses a Request for a three month extension of time making this response due **August 17, 2004**. Applicant encloses a cheque in the amount of **$950.00 U.S.** funds the required fee for the three month extension of time for a large entity. If there is any deficiency or surplusage of the fees required for the Extension of Time fee, please obtain any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicants' Agent.

IN THE SPECIFICATION

In the specification at top of first page prior to the first line insert as follows:

This Application is a National Phase Entry Application of PCT claiming priority from Application No. PCT/CA01/00956 filed June 28, 2001.

IN THE CLAIMS

1. (currently amended) A method of treating iron induced cardiac disease in a **heavily transfused** patient **experiencing an** ~~with~~ iron overload **condition of the heart**, ~~such as in thalassemia or the like~~ **said method** comprising administering to the **heavily transfused** patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to **stabilize/reduce/iron accumulation in the heart resulting from being heavily transfused and preventing further iron accumulation in the heart normally associated with** ~~treat~~ iron induced cardiac disease ~~normally associated with iron overload~~.

2. (currently amended) A method of preventing iron induced cardiac disease in a **heavily transfused** patient **experiencing an** ~~with~~ iron overload **condition of the heart**, ~~such as in thalassemia or the like~~ **said method** comprising administering to the **heavily transfused** patient a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to **prevent further iron accumulation in the heart normally associated with** ~~treat~~ iron induced cardiac disease ~~normally associated with iron overload~~.

8. (currently amended) ~~An~~ **A pharmaceutical composition for iron induced cardiac disease comprising an** effective therapeutic amount of **the orally administered iron chelator** deferiprone or a physiologically acceptable salt thereof for the prevention of ~~the risk of~~ heart disease in **heavily transfused** patients ~~having~~ **risking an** iron overload **condition of the heart**, ~~such as in thalassemia or the like, comprising an effective amount of deferiprone or a physiologically acceptable salt thereof~~ **said therapeutic amount being** sufficient to ~~treat~~ **prevent further iron accumulation in the heart associated with** iron induced cardiac disease ~~normally associated with iron overload~~.

9. (currently amended) ~~An~~ **A pharmaceutical composition for iron induced cardiac disease comprising an** effective therapeutic amount of **the orally administered iron chelator** deferiprone or a physiologically acceptable salt thereof for the stabilization of ~~the risk of~~ heart disease in **heavily transfused** patients ~~having~~ **experiencing** iron overload **of the heart**, ~~such as in thalassemia or the like comprising an effective amount of deferiprone or a physiologically acceptable salt thereof~~ **said therapeutic amount being** sufficient to **stabilize iron accumulation in the heart and prevent further iron accumulation in the heart associated with** ~~treat~~ iron induced cardiac disease ~~normally associated with iron overload~~.

10. (currently amended) ~~An~~ **A pharmaceutical composition for iron induced cardiac disease comprising an** effective therapeutic amount of **the orally administered iron chelator** deferiprone