(13)

1004338

Apo-Pharma Inc.
150 Signet Drive
Toronto, ON, Canada, M9L 1T9

Phone: (416) 749-9300
Fax: (416) 401-3849

UNIVERSITY HEALTH NETWORK
Dept of Hematology-Toronto Gen Hosp
200 ELIZABETH ST , 8N-887
TORONTO ON M5G 2C4

Payment No. : 2000012168
Payment Date : 05/26/2011
Vendor No. : 111850

Page : 1 of 1

Invoice Number	Invoice Date	Document Number Text	Gross Amount	Discount	Net Amount
TO MARJORIE	05/25/2011	1900010415			
Disord" Prog.		Unrestric'd Grant for "Red Blo Cell	80,000.00	0.00	80,000.00
		Cheque Total.....			$ 80,000.00

Apo-Pharma Inc.
200 Barmac Drive
Toronto, ON, Canada, M9L 2Z7
416-749 9300

Bank of Montreal
100 King St. W.,P.O. BOX3-CSC
Toronto, ON M5X 1A3
00022-001

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0002

1004338

DATE 05262011
M M D D Y Y Y Y

PAY TO THE ORDER OF UNIVERSITY HEALTH NETWORK $ 80,000.00

EIGHTY THOUSAND DOLLARS

UNIVERSITY HEALTH NETWORK
Dept of Hematology-Toronto Gen Hosp
200 ELIZABETH ST , 8N-887
TORONTO ON M5G 2C4

PER _____

PER _____

⑈01004338⑈ ⑆97892⑈001⑆ 1230⑈902⑈

University Health Network
Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital

June 13, 2011

Foundation Office
Grants Coordinator, Finance & Grants
TGH: RFE 5S-801
416-340-4800 ext. 2010

Re: Red Blood Cell Disorders Program Fund
5790 5120 0708

Foundation Office
Toronto General Hospital

Please find enclosed three checks to be deposited to the Red Blood Cell Disorders Program Foundation account # 5790 5120 0708.

1) [redacted]
2) [redacted]
3) Apo-Pharma: 5/26/11 $80,000

Thank you for attending to this matter.

Erik Yeo MD FRCPC
Head of Red Blood Cell Disorders and Thrombosis and Hemostasis
Head of Hematology
University Health Network
Toronto General Hospital (EN885)
14-4069

ApoPharma Inc.
Innovative Drug Division of Apotex Inc.

June 1, 2011

Dr. Richard Ward
University Health Network
Dept. of Hematology – TGH
200 Elizabeth Street, 8N-887
Toronto, Ontario
M5G 2C4

RE: UNRESTRICTED GRANT FOR RED-BLOOD CELL DISORDERS PROGRAM

Dear Dr. Ward:

Please find enclosed our cheque for $80,000.00 which represents an unrestricted grant for "Red-Blood Cell Disorders Program.

We wish you every success in the program.

Sincerely,

Fernando Tricta
Vice-President
Medical Affairs

APOPHARMA INC., 200 Barmac Drive, Toronto, Ontario M9L 2Z7
Dr. Fernando Tricta ~ Tel: 416-401-7332 ~ Fax: 416-401-3867 ~
ftricta@apotex.com

Benign Hematology
Toronto General Hospital
200 Elizabeth Street, 8N-887
Toronto, ON M5G 2C4

Tel: 416 340 5233
Fax: 416 340 3799
richard.ward@uhn.on.ca

University Health Network
Toronto General Hospital | Toronto Western Hospital | Princess Margaret Hospital

By Email: ftricta@apotex.com

Dr F Tricta
Vice President, Medical Affairs
Apopharma Inc
200 Barmac Drive,
Toronto, Ontario M9L 2Z7

17th May 2011

Dear Fernando,

Further to your email, dated May 13th, I am delighted that ApoPharma has agreed to provide an unrestricted grant of CAD$ 80,000 to the Red Blood Cell Disorders Program at the Toronto General Hospital. Please make the cheque payable to "Department of Hematology, University Health Network c/o Erik Yeo" and mail to the address above.

We envisage that the funds will be utilised for some of the following activities over the coming 12 months:

- Analysis and reporting of our centre's experience with Deferiprone
- Analysis of our cardiac data with respect to Deferiprone
- Initiation of a research study evaluating 2D-ECHO, Perfusion cardiac MRI and cardiac catheterisation in Sickle Cell Disease
- Linking with other US centres on a common protocol for Deferiprone-Deferasirox combination therapy
- Development of a Clinical database for the RBCD Program at TGH
- Prospective evaluation of relaxed CBC monitoring frequency for Deferiprone
- Pharmaco-vigilance/Safety Monitoring/Reporting (LA-04 Compassionate Use)
- Study Evaluating compliance and barriers to compliance with chelating agents
- Manuscript on Pregnancy outcomes in Thalassemia and Sickle Cell Disease
- Manuscript on Osteopenia/Osteoporosis in Sickle Cell Disease
- Continuing professional development of RBCD team members

I would be happy to update on the progress of these projects during the year and work with you to achieve sustainable funding for future initiatives.

Yours sincerely,

Richard Ward
Staff Hematologist, University Health Network
Red Blood Cell Disorders Program, Toronto General Hospital

Richard Ward MRCP (UK), FRCPath (UK)
Division of Medical Oncology & Hematology, Dept of Medicine, University Health Network
Assistant Professor, Division of Hematology, Dept of Medicine, University of Toronto
CPSO: # 89247 OHIP: # 024759

Benign Hematology
Toronto General Hospital
200 Elizabeth Street, 8N-887
Toronto, ON M5G 2C4

Tel: 416 340 5233
Fax: 416 340 3799
richard.ward@uhn.on.ca

University Health Network
Toronto General Hospital | Toronto Western Hospital | Princess Margaret Hospital

By Email: ftricta@apotex.com

Dr F Tricta
Vice President, Medical Affairs
Apopharma Inc
200 Barmac Drive,
Toronto, Ontario M9L 2Z7

8th February 2011

Dear Fernando,

I would like to thank Michael and yourself for meeting with me and Dr Nada Miscevic, Benign Hematology trials director, recently.

We are pleased to hear that Apopharma is interested in pursuing research activity with the RBCD clinical program at UHN, helping to advance patient care further.

To summarise our current status, we have ~150 patients with Thalassemia syndromes and 250 patients with Sickle Cell Disease, projected to increase to 430 by the end of 2011. We recognise, in particular, the strength of the cardiac program and have established a cardiac-RBCD research group, which includes cardiologists, MRI cardiac-radiologists, and a clinician scientist interested in animal models of iron. We have also developed relationships with key allied specialties, to aid clinical care and research collaboration, eg labs, nephrology, endocrinology. The clinical program has been stabilised and is now staffed by several Hematologists as well as an ASH-sponsored Fellow. Part of our remit is to promote excellence in Hemoglobinopathy education and training. Timing is therefore right to accelerate the research output of the program. To this end, we would be interested in, but not limited to:

- Analysis of our centre's experience with Deferiprone
- Analysis of our cardiac data with respect to Deferiprone
- Prospective evaluation of relaxed CBC monitoring frequency
- Linking with other US centres on a common protocol for Deferiprone-Exjade combination therapy
- Harnessing the close ties between Sickkids and TGH

Richard Ward MRCP (UK), FRCPath (UK)
Division of Medical Oncology & Hematology, Dept of Medicine, University Health Network
Assistant Professor, Division of Hematology, Dept of Medicine, University of Toronto
CPSO: # 89247 OHIP: # 024759

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Fax: 416 340 3799
richard.ward@uhn.on.ca

University Health Network
Toronto General Hospital | Toronto Western Hospital | Princess Margaret Hospital

- In addition you also mentioned medium-long term work in SCD and possible future pipeline of new chelating agents

We have prepared a proposal requesting an unrestricted grant, to assist with the Fellowship program, and other endeavours for your review and consideration. Please, let us know if any additional information or clarifications are required.

We look forward to hearing from you.

Yours sincerely,

Richard Ward
Staff Hematologist, University Health Network
Red Blood Cell Disorders Program, Toronto General Hospital

Richard Ward MRCP (UK), FRCPath (UK)
Division of Medical Oncology & Hematology, Dept of Medicine, University Health Network
Assistant Professor, Division of Hematology, Dept of Medicine, University of Toronto
CPSO: # 89247 OHIP: # 024759

Apopharma Inc – RBCD Program Grant Request

1. Clinical Fellow; Full Time Salary	Year
2. Research Assistant/Data analyst; part time	$80,000.00
3. Pharmaco-vigilance/Safety Monitoring/Reporting (LA-04 Compassionate Use)	$40,000.00
4. Support staff conference attendance	$30,000.00
5. Research Student/Summer/Part Time	$10,000.00
	$15,000.00
	$175,000.00

2 or 3 yrs

350,000 (2 yrs)
525,000 (3 Yrs)

(17)

ApoPharma
Innovative Drug Division of Apotex Inc.

24 March 2010

Dr. Richard Ward,
Toronto General Hospital,
University Health Network
2NU-210, 585 University Ave.,
Toronto, ON. M5G 2C5

Re: Summary of Product Characteristics and Safety & Efficacy Agreement.

Dear Dr. Ward,

As requested, please find three copies of our new Agreement to share with us the safety & efficacy data of Ferriprox use for you, Dr. Pendergrast & Dr. Yeo. As well, I have included a copy our Summary of Product Characteristics. I have enclosed the following;

- Summary of Product Characteristics (Ferriprox/23 September 2009)
- Three copies of the Agreement for your review
- A Flowchart for Request for Compassionate Use of Ferriprox.

If the Agreement is acceptable, please have each physician sign their respective agreement and return a copy to me via email. **Please keep the remaining signed copy for your files. Please note, since each SAP Authorization is physician specific, each physician is required to obtain their own SAP Authorization, prior to prescribing Ferriprox.**

Should you have any questions or concerns, please do not hesitate to contact me.

Thank you for your interest in Ferriprox.

Sincerely,

Jeff Zindoga, B.Sc.
Clinical Research Associate
ApoPharma Inc.
200 Barmac Drive
Toronto, ON M9L 2Z7
Tel: (416) 401-7602
Fax: (416) 401-3867
Email: jzindoga@apotex.com

Cc: Dr. Jacob Pendergrast
Cc: Dr. Erik Yeo
Cc: LA-04 Master Study File

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg deferiprone.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, capsule-shaped, film-coated tablets imprinted "APO" bisect "500" on one side, plain on the other. The tablet is scored. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ferriprox is indicated for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.

4.2 Posology and method of administration

Deferiprone therapy should be initiated and maintained by a physician experienced in the treatment of patients with thalassaemia.

Posology
Deferiprone is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dose per kilogram body weight should be calculated to the nearest half tablet. See table below for recommended doses for body weights at 10 kg increments.

Dose table
To obtain a dose of about 75 mg/kg/day, use the number of tablets suggested in the following table for the body weight of the patient. Sample body weights at 10 kg increments are listed.

Body weight (kg)	Total daily dose (mg)	Dose (mg, three times/day)	Number of tablets (three times/day)
20	1500	500	1.0
30	2250	750	1.5
40	3000	1000	2.0
50	3750	1250	2.5
60	4500	1500	3.0
70	5250	1750	3.5
80	6000	2000	4.0
90	6750	2250	4.5

A total daily dose above 100 mg/kg body weight is not recommended because of the potentially increased risk of adverse reactions (see sections 4.4, 4.8, and 4.9).

Due to the serious nature of agranulocytosis, that can occur with the use of deferiprone, special monitoring is required for all patients. Caution must be used when the patients' absolute neutrophil

count (ANC) is low, as well as when treating patients with renal insufficiency or hepatic dysfunction. (see section 4.4).

Paediatric population
There are limited data available on the use of deferiprone in children between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age.

Method of administration
For oral use

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy (see section 4.6).
- Breastfeeding (see section 4.6).
- Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.5).

4.4 Special warnings and precautions for use

Neutropenia/Agranulocytosis
Deferiprone has been shown to cause neutropenia, including agranulocytosis. The patient's neutrophil count should be monitored every week.

In clinical trials, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Neutropenia and agranulocytosis resolved once therapy was withdrawn. If the patient develops an infection while on deferiprone, therapy should be interrupted and the neutrophil count monitored more frequently. Patients should be advised to report immediately to their physician any symptoms indicative of infection such as fever, sore throat and flu-like symptoms.

Suggested management of cases of neutropenia is outlined below. It is recommended that such a management protocol be in place prior to initiating any patient on deferiprone treatment.

Treatment with deferiprone should not be initiated if the patient is neutropenic. The risk of agranulocytosis and neutropenia is higher, if the baseline absolute neutrophil count (ANC) is less than 1.5×10^9/l.

In the event of neutropenia:
Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood cell (CBC) count, with a white blood cell (WBC) count, corrected for the presence of nucleated red blood cells, a neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly CBC, WBC, neutrophil and platelet counts continue to be obtained for three consecutive weeks, to ensure that the patient recovers fully. Should any evidence of infection develop concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate therapeutic regimen instituted.

In the event of severe neutropenia or agranulocytosis:
Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

Limited information is available regarding rechallenge. Therefore, in the event of neutropenia, rechallenge is not recommended. In the event of agranulocytosis, a rechallenge is contraindicated.

Carcinogenicity/mutagenicity/effects on fertility
In view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded (see section 5.3). No animal studies to evaluate the potential effects of deferiprone on fertility have been reported.

Serum ferritin concentration/plasma Zn^{2+} concentration
It is recommended that serum ferritin concentrations, or other indicators of body iron load, be monitored every two to three months to assess the long-term effectiveness of the chelation regimen in controlling the body iron load. Interruption of therapy with deferiprone should be considered if serum ferritin measurements fall below 500 µg/l.

Monitoring of plasma Zn^{2+} concentration, and supplementation in case of a deficiency, is recommended.

HIV positive or other immune compromised patients
No data are available on the use of deferiprone in HIV positive or in other immune compromised patients. Given that deferiprone can be associated with neutropenia and agranulocytosis, therapy in immune compromised patients should not be initiated unless potential benefits outweigh potential risks.

Renal or hepatic impairment and liver fibrosis
There are no data available on the use of deferiprone in patients with renal or hepatic impairment. Since deferiprone is eliminated mainly via the kidneys, there may be an increased risk of complications in patients with impaired renal function. Similarly, as deferiprone is metabolised in the liver, caution must be exercised in patients with hepatic dysfunction. Renal and hepatic function should be monitored in this patient population during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered.

In thalassaemia patients there is an association between liver fibrosis and iron overload and/or hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver histology is recommended.

Discoloration of urine
Patients should be informed that their urine may show a reddish/brown discoloration due to the excretion of the iron-deferiprone complex.

Chronic overdose and neurological disorders
Neurological disorders have been observed in children treated with 2.5 to 3 times the recommended dose for several years. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended (see sections 4.8 and 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Due to the unknown mechanism of deferiprone induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.3).

Interactions between deferiprone and other medicinal products have not been reported. However, since deferiprone binds to metallic cations, the potential exists for interactions between deferiprone and trivalent cation-dependent medicinal products such as aluminium-based antacids. Therefore, it is not recommended to concomitantly ingest aluminium-based antacids and deferiprone.

The safety of concurrent use of deferiprone and vitamin C has not been formally studied. Based on the reported adverse interaction that can occur between deferoxamine and vitamin C, caution should be used when administering deferiprone and vitamin C concurrently.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential must be advised to avoid pregnancy due to the clastogenic and teratogenic properties of the medicinal product. These women should be advised to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant (see section 4.3).

Breastfeeding
It is not known whether deferiprone is excreted in human milk. No prenatal and postnatal reproductive studies have been conducted in animals. Deferiprone must not be used by breastfeeding mothers. If treatment is unavoidable, breast feeding must be stopped (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most serious adverse reaction reported in clinical trials with deferiprone is agranulocytosis (neutrophils $<0.5 \times 10^9$/l), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). The observed incidence of the less severe form of neutropenia (neutrophils $<1.5 \times 10^9$/l) is 4.9% (2.5 cases per 100 patient-years). This rate should be considered in the context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism.

Episodes of diarrhoea, mostly mild and transient, have been reported in patients treated with deferiprone. Gastrointestinal effects are more frequent at the beginning of therapy and resolve in most patients within a few weeks without the discontinuation of treatment. In some patients it may be beneficial to reduce the dose of deferiprone and then scale it back up to the former dose. Arthropathy events, which ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability, have also been reported in patients treated with deferiprone. Mild arthropathies are generally transient.

Increased levels of serum liver enzymes have been reported in patients taking deferiprone. In the majority of these patients, the increase was asymptomatic and transient, and returned to baseline without discontinuation or decreasing the dose of deferiprone (see section 4.4).

Some patients experienced progression of fibrosis associated with an increase in iron overload or hepatitis C.

Low plasma zinc levels have been associated with deferiprone, in a minority of patients. The levels normalised with oral zinc supplementation.

Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.4 and 4.9).

Adverse reaction frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100).

SYSTEM ORGAN CLASS	VERY COMMON (≥1/10)	COMMON (≥1/100 to <1/10)
Blood and lymphatic system disorders		Neutropenia Agranulocytosis
Metabolism and nutrition disorders		Increased Appetite
Nervous system disorders		Headache
Gastrointestinal disorders	Nausea Abdominal Pain Vomiting	Diarrhoea
Musculoskeletal and connective tissue disorders		Arthralgia
Renal and urinary disorders	Chromaturia	
General disorders and administration site conditions		Fatigue
Investigations		Increased liver enzymes

4.9 Overdose

No cases of acute overdose have been reported. However, neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. The neurological disorders progressively regressed after deferiprone discontinuation.

In case of overdose, close clinical supervision of the patient is required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron chelating agents, ATC code: V03AC02

The active substance is deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one), a bidentate ligand which binds to iron in a 3:1 molar ratio.

Clinical studies have demonstrated that deferiprone is effective in promoting iron excretion and that a dose of 25 mg/kg three times per day can prevent the progression of iron accumulation as assessed by serum ferritin, in patients with transfusion-dependent thalassaemia. However, chelation therapy may not necessarily protect against iron-induced organ damage.

Deferiprone has been investigated in 247 patients in two phase III trials and a compassionate use programme. Serum ferritin was chosen as the primary efficacy criterion in the studies. In one study of two-year duration deferiprone was compared to deferoxamine. The mean serum ferritin levels were not significantly different in the two treatment groups, but mean hepatic iron concentration in deferiprone treated patients seems to increase more than in deferoxamine treated patients. Therefore deferiprone at the recommended dose could be less effective than deferoxamine.

The other study was a supportive open, non-comparative study. In this study patients maintained serum ferritin values at pre-study levels. The primary end-point was the incidence of agranulocytosis, which occurred at a frequency of 1.2%.

5.2 Pharmacokinetic properties

Absorption
Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract. Peak serum concentration is reported to occur 45 to 60 minutes following a single dose in fasted patients. This may be extended to 2 hours in fed patients.

Following a dose of 25 mg/kg, lower peak serum concentrations have been detected in patients in the fed state (85 µmol/l) than in the fasting state (126 µmol/l), although there was no decrease in the amount of deferiprone absorbed when it was given with food.

Biotransformation
Deferiprone is metabolised predominantly to a glucuronide conjugate. This metabolite lacks iron-binding capability due to inactivation of the 3-hydroxy group of deferiprone. Peak serum concentrations of the glucuronide occur 2 to 3 hours after administration of deferiprone.

Elimination
In humans, deferiprone is eliminated mainly via the kidneys; 75% to 90% of the ingested dose is reported as being recovered in the urine in the first 24 hours, in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex. A variable amount of elimination via the faeces has been reported. The elimination half-life in most patients is 2 to 3 hours.

5.3 Preclinical safety data

Non-clinical studies have been conducted in animal species including mice, rats, rabbits, dogs and monkeys.

The most common findings in non-iron-loaded animals at doses of 100 mg/kg/day and above were hematologic effects such as bone marrow hypocellularity, and decreased WBC, RBC and/or platelet counts in peripheral blood.

Atrophy of the thymus, lymphoid tissues, and testis, and hypertrophy of the adrenals, were reported at doses of 100 mg/kg/day or greater in non-iron-loaded animals.

No carcinogenicity studies in animals have been conducted with deferiprone. The genotoxic potential of deferiprone was evaluated in a set of *in vitro* and *in vivo* tests. Deferiprone did not show direct mutagenic properties; however, it did display clastogenic characteristics in *in vitro* assays and *in vivo* in animals.

Deferiprone was teratogenic and embryotoxic in reproductive studies in non-iron-loaded rats and rabbits at doses at least as low as 25 mg/kg/day. No prenatal and postnatal reproductive studies have been conducted in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Magnesium stearate
Colloidal silicon dioxide

Coating
Hypromellose
Macrogol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles with child resistant closure (polypropylene).
Each pack contains one bottle of 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Darwinweg 20
2333 CR Leiden
Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/99/108/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/08/1999
Date of latest renewal: 23/09/2009

10. DATE OF REVISION OF THE TEXT

23/09/2009

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

ApoPharma
Innovative Drug Division of Apotex Inc.

24 March 2010

Dr. Richard Ward
Toronto General Hospital,
University Health Network
2NU-210, 585 University Ave.,
Toronto, ON.
M5G 2C5

Program Code: LA-04
Program Title: The Compassionate Use of Ferriprox (Deferiprone) in Patients with Transfusion Dependent Anemia and Chronic Iron Overload

Re: Agreement to share Safety & Efficacy Outcome of Ferriprox use

Dear Dr. Ward,

This letter will act to confirm our agreement to share safety & efficacy data of Ferriprox use. As a drug manufacturer, ApoPharma Inc. is obligated to report to regulatory agencies all safety data obtained from this program. As per LA-04 Compassionate Use Program Protocol, patients will be monitored weekly and Case Report Forms will be forwarded to ApoPharma Inc. quarterly. Pending Health Canada approval, ApoPharma will ship drug in semi-annual batches, but data will be submitted quarterly. The agreement will be for the length of the patients' involvement in the Compassionate Use Program

The treating physician agreed to be responsible for submitting a Special Access Request (SAR) to the Therapeutic Products Directorate (TPD) on behalf of the patient, and to follow regulatory requirements for the use of a non-approved investigational product on a compassionate use basis.

To protect patient's rights, patients and their authorized legal representatives will sign an informed consent form prior to any procedures of the program. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) may also be involved to review and approve the program.

If a **Serious Adverse Event (SAE)** occurs, it is the responsibility of the treating physician to report all SAEs to the appropriate Regulatory Authorities in compliance with local regulatory requirements and timelines. ApoPharma Inc. must be notified **within 24 hours** of the occurrence or notification by the patient. The event must be faxed to ApoPharma Inc. using a standard ApoPharma SAE form. **Notification should be made to the: Medical Safety Division, ApoPharma Inc., Tel: +1-416-401-7650. The completed SAE form should be faxed to: Fax: +1-416-401-3916.** The treating physician must also report SAEs to their respective IRB/IEC responsible for the program, if required.

Please sign below to acknowledge receipt of this letter and return it to my attention.

ApoPharma
Innovative Drug Division of Apotex Inc.

Kind regards,

Liqi Chen

Liqi Chen
Project Leader, Clinical Research
Tel: (416) 401-7527
Fax: (416) 401-3867
Email: lchen1@apotex.com

Acknowledgement of receipt and acceptance of this letter:

(Toronto General Hospital)

Name: Dr. Richard Ward

Name: R Ward
Signature

Date: **March 24th 2010**

Ward, Ronald

(18)

From: Dian Shaw <dshaw@apotex.com>
Sent: Friday, May 07, 2010 1:40 PM
To: Ward, Richard
Subject: RE: TGH
Attachments: Ferriprox R-54 EN - FCT SPC only.pdf

OK. Here it is just in case.

Dian

From: Ward, Richard [mailto:Richard.Ward@uhn.on.ca]
Sent: May-07-10 1:38 PM
To: Dian Shaw
Subject: RE: TGH

I don't remember getting it, only the revised contract.

Richard Ward MRCP (UK), FRCPath (UK)
Benign Hematology – University Health Network
Red Blood Cell Disorders Program, Toronto General Hospital
8N-887, 200 Elizabeth St,
Toronto, ON. M5G 2C4
Tel: 416 340 4069
Fax: 416 340 3799
Pager: 416 790 8066
richard.ward@uhn.on.ca

From: Dian Shaw [mailto:dshaw@apotex.com]
Sent: Friday, May 07, 2010 1:35 PM
To: Ward, Richard
Subject: RE: TGH

The SPC (SmPC) was sent approx 24 Marc 2010.

Jeff is on his way to personally drop it off as we speak. Here is his Cell [redacted] so that you can arrange where to meet him.

Dian

From: Ward, Richard [mailto:Richard.Ward@uhn.on.ca]
Sent: May-07-10 1:31 PM
To: Dian Shaw
Subject: RE: TGH

Thanks.
A few of the emails from Jeff I don't have.
I don't think I have the SPC.
Otherwise Ok.
Is Jeff sending the disk today? not heard from him yet.

Thanks

Richard

From: Dian Shaw [mailto:dshaw@apotex.com]
Sent: Friday, May 07, 2010 1:28 PM
To: Ward, Richard
Cc: Jeff Zindoga
Subject: RE: TGH

Hi Richard:

Please ensure that you have the following:

1. all original signed ICFs
2. Copy of the protocol
3. IB
4. SPC
5. All communication with ApoPharma
6. All data recorded in the CRFs and or communicated to ApoPharma are recorded in the patients hospital file. The source must be available. The CFRs are NOT SOURCE document
7. Drug request/receipt and dispensing records

Please let me know if you have any questions. You may contact me over the week either by email or telephone ([redacted]. Good luck.

Dian

From: Ward, Richard [mailto:Richard.Ward@uhn.on.ca]
Sent: May-07-10 11:14 AM
To: Dian Shaw
Subject: Re: TGH

Can you courier today?

From: Dian Shaw <dshaw@apotex.com>
To: Ward, Richard
Sent: Fri May 07 11:13:04 2010
Subject: RE: TGH

Do you know the exact date. Jeff will drop off a CD on Monday.

Dian

From: Ward, Richard [mailto:Richard.Ward@uhn.on.ca]
Sent: May-06-10 4:31 PM
To: Dian Shaw
Subject: TGH

Hi Dian
I understand that Dr Yeo's research assistant, Nada Miscevic will be in touch.

I know you are going through the data your end, but I think the big hole this end is the start dates. Mui has been sending these through but not always recorded on our copy.
Is it possible to print and send us your entire dataset for our 24 pts? If not can you send all the start dates and AE info, as these are probably the 2 important bits.

The audit is next week.
Thanks, Richard

Richard Ward MRCP (UK), FRCPath (UK)
Benign Hematology – University Health Network
Red Blood Cell Disorders Program, Toronto General Hospital
8N-887, 200 Elizabeth St,
Toronto, ON, M5G 2C4
Tel: 416 340 4069
Fax: 416 340 3799
Pager: 416 790 8066
richard.ward@uhn.on.ca

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(19)

Ward, Ronald

From: Jeff Zindoga <jzindoga@apotex.com>
Sent: Friday, April 30, 2010 10:39 AM
To: Ward, Richard
Subject: FW: LA-04 inspection at TGH

P.S. My manager Dian Shaw requested, that in future communication regarding this matter, please email her directly at dshaw@apotex.com and 'cc' me.

Thanks,
Jeff.

From: Jeff Zindoga
Sent: Friday, April 30, 2010 9:55 AM
To: 'Ward, Richard'
Subject: LA-04 inspection at TGH

Hi Richard,

As a follow-up to your phone conversation, please let us know as soon as you have more details regarding the internal inspection of the Compassionate Program and how we can be of assistance.

Regards,
Jeff

Jeff F. Zindoga, B.Sc.
Clinical Research Associate
ApoPharma Inc.
Innovative Drug Division of Apotex Inc.
200 Barmac Dr.,
Toronto, ON. M9L 2Z7
Tel: 416 401 7602
Toll Free: 1 800 268 4623 ext. 7602
Fax: 416 401 3867
Email: jzindoga@apotex.com

(23)

Christopher Paige

From: McGill, Peggy [Peggy.McGill@uhn.ca]
Sent: Monday, January 09, 2012 1:50 PM
To: Christopher Paige
Subject: FW: Apotex

Pharmacy does not show this revenue either.

Peggy

Peggy McGill
Senior Finance Director, Research
Hydro Place Building, Room 1047
10th floor, Suite 1056
700 University Avenue
Toronto, ON
M5G 1Z5
Tel: (416) 581-7819
Fax: (416) 946-2098
Email: peggy.mcgill@uhn.on.ca

From: Bon, Alex
Sent: Monday, January 09, 2012 1:47 PM
To: McGill, Peggy
Cc: Ngan, Raymond; Fung, Esther
Subject: RE: Apotex

Peggy,
We have not been able to locate such a cheque.
Alex

From: McGill, Peggy
Sent: Monday, January 09, 2012 13:41
To: Bon, Alex
Subject: Apotex

HI Alex

Have you had a chance to check into this? Chris Paige is waiting for my response.

Thanks

Peggy

Peggy McGill
Senior Finance Director, Research
Hydro Place Building, Room 1047
10th floor, Suite 1056
700 University Avenue
Toronto, ON
M5G 1Z5
Tel: (416) 581-7819
Fax: (416) 946-2098

Email: peggy.mcgill@uhn.on.ca

From: McGill, Peggy
Sent: Thursday, January 05, 2012 4:18 PM
To: Bon, Alex
Subject: FW: Re:

Hi Alex

Do you know is UHN has received an unrestricted educational grant form Apotex? We have check our research records and cannot see one but it may flow into pharmacy.

Thanks

Peggy

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Senior Finance Director, Research
Hydro Place Building, Room 1047
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700 University Avenue
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M5G 1Z5
Tel: (416) 581-7819
Fax: (416) 946-2098
Email: peggy.mcgill@uhn.on.ca

From: Christopher Paige
To: McGill, Peggy <Peggy.McGill@uhn.ca>; Paul Macpherson
Sent: Mon Jan 02 11:07:43 2012
Subject:

Peggy and Paul: Best wishes for the new year and all that..... would one of you be able to tell me if someone at UHN was the recipient of an "unrestricted educational grant" from Apotex.

Christopher Paige

From: McGill, Peggy [Peggy.McGill@uhn.ca]
Sent: Tuesday, January 10, 2012 12:06 PM
To: Christopher Paige
Subject: RE: Apotex

Hi Chris

We have not receive any cheques from Apopharma.

Peggy

Peggy McGill
Senior Finance Director, Research
Hydro Place Building, Room 1047
10th floor, Suite 1056
700 University Avenue
Toronto, ON
M5G 1Z5
Tel: (416) 581-7819
Fax: (416) 946-2098
Email: peggy.mcgill@uhn.on.ca

From: Christopher Paige [mailto:paige@uhnresearch.ca]
Sent: Tuesday, January 10, 2012 10:26 AM
To: McGill, Peggy
Subject: RE: Apotex

would your search have covered Apopharma as a division of Apotex

---

From: McGill, Peggy [mailto:Peggy.McGill@uhn.ca]
Sent: Monday, January 09, 2012 1:50 PM
To: Christopher Paige
Subject: FW: Apotex

Pharmacy does not show this revenue either.

Peggy

Peggy McGill
Senior Finance Director, Research
Hydro Place Building, Room 1047
10th floor, Suite 1056
700 University Avenue
Toronto, ON
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Tel: (416) 581-7819
Fax: (416) 946-2098
Email: peggy.mcgill@uhn.on.ca

From: Bon, Alex
Sent: Monday, January 09, 2012 1:47 PM
To: McGill, Peggy

Cc: Ngan, Raymond; Fung, Esther
Subject: RE: Apotex

Peggy,
We have not been able to locate such a cheque.
Alex

From: McGill, Peggy
Sent: Monday, January 09, 2012 13:41
To: Bon, Alex
Subject: Apotex

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Have you had a chance to check into this? Chris Paige is waiting for my response.

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Peggy

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From: McGill, Peggy
Sent: Thursday, January 05, 2012 4:18 PM
To: Bon, Alex
Subject: FW: Re:

Hi Alex

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Fax: (416) 946-2098
Email: peggy.mcgill@uhn.on.ca

From: Christopher Paige
To: McGill, Peggy <Peggy.McGill@uhn.ca>; Paul Macpherson
Sent: Mon Jan 02 11:07:43 2012
Subject:

Peggy and Paul: Best wishes for the new year and all that..... would one of you be able to tell me if someone at UHN was the recipient of an "unrestricted educational grant" from Apotex.

Christopher Paige

From: Chan, Charlie [Charlie.Chan@uhn.ca]
Sent: Tuesday, January 31, 2012 4:16 PM
To: Martin, Bella; Paige, Christopher - UHN Research; Howard, Gillian
Subject: FW: private and confidential

FYI

Charles K.N. Chan MD, FRCPC, FCCP, FACP
Vice-President Medical Affairs & Quality
University Health Network
Professor & Vice-Chair of Medicine
University of Toronto

charlie.chan@uhn.ca

Tel: 1-416-340-3695 Fax: 1-416-340-3849

From: Chan, Charlie
Sent: Tuesday, January 31, 2012 4:15 PM
To: Yeo, Dr. Erik; Ward, Richard
Cc: Moore, Malcolm; Cole, Edward
Subject: private and confidential

Erik and Richard:

I am following up on the fellowship agreements that the RBCD program signed with Apotex and [redacted] I believe Erik was going to look hem up and send copies along so we have on file and they will also influence how we manage these supports.

I have not received any copy.

Charles K.N. Chan MD, FRCPC, FCCP, FACP
Vice-President Medical Affairs & Quality
University Health Network
Professor & Vice-Chair of Medicine
University of Toronto

charlie.chan@uhn.ca

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