

ORAL FORMULATIONS OF DEFERASIROX

Field of the Invention

Compositions and technologies of manufacturing medicaments for Exjade™ (deferasirox) with high drug loading to potentially reduce variability of the gastric emptying, minimize food effect, prevent gastric irritation and also reduce the size and delivery route of the dosage form to improve patient compliance.

Background of the Invention

Exjade™ (deferasirox) is a marketed product from Novartis that is formulated as dispersible tablets in 125mg, 250mg and 500mg dose strengths. Exjade™ (deferasirox) is given once daily for the treatment of chronic iron overload due to blood transfusions, which is referred to by medical professionals and clinicians as transfusional hemosiderosis, in patients 2 years of age and older.

Due to the poor solubility of Exjade™ (deferasirox), a high dose is required to achieve the desired therapeutic effect, which results in unwanted side effects, such as gastrointestinal (GI) irritation and kidney toxicity. The poor solubility of Exjade™ (deferasirox) also presents technical difficulties in developing pharmaceutical formulations, as seen from the solubility profile summarized in Table 1. To meet the high dose requirement and reduce pill burden Exjade™ (deferasirox) was developed as dispersible tablets with about 29.4% drug load. The disadvantage of this type of formulation is that the tablets have to be dispersed in water or appropriate liquid, such as in orange juice or apple juice and stirred until a fine suspension is obtained prior to administration. Further, the dispersible tablets have to be taken at least 30 minutes before food.

Table 1. Exjade™ (deferasirox) Solubility Profile

pH	Solubility (mg/ml) at 37°C
water	0.02
1	< 0.01
2	< 0.01
3	< 0.01
4	< 0.01
5	< 0.01
7.5	0.167

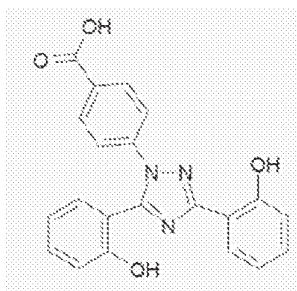
Gastrointestinal (GI) irritation has been reported for patients using the current dispersible tablets. Upper gastrointestinal ulceration and hemorrhage has also been reported in patients, including children and adolescents. Multiple ulcers have been observed in some patients. Stomach bleeding is a severe side effect that occurs for patients currently under Exjade therapy because of acidity of Exjade™ (deferasirox), and local accumulation of drug content. Therefore, it is desirable to re-formulate an Exjade™ (deferasirox) dispersible formulation to limit the direct contact of drug compound with stomach mucosa. It is further desirable to provide a high load deferasirox formulation that has no food effect. For instance, as enteric coated form or multi-particulate form where dosage form is emptied faster from the stomach. In addition, data from THALASSA (NTDT) study placebo arms (contains all components in Exjade™ dispersible tablets (except API) suggest that excipients in the marketed dispersible formulation could contribute to GI adverse effects (AE) profile of Exjade™.

The current invention describes formulated compositions and the corresponding technology of manufacturing tablets for Exjade™ (deferasirox) to prevent gastrointestinal irritation, having no food effect and improve patient compliance.

With aforementioned cumbersome in drug administration, it is also desirable to re-formulate the current dispersible Exjade™ (deferasirox) tablets into swallowable (ingestable, orally administerable) tablets and sachets, which increase the drug load by up to and greater than 100% of the current dispersible tablet and sachet per dose requiring less pill burden while maintaining equivalent pharmacokinetic profile, and consequently the therapeutic outcome as compared to commercially marketed dispersible Exjade™ (deferasirox) tablets.

Summary of the Invention

An aspect of the present invention provides a tablet for treating diseases which cause an excess of metal, such as iron, in a human or animal body or are caused by an excess of metal in a human comprising Exjade™ (deferasirox) of the formula I:



or a pharmaceutically acceptable salt thereof present in an amount of from 45% to 60% by weight based on the total weight of the tablet, said tablet having a reduced release under gastric conditions and fast release at near neutral pH or at neutral pH.

Typically, a drug product that shows faster dissolution will have a much higher exposure level when tested in humans. Surprisingly, in the current case, Exjade™ (deferasirox) tablets formulated to have slower release showed much higher bioavailability and no food effects when compared with commercial dispersible tablets, which have a faster dissolution rate but which exhibit significantly lower exposure levels. The characteristics of the new swallowable (ingestible, orally administerable) tablets and sachets, such as its disintegration time and dissolution are uniquely needed to reach the intended exposure levels.

Another aspect of the present invention provides a coated tablet comprising (a) deferasirox or a pharmaceutically acceptable salt thereof, and (b) at least one pharmaceutically acceptable excipient suitable for the preparation of tablets, wherein deferasirox or a pharmaceutically acceptable salt thereof is present in an amount of from 45% to 60% by weight based on the total weight of the tablet. The tablets are optionally enteric coated.

Another aspect of the present invention provides a sachet comprising (a) deferasirox or a pharmaceutically acceptable salt thereof, and (b) at least one pharmaceutically acceptable excipient suitable for the preparation of sachets, wherein deferasirox or a pharmaceutically acceptable salt thereof is present in an amount of from 45% to 60% by weight based on the total weight of the sachet.

Another aspect of the present invention provides a coated deferasirox tablet comprising:

- (i) at least one filler in an amount of about 10% to 40 % by weight based on the total weight of the tablet;
- (ii) at least one disintegrant in an amount of about 1% to 10% in weight based on the total weight of the tablet;
- (iii) at least one binder in an amount of about 1% to 5% by weight based on the total weight of the tablet;
- (iv) at least one surfactant in an amount of about 0.0% to 2% by weight based on the total weight of the tablet;
- (v) at least one glidant in an amount of about 0.1% to 1% by weight based on the total weight of the tablet;
- (vi) at least one lubricant in an amount of less than about 0.1% to 2% % by weight based on the total weight of the tablet; and
- (vii) a coating.

Another aspect of the present invention provides a process for the preparation of a coated deferasirox tablet according to any one of the preceding claims, which process comprises

- (i) mixing deferasirox or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient;
- (ii) wet-granulating the mixture obtained in step (i) in a high shear granulator followed by drying and screening to produce a granulate;
- (iii) mixing the granulates obtained in step (ii) with at least one pharmaceutically acceptable excipient to form a mixture;
- (iv) compressing the mixture obtained in step (iii) to form a tablet; and
- (v) coating the tablet.

Yet another aspect of the present invention provides a process for the preparation of a coated deferasirox tablet, comprising the steps of:

- (i) mixing deferasirox or a pharmaceutically acceptable salt and at least one pharmaceutically acceptable excipient;
- (ii) wet-granulating the mixture obtained in step (i) in a high shear granulator;
- (iii) extruding and spheronizing the wet granulates obtained in step (ii);
- (iv) drying the extruded and spheronized pellets; and
- (v) coating the pellets.

Brief Description of the Drawings

Figure 1 depicts a flow chart showing the manufacturing process of coated deferasirox tablets prepared by wet granulation

Figure 2 summarizes the dissolution profile of deferasirox from tablets prepared by wet granulation.

Figure 3 summarizes the dissolution profile of deferasirox from enteric coated tablets prepared by wet granulation.

Figure 4 summarizes the actual pharmacokinetic profiles of the commercial deferasirox tablets as well as those prepared using wet granulation technique

Figure 5 summarizes the dissolution profile of deferasirox capsule consisting of pellets prepared by extrusion spheronization.

Figure 6 summarizes the dissolution profile of deferasirox capsules consisting of enteric coated pellets prepared by extrusion spheronization.

Figure 7 summarizes deferasirox mean concentration versus time profiles for the invented formulations.

Figure 8 summarizes inter-subject variabilities in pharmacokinetic parameters AUC_{last} , AUC_{inf} , and C_{max} for the invented formulations.

Figure 9 summarizes a deferasirox C_{max} comparison in the invented formulation versus commercially available formulation for healthy volunteers.

Figure 10 summarizes steady state deferasirox C_{2h} values versus C_{max} for the invented formulation versus commercially available formulation.

Figure 11 summarizes a scatterplot of deferasirox C_{2h} for the invented formulation on Day 1 versus percent change from baseline in serum creatinine at Week 4.

Detailed Description of the Invention

The current commercial formulation of Exjade™ (deferasirox) is a dispersible tablet. The current formulation is dosed under fasted state due to a GI irritation issue. The new intended swallowable (ingestable, orally administerable) deferasirox tablets have an improved GI irritation AE profile due to a slower release profile and removal of sodium lauryl sulfate and lactose from the dispersible formulation. The invented formulation allows for patient compliance, no food effects and reduced GI irritation as compared to the current marketed Exjade™ (deferasirox) product.

The present invention provides a Exjade™ (deferasirox) formulation having a unique combination of excipients and a surfactant (e.g., a poloxamer) that are compatible with deferasirox at physiological pH environment. The invented formulation also possesses certain improved *in vitro* characteristics.

The invented process allows for and contributes to the high deferasirox loading. Wet granulation of the deferasirox active can be done with high drug loading (40-80% by weight) and compressed into tablets for enteric coating to achieve a final deferasirox loading of about 45-60% by weight, preferably 56% by weight.

A suitable dose of deferasirox ranges from 90 to 360 mg, especially, 90 mg, 180 mg, 360 mg unit dosage for film coated tablets and 100 to 400 mg, especially, 100mg, 200mg, 400mg unit dosage for granule formulation filled into stick-packs. The dose of deferasirox administered to a patient depends on numerous factors such as weight of patient, the severity of symptom and the nature of any other drugs being administered. The current product of deferasirox is presented on the market with three dosage strengths, 125 mg, 250 mg and 500 mg. The present invention provides exemplary embodiments for manufacturing swallowable (ingestable, orally administerable)

deferasirox tablets with different dissolution profiles that correspond to commercial Exjade™ (deferasirox) product. From a human clinical study, the invented deferasirox formulation demonstrated higher bioavailability, as compared to the previous marketed Exjade™ (deferasirox) formulation. Therefore the therapeutic dose was adjusted accordingly to achieve comparable pharmacokinetic profile and similar therapeutic effect. In summary, the invented formulation was developed with higher deferasirox loading and superior bioavailability. Lowering the dose will eventually improve patient compliance.

In an exemplary embodiment, one or more pharmaceutically acceptable excipients are present in the deferasirox dispersible tablets, including but not limited to conventionally used excipients: at least one filler, e.g., lactose, ethylcellulose, microcrystalline cellulose; at least one disintegrant, e.g. cross-linked polyvinylpyrrolidinone, e.g. Crospovidone®; at least one binder, e.g. polyvinylpyrrolidone, hydroxypropylmethyl cellulose; at least one surfactant, e.g. sodium laurylsulfate, poloxamer; at least one glidant, e.g. colloidal silicon dioxide; and at least one lubricant, e.g. magnesium stearate.

In one embodiment, the deferasirox granules and film-coated tablets will include the following compendial excipients: microcrystalline cellulose, povidone, crospovidone, poloxamer 188, colloidal silicon dioxide, and magnesium stearate. Opadry coating material (hypromellose, titanium dioxide, polyethylene glycol, Macrogol, talc and FD&C blue #2/Indigo carminine aluminum lake (C.I. 7305, E132)) is used for the film-coated tablets. Among the above excipients, only poloxamer 188 and the coating material represent new excipients for Exjade; lactose and sodium lauryl sulphate would no longer be present.

Reference is made to the extensive literature on the subject for these and other pharmaceutically acceptable excipients and procedures mentioned herein, see in particular Handbook of Pharmaceutical Excipients, Third Edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete edited by H.P. Fiedler, 4th Edition, Editor Cantor, Aulendorf and earlier editions.

Suitable fillers according to the invention include but are not limited to microcrystalline cellulose, including but not limited to Avicel™ PH 102, PH 101.

Suitable disintegrants according to the invention include but are not restricted to: maize starch, CMC-Ca, CMC-Na, microcrystalline cellulose, cross-linked polyvinylpyrrolidone (PVP), e.g. as known and commercially available under the trade names Crospovidone®, Polyplasdone®, available commercially from the ISP company, or Kollidon® XL, alginic acid, sodium alginate and guar gum. In one embodiment, cross-linked PVP, e.g. Crospovidone® is used.

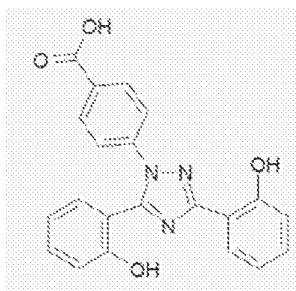
Suitable binders include but are not restricted to: starches, e.g. potato, wheat or corn starch, microcrystalline cellulose, e.g. products such as Avicel®, Filtrak®, Heweten® or Pharmacel®; hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, e.g. hydroxypropylmethyl cellulose-Type 2910 USP, hypromellose, and polyvinylpyrrolidone, e.g. Povidone® K30 from BASF. In one embodiment, polyvinylpyrrolidone is used, most preferably PVP K 30™.

Suitable surfactants according to the invention include but are not restricted to: sodium laurylsulfate, betain, quaternary ammonium salts, polysorbates, sorbitan esters and a poloxamer. In one embodiment, the surfactant is a poloxamer, preferably Pluronic™ F68 grade.

Suitable glidants include but are not restricted to: silica; colloidal silica, e.g. colloidal silica anhydrous, e.g. Aerosil® 200, magnesium trisilicate, powdered cellulose, starch and talc. Preferably, colloidal silicon dioxide is used.

Suitable lubricants include but are not restricted to: Mg-, Al- or Ca-stearate, PEG 4000 – 8000, talc, sodium benzoate, glyceryl mono fatty acid, e.g. having a molecular weight of from 200 to 800 Daltons, e.g. glyceryl monostearate (e.g. Danisco, UK), glyceryl dibehenate (e.g. CompritolATO888™, Gattefossé France), glyceryl palmitostearic ester (e.g. Precirol™, Gattefossé France), polyoxyethylene glycol (PEG, BASF), hydrogenated cotton seed oil (Lubitrab™, Edward Mendell Co Inc), castor seed oil (Cutina™ HR, Henkel). In one embodiment, magnesium stearate is used.

Accordingly, in an exemplary embodiment, the present invention provides a tablet for treating diseases which cause an excess of metal, such as iron, in a human or animal body or are caused by an excess of metal in a human comprising Exjade™ (deferasirox) of the formula I:



I

or a pharmaceutically acceptable salt thereof present in an amount of from 45% to 60% by weight based on the total weight of the tablet where said tablet having a reduced release under gastric conditions and fast release at near neutral pH or at neutral pH.

Typically, a drug product that shows faster dissolution will have a much higher exposure level when tested in humans. Surprisingly, in the current case, Exjade™ (deferasirox) tablets formulated to have slower release showed much higher bioavailability when compared with commercial dispersible tablets, which have a faster dissolution rate but which exhibit significantly lower exposure levels. The characteristics of the new swallowable (ingestible, orally administerable) tablets, such as its disintegration time and dissolution are uniquely needed to reach the intended exposure levels.

In a separate embodiment, the present invention provides a coated tablet comprising (a) deferasirox or a pharmaceutically acceptable salt thereof, and (b) at least one pharmaceutically acceptable excipient suitable for the preparation of tablets, wherein deferasirox or a pharmaceutically acceptable salt thereof is present in an amount of from 45% to 60% by weight based on the total weight of the tablet, wherein the tablets are optionally enteric coated.

In a separate embodiment, the present invention provides a coated deferasirox tablet comprising:

- (i) at least one filler in an amount of about 10% to 40% by weight based on the total weight of the tablet;
- (ii) at least one disintegrant in an amount of about 1% to 10% in weight based on the total weight of the tablet;

(iii) at least one binder in an amount of about 1% to 5% by weight based on the total weight of the tablet;

(iv) at least one surfactant in an amount of about 0.0% to 2% by weight based on the total weight of the tablet;

(v) at least one glidant in an amount of about 0.1% to 1% by weight based on the total weight of the tablet;

(vi) at least one lubricant in an amount of less than about 0.1% to 2% % by weight based on the total weight of the tablet; and

(vii) a coating, wherein the coating comprises a functional or non-functional polymer.

A. Manufacturing of Tablets by Wet Granulation process

According to one embodiment, the present invention provides a process for the preparation of a coated deferasirox tablet according to any one of the preceding claims, which process comprises:

(i) mixing deferasirox or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient;

(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator followed by drying and screening to produce a granulate;

(iii) mixing the granulates obtained in step (ii) with at least one pharmaceutically acceptable excipient to form a mixture;

(iv) compressing the mixture obtained in step (iii) to form a tablet; and

(v) coating the tablet, wherein the coating further comprises a functional or non-functional polymer.

A flow chart showing the manufacturing process of coated deferasirox tablets prepared by wet granulation is summarized in Figure 1.

In accordance with the invented process, the wet granulation step is performed using 40-80% by weight of deferasirox, a poorly soluble drug with PVP K-30TM as a binding agent, AvicelTM PH 101 as a filler, crospovidone as a disintegrating agent and SLS or

Poloxamer as a solubilizing agent. Water was used as granulation media. The granules were mixed with external excipients, e.g., Avicel™ PH102, crospovidone, Aerosil™ as glidant and magnesium stearate as an anti-sticking agent. The final granules were compressed into tablets and enterically coated using Acryl-EZE™ 93F, a Eudragit™ based polymer. The tablets has shown optimal hardness, friability and disintegration time. The dissolution profile of the coated deferasirox tablet is bioequivalent to the commercial Exjade (deferasirox) tablets, as shown in Figure 2.

Furthermore, in a related embodiment, the present invention provides a formulation with a full enteric coating. The enteric coating compris Opydry® 03K19229 and Acryl-EZE™ was applied to a deferasirox tablet core at level of 5-15% by weight gain. An addition of sub-coating, such as Opydry™ 03K19229, enhanced the effectiveness of enteric coating. Full enteric protection is achieved after greater than 5% by weight gain. No major impact on deferasirox drug release was observed for enteric-coated deferasirox tablets after two hours acid treatment. Except for 10 minutes of the delay initially, the deferasirox drug release profiles are comparable to commercial Exjade™ (deferasirox) product, as shown in Figure 3.

In general, after reaching the small intestine, the enteric coated tablets release the drug slowly. However, in the present invention, the use of unique polymer, for example PVP, as binder produces fast release of drug without any significant lag time. This will be helpful for achieving bioequivalency of the formulation as compared to reference product, which is a non-enteric dispersible tablet.

The medicament of the invention may be in any suitable form including, e.g. tablets, pellets, granules, multi-particulates, beads, mini-tabs, spherules, beadlets, microcapsules, milli-spheres, nano-capsules, micro-spheres, platelets or capsules depending upon the desired route of delivery.

An embodiment provides that the medicaments such as pellet and micro-particulates are filled in capsules, caplets or the like for oral delivery.

In another embodiment, the deferasirox medicament is packaged for use by the patient or caregiver. For example, the medicament can be packaged in a foil or other suitable package and is suitable for mixing into a food product (e.g. applesauce and other food vehicles) or into a drink for consumption by a patient.

B. Manufacturing multi-particulates using a extrusion spheronization

In a separate exemplary embodiment, the present invention provides a process for the preparation of a coated deferasirox tablet, which comprises the steps:

- (i) mixing deferasirox or a pharmaceutically acceptable salt and at least one pharmaceutically acceptable excipient;
- (ii) wet-granulating the mixture obtained in step (i) in a high shear granulator;
- (iii) extruding and spheronizing the wet granulates obtained in step (ii);
- (iv) drying the extruded and spheronized pellets; and
- (v) coating the pellets.

Accordingly, manufacturing deferasirox multi-particulates using a fluidized process technique or other pelletization techniques includes but is not limited to the following considerations:

- a) Pre-wetting: Water is evenly distributed to the dry blend of drug and Avicel™ PH105 in a high shear granulator.
- b) Pelletization: The pre-wetted blend was pelletized by mechanical and gravitational forces acting on the blend while being processed. Moisture (water) was constantly applied. Once the pellets reached the desired particle size range, a small percentage of the dry blend (or excipient alone) was incorporated on the pellets to stop growth and smooth the pellet surface.
- c) Drying: The drying of the pellets was performed in a fluid-bed processor. The pellets were dried to moisture content below 3% by weight.

The following examples illustrate aspects of the invention and are not a limitation on the present invention. Formulations for preparing tablets are set out below. In one aspect the tablets are formulated utilizing enteric coatings.

Example 1: Enteric coated wet granulated deferasirox tablets comprising a surfactant, sodium lauryl sulfate (SLS)

Granulation	
Internal phase	
Ingredient	Weight % (range)
Deferasirox	55.97 %
Avicel™ PH 101 / 105	14.4% (5-25)
PVP K-30™	2.25% (1-5)
Crospovidone	2% (1-5)
SLS	0.375 % (0-1)
External phase	
Ingredient	Weight % (range)
Dried Granules	75%
Avicel™ PH 102	18.5% (5-25)
Crospovidone	5% (2-10)
Aerosil™	0.5ranges% (0.1-1)
Magnesium Stearate	1% (0.1-2)
Subcoating	
Opadry™ 03K19229	1% (0-2)
Enteric coating	
Eudragit™ (Acryl EZE 93F)	7% (5-20)

Example 2: Enteric coated wet granulated deferasirox tablets comprising a poloxamer (Pluronic™ F68 grade)

Granulation	
Internal phase	
Ingredient	Weight % (range)
Deferasirox	55.97 %
Avicel™ PH 101 / 105	14.4% (5-25)
HPMc™ 3 cps	2.25% (1-5)
Crospovidone	2% (1-5)
Pluronic™	0.375 % (0-1)
External phase	
Ingredient	Weight % (range)
Dried Granules	75%
Avicel™ PH 102	18.5% (5-25)
Crospovidone	5% (2-10)
Aerosil™	0.5ranges% (0.1-1)
Magnesium Stearate	1% (0.1-2)
Subcoating	
Opadry™ 03K19229	1% (0-2)
Enteric coating	
Eudragit™ (Acryl EZE™ 93F)	7% (5-20)

Example 3: Composition of Deferasirox Pellets Manufactured by Extrusion-Spheronization Granulation

Ingredient	Weight % (range)
Deferasirox	60-80 %
Avicel™ PH 101 / 105	8-32%
PVP K-30™ or HPMC™ 3cps or HPC EXF™	2-5%
Crosspovidone	5%
SLS / Poloxamer™	1-2%

Enteric coating	
Eudragit™ (Acryl EZE™ 93F)	5-20%

Example 4: Composition of Deferasirox Pellets Manufactured by Fluidized Technique

Granulation	
Ingredient	Weight %
ICL670™	70-80%
Avicel™ PH 105	20-30%

The compositions of the present invention and manufacturing processes provide coated tablets of Exjade (deferiasirox) and thereby minimize local GI irritation. When compared to the dispersible Exjade (deferiasirox) tablets having a 29.4% drug load, The present invented methods and corresponding invented improved deferiasirox formulations increase the drug load for producing swallowable (ingestable) deferiasirox tablets that improve patient compliance.

Example 5: Deferasirox coated tablets prepared by wet granulation using non-functional coating

**Deferasirox
Tablets: Invented
doses**

Variant A				
Component	% (w/w) (range)	mg/648mg tab	mg/324mg tab	mg/162mg tab
Deferasirox	55.56	360.00	180.00	90.00
Microcrystalline cellulose PH101™	15.09	97.81	48.91	24.45
Microcrystalline cellulose PH102™	18.00	116.64	58.32	29.16
Poly Vinyl Pyrrolidone K-30™	2.25	14.58	7.29	3.65
Crospovidone	7.00	45.36	22.68	11.34
Pluronic™ F68	0.10	0.65	0.32	0.16
Aerosil™	0.50	3.24	1.62	0.81
Magnesium Stearate	1.50	9.72	4.86	2.43
Total	100.00	648.00	324.00	162.00
Coating				
Opadry™ Blue	3.00	19.44	9.72	4.86
Final tablet weight	103.00	667.44	333.72	166.86

**Invented Deferasirox Pediatric
Granule Doses**

Variant A				
Component	% (w/w)	mg/720mg tab	mg/360mg tab	mg/180mg tab
Deferasirox	55.56	400.00	200.00	100.00
Microcrystalline cellulose PH101™	15.09	108.68	54.34	27.17
Microcrystalline cellulose PH102™	18.00	129.60	64.80	32.40
PolyVinyl Pyrrolidone K-30™	2.25	16.20	8.10	4.05
Crospovidone	7.00	50.40	25.20	12.60
Pluronic™ F68	0.10	0.72	0.36	0.18
Aerosil™	0.50	3.60	1.80	0.90
Magnesium Stearate	1.50	10.80	5.40	2.70
Total	100.00	720.00	360.00	180.00

Summary of Deferasirox Variants Used in Clinical Pharmacokinetic (PK) Study

	Variant A	Variant B	Variant C
Materials	Qty (%)	Qty (%)	Qty (%)
Deferasirox	55.56	55.56	54.08
Cellulose microcrystalline	15.09	14.19	13.82
Crospovidone	7.00	7.0	6.81
Polyvinylpyrrolidone K30 TM	2.25	2.25	2.19
Poloxamer TM 188	0.10	1.00	0.97
Cellulose MKR TM GRN	18.00	18.00	17.52
Aerosil TM	0.50	0.50	0.49
Magnesium stearate	1.50	1.50	1.46
Eudragit TM L 100-55	-	-	2.17
Hypromellose 5cps	-	-	0.11
Sodium hydroxide	-	-	0.03
Triethyl citrate	-	-	0.28
Polysorbate TM 80	-	-	0.002
Glycerol monostearate	-	-	0.06
Total weight (mg)	100.00	100.00	100.00
Tablet properties			
Tooling	19x7.5	19x7.5	19x7.5
	Ovaloid	Ovaloid	Ovaloid
Mean weight (mg)	910.24	916.22	903.62
Compression force (kN)	25.00	25.00	25.00
Mean hardness (N)	267.60	231.70	236.70
% friability	0.00	0.02	0.11
Dissolution Time (DT, min.) with discs	3.42	5.45	6.45
Mean thickness (mm)	6.96	6.86	6.92

Granule Size for Deferasirox Variant A Formulation Corresponding to a Representative Batch for a Pilot Phase

		Weight of granules on screens (g) Screen Size (mm)														
		Water (%)	Water addition time (min)	LOD (%)	Bulk Density (g/ml)	Tap Density (g/ml)	1.4	1.0	0.71	0.5	0.25	0.18	0.125	0.09	Pan	Total (g or %)
Clinical Deferasiro x Batch	5K g	26	7		0.49	0.65	0	7.4	17.1	10.9	14.3	7.1	10.6	9.4	23.3	100.1
							0.00%	7.39%	17.08%	10.89%	14.29%	7.09%	10.59%	9.39%	23.28 %	100.00 %
Pilot phase DoE batch	20 Kg	26	7		0.47	0.66	0	0	3.7	7.6	9.2	5.2	6.3	5.1	12.7	49.8
							0.00%	0.00%	7.43%	15.26%	18.47%	10.44%	12.65%	10.24%	25.50 %	100.00 %

Patient Data from the clinical study are summarized in Table 2.

Table 2. PK results from deferasirox tablets prepared by wet granulation with non-functional coating

	Cmax			AUC		
	A	B	C	A	B	C
0501_00001	0.906	1.239	0.112	0.891	1.339	0.276
0501_00008	1.576	1.897	1.554	1.624	1.449	1.475
0501_00013	1.347	1.516	1.046	1.433	1.785	1.305
0501_00020	0.952	1.153	1.202	0.943	1.087	1.154
0501_00023	1.727	1.225	1.765	1.567	0.974	1.574
0501_00026	0.981	1.133	1.420	0.963	0.998	1.018
0501_00027		2.293	1.122		2.477	1.015
0501_00031	1.820	2.482	1.664	2.031	3.152	2.060
0501_00035	1.778	1.517	1.672	1.246	1.015	1.249
0501_00038	1.412	1.858	1.350	1.673	2.233	1.126
0501_00049	1.714	2.233	1.467	1.929	1.525	1.752
0501_00052	1.176	1.244	1.538	1.774	1.564	1.538
0501_00053	1.057	1.340	1.091	0.894	1.269	1.138
0501_00054	0.781	0.769	0.369	0.791	0.789	0.380
0501_00055	1.652	1.326	1.380	2.039	1.094	2.672
0501_00075	1.317	1.268	1.380	1.010	1.388	1.318
0501_00088	1.604	1.580	0.921	1.552	1.452	1.075
0501_00093	1.689	1.713	1.976	1.767	1.924	1.472
0501_00104	1.827	1.556	1.519	1.489	1.360	1.495
0501_00107	1.352	1.060	0.725	1.370	1.357	0.614

The dissolution profile for clinical deferasirox variants A, B, and C (500MG) is highlighted in Table 3.

Table 3. Dissolution data for Clinical Variants A, B, and C (500mg).

Treatment	Geo-mean ratio	90% CI	
		Lower	Upper
A: 500mg tablet with 0.1% Pluronic™	1.38	1.18	1.62
B: 500mg tablet with 1.0% Pluronic™	1.43	1.22	1.67
C: 500mg tablet with 1.0% Pluronic™ + modified-release enteric coating	1.15	0.99	1.35

- Data for C_{max} were comparable to those for AUC.
- Median T_{max} (3-4 hrs) appeared to be similar with all formulations.
- Deferasirox PK was slightly less variable with variants A, and B (CV 23-38%), and slightly more variable with variant C (CV 54-61%) as compared to a conventional marketed commercial formulation (CV 31-49%).
- PK data with the current formulation in this study were consistent with data from previous studies.

Example 6 High load deferasirox formulation no food effect studies.

Six clinical studies have been initiated with corresponding pharmacology studies in healthy adult volunteers. Four studies have been completed and two studies are ongoing. In the initial clinical pharmacology study for variant selection (study 1), the tablet variant selected for development displayed suprabioavailability: both AUC and C_{max} for the invented deferasirox formulation were approximately 40% higher compared to the current dispersible tablet (DT) at a single dose of 1500 mg. Therefore, the subsequent clinical pharmacology studies used strength-adjusted formulations (400 mg granules and 360 mg FCT to match the 500 mg DT), in line with EMA/618604/2008

Rev. 7, which states that "If suprabioavailability is found, development of a lower dosage strength should be considered".

Study 2 (pivotal study with FCT) and study 3 (pilot study with granules) both demonstrated fully equivalent exposure with an AUC_{last} ratio of 100%. However, C_{max} did not meet the standard bioequivalence criteria (as summarized in Table 4): values were higher for both strength-adjusted formulations.

The food effect study 4 (granules) showed overall equivalence of the administration with a soft food (apple sauce or yogurt) or with a low-fat meal when compared to fasting intake with water. The exposure after administration with a high-fat meal was close to the equivalence limits of 80% to 125% for AUC_{last}.

Table 4. Summary of pharmacokinetic comparisons for invented deferasirox formulation

Study No.	N	deferasirox dose [mg] (form)	food	AUClast ratio (90%CI)	Cmax ratio (90%CI)
Completed Studies					
1	2	1500(F) /	fasted/fasted	1.38 (1.179- 1.620)	1.39 (1.164- 1.661)
	0	1500(DT)			
2	3	1080(F) /	fasted/fasted	1.00 (0.932- 1.078)	1.30 (1.203- 1.400)
	2	1500(DT)			
3	2	1200(G) /	fasted/fasted	1.00 (0.915- 1.099)	1.18 (1.050- 1.323)
	0	1500(DT)			
4	2	1200(G) /	applesauce/wat	0.996 (0.934- 1.063)	0.972 (0.891- 1.061)
	4	1200(G)	er		
		1200(G) /	yogurt/water	0.986 (0.924- 1.052)	0.988 (0.905- 1.077)
		1200(G)			
	2	1200(G) /	breakfast/water	0.917 (0.845- 0.995)	0.887 (0.789 - 0.997)
	4	1200(G)			
		1200(G) /	high-fat	1.194 (1.099- 1.298)	0.949 (0.843- 1.069)
		1200(G)	breakfast/ water		
Ongoing Studies (results expected by Dec 2013)					
5		1080(F) / 1080(F)	fed/fasted	TBD	TBD
6		1200(G) /	fasted/fasted	TBD	TBD
		1500(DT)			

DT: dispersible tablets (current formulation); F: film-coated tablets; G: granules; N= number of subjects. Study 3 also tested dose linearity (at 400mg/800mg/1200mg) for the granules.

Study No.	N deferasirox dose [mg] (form)	food	AUC _{last} ratio (90%CI)	C _{max} ratio (90%CI)
Values outside the equivalence limits [0.8-1.25] are highlighted in bold				

The two remaining clinical pharmacology studies (to be conducted in 2H2013) aim to confirm the comparative bioavailability results for the granules, and to test the food effect for the FCT.

The new Exjade formulations represent a significant improvement in patient care and support compliance with chelation therapy because of the improved pharmaceutical properties and because of the changes in composition. These improvements are expected to provide for a positive benefit risk due to the importance of compliance/adherence to chelation therapy for patients with chronic iron overload aged 2 years and older:

- a lower inter-subject variability in exposure (CV% geometric mean in study F2102 for FCT and DT: AUC_{last} 39.2% vs 49.7%, C_{max} 27.5% vs 33.4%, respectively) and the absence of a substantial food effect (study 4) suggest that the new formulations achieve a more predictable dose-exposure relationship in clinical practice.
- the absence of a substantial food effect (study 4) which obviates the requirement to take the drug on an empty stomach at least 30 minutes before food and therefore allows patients more convenience and flexibility in the scheduling and administration of their daily dose.
- a more palatable alternative to the currently approved dispersion, particularly for elderly and pediatric patients (an aspect that was investigated in one of the measures of the currently approved Exjade EU PIP).
- The currently approved Exjade tablet is formulated with sodium lauryl sulphate, which may be associated with gastrointestinal tract irritation. Exjade currently also contains lactose and so is not recommended in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency. Novartis believes the exclusion of lactose and sodium lauryl sulfate in the new formulations will improve the gastrointestinal tolerability of the product. This is supported by the recently completed one year study 2209 where NTDT patients in the placebo arm, which contained the same excipients as the currently marketed Exjade formulation, reported GI adverse event rates that were comparable to the active treatment arm (42.9% for placebo vs. 36.4% for Exjade 10 mg/kg).

While the 90% CI for C_{max} with both the FCT (in the pivotal study 2) and the granules (in the pilot study) were not fully contained within the equivalence limits of 80% to 125%, the observed differences in C_{max} not clinically meaningful for the new formulations of this innovator drug based on the following rationale:

- total drug exposure (AUC) is the key parameter predicting safety and efficacy of deferasirox; chelation efficacy for iron chelators is commonly accepted to be related to AUC. In a 24-hour PK study following a single 35 mg/kg dose of oral deferasirox that was published by Chirnomas et al (2009), patients with inadequate response to deferasirox had significantly lower systemic drug exposure compared with control patients ($P < 0.00001$). C_{max}, volume of distribution/bioavailability (Vd/F), and elimination half-life ($t(1/2)$) were not different between the groups.
- no effect on the QT interval (a typical C_{max}-related toxicity) was observed in the thorough QT study (submitted with the original application in 2005); in that study, healthy volunteers (in whom exposure is higher than in iron-overloaded patients) were given doses of up to 40 mg/kg in order to achieve high C_{max} levels
- the range of C_{max} values observed in previous healthy volunteer studies with over 200 subjects is consistent with the range of C_{max} values observed with the new formulations (see below)
- a large amount of safety, efficacy and exposure data exist for the current formulation (see below for details)
- in previously submitted patient studies, only minor safety findings such as nausea and headaches were noted at T_{max} (see below for details)
- a statistical analysis to correlate pharmacokinetic parameters (C_{trough} as a proxy of AUC, C_{2h} as a proxy for C_{max}) with renal effects in the large, one year patient study A2409 indicates that creatinine changes are more strongly correlated with AUC than with C_{max} (see below for details)
- Exjade™ (deferasirox) is titrated based on efficacy and tolerability: the recommended starting dose is 20 mg/kg/day, with up-titration recommended in 5-10mg/kg steps every 3-6 months. Therefore, patients would only be exposed to the highest approved dose (40 mg/kg/day for the current formulation) after an extended period of up-titration with confirmed tolerability
- the absence of a significant food effect results in a lower risk of increased exposure when the drug is taken with a meal. With the currently approved DT formulation,

ingestion of 20 mg/kg with a high fat meal (previous study for commercially marketed formulation) resulted in an average C_{max} of 138 μM in healthy volunteers, whereas dispersion in water (study 2120) resulted in a lower C_{max} of 71 μM in healthy volunteers. In the patient study A0105F, exposure nearly doubled (to a variable extent) when Exjade was given after a high-fat breakfast. No such effect was observed with the new granule formulation (Table 4).

Figure 7 summarizes mean concentration ($\mu\text{mol/L}$)-time profiles of the key pharmacokinetic results for studies 1 (non-strength-adjusted tablet comparison), 2 (pivotal strength-adjusted FCT study), 3 (pilot strength-adjusted granule study), and 4 (granule food-effect study).

Individual C_{max} values from Study 2 and Study 3 are within the range of historical C_{max} values observed with the current commercially marketed DT formulation: Figure 8 includes C_{max} data from (1) previous CP studies in healthy subjects given 20 mg/kg deferasirox DT, (2) FCT treatment in Study 2, and (3) granule treatment in Study 3.

Clinical data has been generated and analyzed from a one-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral deferasirox formulation (20 mg/kg/day) in 1744 patients with transfusion dependent iron overload; thalassemia, MDS, SCD, and rare anemias (Study 7). Study 7 used sparse PK sampling: in addition to efficacy and safety data, deferasirox PK data were collected in a large sub-group of patients (~600) at pre-dose (C_{trough} , a proxy for AUC) and 2 hours post-dose (C_{2h} ; a proxy for C_{max}) on day 1, week 12 and week 28. As shown in Figure 9, the C_{max} values for the new high load deferasirox formulations at steady-state (predicted by a nonparametric superposition approach) in studies 2 and 3 lie within the range of observed steady-state deferasirox C_{2h} values with the current DT formulation. Of note, deferasirox exposure in healthy subjects is generally higher than in iron-overloaded patients; in addition, the sampling time point in Study 7 (C_{2h}) underestimates C_{max} (since deferasirox T_{max} usually occurs between 2 and 4 hours post-dose). Since clinical safety data were assessed within this range of C_{max} , it is unlikely that C_{max} observed with the new formulations would lead to additional safety issues.

Deferasirox C_{max} values in healthy volunteers are generally higher than in patients. Two healthy volunteer studies in the initial registration package in 2005 were therefore reviewed for potential C_{max} -related adverse events. In the thorough QT healthy volunteer study (which found no effect of Exjade on the QT interval), 44 volunteers received ExjadeTM (deferasirox 40 mg/kg immediately after consumption of a high-fat

breakfast to maximize C_{max} . C_{max} averaged 256 μM (range 134-472 μM). Safety findings in these subjects were limited to GI symptoms (diarrhea/loose stools, flatulence, and nausea) in 18% of patients, and headache and dizziness in one patient each (2%). In a study (a randomized crossover study in 28 healthy volunteers to evaluate the bioequivalence of a single 20 mg/kg dose of Exjade™ dispersed in fruit juice or water), three HV subjects reported loose stools 2.5 to 5 hours after Exjade intake, each on two separate occasions, lasting for 5-30 minutes.

In addition, a new analysis of creatinine and creatinine clearance changes was performed to explore whether deferasirox-associated renal changes are a function of peak exposure (C_{max}) or of overall exposure (AUC). The analysis used data from the large multicenter study 7, in which C_{trough} (a proxy of AUC) and deferasirox C2h (a proxy of C_{max}) was collected at multiple time points. Even though both PK parameters correlate with dose, the analyses summarized below indicate that renal functional changes are more closely associated with AUC than with C_{max} .

Based on study 7 data, the relationship between PK parameters at steady state (C_{trough} and C2h) and serum creatinine was investigated by using a linear mixed model of log-transformed creatinine values (1990 observations at week 12 and 28) with patient included in model as a random effect. After log-transformation, baseline creatinine levels, C2h and C_{trough} were included as predictors in the model. As shown in Table 5, a far higher slope (estimate) was observed for $\log(C_{trough})$ than for $\log(C2h)$, indicating a higher correlation with C_{trough} (a proxy of AUC) than with C2h (a proxy of C_{max}). For a 30% increase in C_{max} (as observed for the FCT), the serum creatinine ratio would be 1.0087 ($=1.3^{0.03287}$) with upper bound of the 95% CI of 1.0127 (with all other factors held constant). The potential of multicollinearity for $\log(C2h)$ and $\log(C_{trough})$ was assessed in the statistical model described above and did not show any multicollinearity issue (Variance Inflation Factor (VIF)=1.56 and condition index <30).

Table 5. Linear mixed effect model of percent change in serum creatinine for deferasirox formulations

Parameter	Estimate	Standard error	T value	Pr > t	Lower	Upper
Log(baseline creatinine)	0.9593	0.01226	78.22	<0.0001	0.9391	0.9795
Log(C2h)	0.03287	0.007786	4.22	<0.0001	0.02005	0.04569

Parameter	Estimate	Standard error	T value	Pr > t	Lower	Upper
Log(C _{trough})	0.06504	0.004803	13.54	<0.0001	0.05713	0.07295

Day 1 C_{2h} values did not predict the extent of creatinine changes at week 4 (N=682): the slope of the linear regression between Day 1 C_{2h} and percent change in serum creatinine at week 4 was 0.03 (-0.01, 0.08), with a p-value of 0.22, and R-square < 0.01, as summarized in Figure 11.

There was no statistical difference in the rate of serum creatinine increases (either >33% over baseline, or >33% over baseline and >ULN) between patients whose C_{2h} value was below the median (56.5 µmol/L in this analysis) and those whose C_{2h} value was at or above the median, based on the Chi-square test in a population exposed to a dose of approximately 20mg/kg (N=528; Table 6). A similar analysis was performed considering another classification for Day 1 C_{2h} using quartiles (< Q1; Q1 - < median; median - < Q3; ≥ Q3) and results led to the same conclusion.

Table 6. Statistical analysis of C_{2h} on day 1 versus notable serum creatinine values at week 4 (dose range 17.5 - 22.5 mg/kg) for deferasirox formulation

	Day1 C _{2h} <median (N=264); % (N)	Day1 C _{2h} ≥median (N=264); % (N)	Chi-square test p-value
SCr increase >33% from baseline at week 4	14.39% (38)	18.56% (49)	0.197 (NS)
SCr increase >33% from baseline and >ULN at week 4	5.68% (15)	7.58% (20)	0.382 (NS)

A covariate analysis by an ordinal logistic regression model was performed to further elucidate the impact of each PK parameter on renal function, as summarized in Table 7. C_{trough} had a strong impact on creatinine clearance (CRCL) change in categories, but C_{2h} had almost no impact (p-value=0.994), after adjusting for C_{trough}. A C_{2h} increase by 1.3-fold would provide an odds ratio (OR) of 0.999 (0.872; 1.146). This suggests that the new invented deferasirox formulations (comparable AUC but higher C_{max} than the current marketed formulation) would result in a comparable effect on renal function.

All analyses summarized in this section will be described in full detail in the registration dossiers for the FCT and the granules.

Table 7. Summary results of ordinal logistic regression model analysis based on week 12 data

Parameter	Estimate	Std error	Pr > ChiSq	OR* for a 2-fold increase in PK parameter (95% CI)	OR* for a 30% increase in PK parameter (95% CI)
Log(baseline creatinine clearance)	-10.3474	0.6405	<0.0001		
Log(C _{2h})	-0.00203	0.2663	0.9939	0.999 (0.695, 1.434)	0.999 (0.872; 1.146)
Log(C _{trough})	0.9346	0.1653	<0.0001	1.911 (1.527, 2.393)	1.278 (1.174; 1.391)
Response profile based on the following CrCl Categories (with ordered value):					
1: 90 ml/min or more (N=766); 2: 60 to <90 ml/min (N=193); 3: 15 to <60 ml/min (N=77);					
*OR : Odds Ratio					

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It is understood that while the present invention has been described in conjunction with the detailed description thereof that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the following claims. Other aspects, advantages and modifications are within the scope of the claims.

Claims

1. A swallowable film coated tablet which contains deferasirox present in an amount of from 45% to 60% by weight based on the total weight of the tablet, and wherein the tablet contains 90 mg, 180 mg or 360 mg of deferasirox, wherein deferasirox is present in free acid form,

wherein the tablet further comprises,

(i) at least one filler in a total amount of 10% to 40 % by weight based on total weight of the tablet, wherein the filler is microcrystalline cellulose;

(ii) at least one disintegrant in a total amount of 1% to 10% by weight based on the total weight of the tablet, wherein the disintegrant is cross-linked polyvinylpyrrolidone (crospovidone);

(iii) at least one binder in a total amount of 1% to 5% by weight based on the total weight of the tablet, wherein the binder is polyvinylpyrrolidone (PVP);

(iv) at least one surfactant in a total amount of up to 2% by weight based on the total weight of the tablet, wherein the surfactant is poloxamer;

(v) at least one glidant in a total amount of 0.1% to 1% by weight based on the total weight of the tablet, wherein the glidant is colloidal silicon dioxide;

(vi) at least one lubricant in a total amount of 0.1% to 2% by weight based on the total weight of the tablet, wherein the lubricant is magnesium stearate; and

(vii) a coating

and wherein the tablet does not contain sodium lauryl sulfate and does not contain lactose.
2. The swallowable film coated tablet according to claim 1, wherein the tablet contains 90 mg of deferasirox.
3. The swallowable film coated tablet according to claim 1, wherein the tablet contains 180 mg of deferasirox.
4. The swallowable film coated tablet according to claim 1, wherein the tablet contains 360 mg of deferasirox.