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August 23, 2011

FAO: Caleb Briggs, Pharm.D.
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By Email: ODAC@fda.hhs.gov

Re: New drug application 021825, Ferriprox (Deferiprone); Proposed indication (use) for this product is for the treatment of patients with transfusional iron overload, when current chelation therapy is inadequate; September 14, 2011

Introduction

At the request of Cooley's Anemia Foundation, we are writing in support of the new drug application (#021825) for the oral chelator Ferriprox, which is to be discussed at the September 14 ODAC meeting. As the medical director (EY) and primary physician (RW) of the Red Blood Cell Disorders Program (RBCDP) at Toronto General Hospital, University Health Network, we represent the largest adult Hemoglobinopathy program in Canada. For the past 2 years, we have gained considerable experience in the safe and effective prescribing of Ferriprox to our patients. Also included in this package are personal testimonies from a few of our patients who have been treated with this drug, outlining their personal stories and perspective.

We cannot state how strongly we support this initiative and our positive clinical experience with Ferriprox when followed within accepted guidelines. Our experience is similar to that reported in the literature in European, Mediterranean and Asian countries (eg England, Italy, Cyprus and Greece, Thailand) where the drug is used in a similar medical population.

As the largest comprehensive Hemoglobinopathy program in Canada, we are aware that smaller centres across the country look to us for a lead in clinical care expertise. We are

aware, that since our change in chelation practice in summer 2009, a number of other patients across Canada, who would greatly benefit from Ferriprox, have now been prescribed it, based on the positive experience we have had, and our ability to offer expert advice to other physicians.

Background to RBCDP

The RBCDP is situated at the Toronto General Hospital and works closely with the pediatric program at the Hospital for Sick Children, Toronto. Together, we care for >80% of Canada's Hemoglobinopathy patients, providing comprehensive and lifelong care. At the present time we have 500 adult patients Sickle Cell Disease and Thalassemia Syndromes. The healthcare team comprises: 4 Hematologists, 2 Nurse Practitioners, 1 Social Worker and clerical support. We also run a Hemoglobinopathy fellowship training program supported in part by an award from the American Society of Hematology. Specialty Hemoglobinopathy clinics are run 5 days per week in dedicated space within the Toronto General Hospital, and care provided involves managing all aspects of iron chelation management. Although the program has been in existence for more than 20 years, the current clinic director and team have been in place since January 2009. Prior to this time the majority of patients were prescribed iron chelation with subcutaneous or intravenous Desferal and with Exjade, although 3 patients had chosen to independently source Ferriprox from overseas. Other patients had received Ferriprox at various times as participants in clinical studies under the responsibility of another Hematologist. In 2009, we moved to regularize Ferriprox for these three patients by obtaining Health Canada SAP approval. At the same time we initiated approval to address the addition of chelation with Ferriprox to our pharmacopeia for all of our chelated patients (see indications below).

RBCDP Indications for Ferriprox

Exjade is the first line iron chelation medication in the RBCDP. The RBCDP uses the following criteria as indications for commencing a patient on Ferriprox:

1. Severe cardiac iron overload whilst chelating with Exjade, Desferal or combination of Exjade and Desferal
2. Severe cardiac iron overload with a cardiac MRI T2* <10msec; Left Ventricular Ejection Fraction <50%; or >10% fall in EF
3. Severe hepatic iron overload unresponsive to Desferal, Exjade or combination of Exjade and Desferal
4. Intolerance, significant adverse event, or refusal to use Exjade or Desferal

Cardiac events are the leading cause of death in patients with β Thalassemia Major. Ferriprox has been reported in many studies to reduce cardiac siderosis, cardiac events, and deaths in this patient population. The decision to commence Ferriprox for a cardiac indication is taken in conjunction with a specialist heart failure cardiologist who is directly allied to the Program.

Amongst our cohort of 160 patients (both thalasseemics and sickle cell) on any chelator, 23 patients were prescribed Ferriprox because of severe cardiac iron overload, 4 for

severe hepatic iron unresponsive to all other chelators, 10 who were intolerant of or had significant adverse events with other chelators, and 3 for other reasons.

RBCDP Experience

In the last 2 years we have prescribed Ferriprox to 40 patients with β Thalassemia Major (39) and Sickle Cell Disease (1) who have complications of transfusion related iron overload, for a total in excess of 30 patient years of Ferriprox therapy. These numbers represent approximately 25% of our chelated population, a proportion in line with that in other major Hemoglobinopathy centres across the World (excluding USA). Half of our patients received standard dose Ferriprox at 75mg/kg/day, the remainder (predominantly those with severe cardiac siderosis) at the higher dose of 100mg/kg/d. 18 patients were prescribed Ferriprox in combination with Desferal or Exjade, and 22 as monotherapy. Of patients still receiving Ferriprox, the longest duration of continuous exposure has been 25 months in a patient with severe cardiac iron overload. Six of 40 patients are no longer taking Ferriprox, three because they have had resolution of their cardiac siderosis and normalisation of cardiac MRI T2* values, 1 moved out of province, 1 had mild but persistent gastrointestinal upset, and 1 was non-compliant with taking the drug. Of note, 5 patients commenced on Ferriprox in the past year have been transitioned from the HSC pediatric program, highlighting the ongoing need for effective alternative iron chelators.

With respect to adverse events, we recognise that total duration of exposure is such that rare adverse effects would not be expected to have been detected to date in our patient cohort. 75-80% of patients are adherent to the prescribed dose more than 90% of the time. Neutropenia (ANC < 1.5), has been observed in 4 patients on 11 occasions, but with no episodes of agranulocytosis (ANC <0.5). All have recovered with close attention or drug at altered dosage. Patients have complied with requests for a CBC every 5-10 days. Consideration could be given to relaxing monitoring to every month after 6-12 months of therapy as this is beyond the period of highest risk for agranulocytosis. Four patients had an asymptomatic transient increase in alanine transaminase (> 5x upper limit of normal), which settled either spontaneously or with transient interruption of Ferriprox. Two of these patients were referred to a Hepatologist who did not definitively implicate Ferriprox in the etiology of the hepatitis's. None of the patients required a liver biopsy as part of further investigation. Four patients had arthralgias, which resolved with dose reduction or interruption. All of our patients on chelation have MRI Ferriscans every 3-6 months. We have no data to support an effect on liver fibrosis as liver biopsy and histological examination is no longer performed as part of routine clinical care, and liver MRI assessment is unable to comment on tissue architecture. However, none of our patients have had clinical or biochemical evidence of cirrhosis or worsening liver function whilst taking Ferriprox.

A recent analysis of serial cardiac MRI T2* and EF measurements in 22 patients from this cohort has demonstrated a mean change in T2* of +2.6 ms/year and also improvement in EF +1.5%/year after an average of 425 days of therapy. These are statistically significant results. To date, the improvements in cardiac T2* in the total patient group ranges from -0.9ms to +25.6ms. There have been no episodes of cardiac failure requiring admission to hospital/CCU. It is important to note these improvements

have been achieved, in the main, without the need for insertion of an intravenous line for continuous IV Desferal (and its attendant risks and toxicities), which is the only other proven effective method for removing cardiac iron.

Canadian Access to Ferriprox

Since 2004 APOTEX ARE CHECKING THIS DATE AND WILL GET BACK TO US, Ferriprox has been available via a compassionate use program (CUP) from Apopharma Inc (a division of Apotex) in conjunction with Section A approval from Health Canada's Special Access Programme. This provides access to non-marketed drugs for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. As part of this process, we gain informed consent from patients informing them as to the status of the drug in Canada, and its published efficacy and safety/toxicity data. A stipulation of approval to supply the drug by Apopharma is the careful logging of regular Complete Blood Counts and other measures to ensure safe use of the drug and drug accountability. Advice is followed to monitor for neutropenia on a weekly basis (every 5-10 days) for the duration of therapy, with reporting of these results to Apopharma as part of pharmacovigilance. The drug is delivered to a single pharmacy (at Toronto General Hospital) and thereafter collected in person by patients or shipped to their home address.

Monitoring of Ferriprox

It is recognised that the time required in preparing, and maintaining the documentation for the CUP (Apopharma) and SAP (Health Canada) is incredibly burdensome and time consuming. We have heard anecdotal reports that this has been a barrier to some US based physicians attempting to access the drug.

We have allocated this role to a single administrative individual under the supervision of a physician (RW). In addition to pre-approval applications to Health Canada and Apopharma, there are ongoing weekly CBC results to monitor and quarterly reporting of these and any adverse events to Apopharma. As well, every 6 months, a renewal request is required from Health Canada. The administrative role includes checking CBC results, reminding patients to attend their community blood lab for blood draws, liaising with patients as to when their supply of medication will need renewing, and liaising with Apopharma for timely delivery of drug to the hospital pharmacy. A shadow chart is kept by the administrator to facilitate all this data collection.

An internal review of the Ferriprox access process, described above, was undertaken by our Institution in 2011. UHN's medical and legal auditors were satisfied that the process and documentation undertaken to obtain and monitor patients receiving Ferriprox was of the standard expected by the institution, and comparable to that required as part of Good Clinical Practice in the setting of research studies.

In Winter 2010/11, an external review of the RBCDP took place. Amongst its findings was that INCLUDE QUOTE ON L1 USAGE HERE.

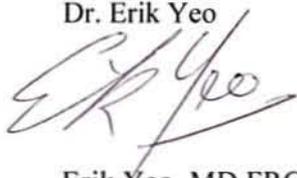
Concluding Comments

We believe that the RBCDP currently has the largest active population of patients receiving chelation with Ferriprox in North America. Our experience is much in line with that seen in other centres across the World (excluding USA). We have had no reason to abandon the use of Ferriprox and continue to use where indicated. As our understanding of the basic science of iron homeostasis improves, along with our ability to closely monitor its effect on vital organs, it is essential that patients and their physicians have access to the full range of iron chelation options, in order to tailor chelation to the individual's personal circumstances and needs.

Disclosure Statement

None of the physicians in the RBCDP have received personal funding of any sort from, nor hold stocks or ownership in Apopharma/Apotex. The RBCD Program and the Division of Hematology have received unrestricted educational grants from Apotex (Ferriprox) and Novartis (Exjade, Desferal). The physicians do not consider there to be any relevant personal conflicts of interest.

Respectfully
Dr. Erik Yeo



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August 24, 2011

To Whom It May Concern:

My name is [REDACTED]. I am a 39 year old Thalassemia Major patient, who has been receiving monthly blood transfusions since I was six months old. I am also a father of 2 boys, ages 6 ½ and 2. I am also a husband, a son, a brother, an uncle, a colleague, and a friend.

In January of 2009, I was admitted to the hospital because I had chest pains at work. Bloodwork revealed I had had some kind of cardiac "event". The first of my cardiac T2 MRI's revealed that my heart had significant iron deposits on it, as a result of my monthly transfusions. These iron deposits were impacting my heart function and causing irregular heart-beats. A "normal" person has ratings of over 20 msec. When my first T2 cardiac MRI results came back in February 2009, my results were 4.5 msec. For the first time in my life, I lived in fear that I would die of a heart attack at any point in time, a very hard situation for anyone to fathom, let alone a 39 year old, who's wife was 3 months pregnant.

I started an aggressive combined treatment of 24 hour Desferal infusion and large amounts of Exjade, the 2 available iron chelators. After 5 months of aggressive chelation therapy with the two, my T2 cardiac MRI results barely improved to 5.5 msec. It was then that I began to explore the option of getting Deferiprone from countries outside of Canada.

Fortunately for me, Dr. [REDACTED] recognized the therapy I needed, and had me commence Deferiprone chelation treatment on a compassionate basis in June 2009, 1 month before my second son was born. The results on my cardiac MRI were immediate and significant, as outlined below

[REDACTED] - 4.5 msec – on Desferal and Exjade
[REDACTED] – 5.5 msec – on Desferal and Exjade
[REDACTED] – 7.5 msec – after 6 months on Deferiprone
[REDACTED] – 8.8 msec – after 13 months on Deferiprone
[REDACTED] – 15.8 msec – after 2 years on Deferiprone

In 2 years, using Deferiprone alone, my cardiac T2 MRI results have significantly improved. My quality of life is back to normal, and I no longer live in fear of dying before my sons are old enough to remember me.

I had been on Deferiprone before, back when it was first introduced in 1991. I had used it without side-effects or issues, but was abruptly removed from it when support and

availability of Deferiprone in Canada ended due to concerns of Deferiprone's inability to remove iron in the liver, another side-effect of blood transfusion therapy. While I understood the concern then, with the advancement of technology, I would like to see that concern re-visited.

When I had my first Liver MRI in 2009, my liver iron level was 11.8. As of my last liver MRI in March 2011, it was down to 0.9. Unlike the cardiac T2 MRI results, where the higher the better, with the liver, the lower the reading the better. Again, significant results and improvement demonstrated by Deferiprone in an area of chelation where it was feared that it was ineffectual. Going from 11.8 to 0.9 proves to me that it is effective at removing liver iron.

I have used both Desferal and Exjade, the two drugs that are used in Canada to treat iron overload. Not only did they not have the effect of Deferiprone, while being treated with them, they ALLOWED the iron deposits to reach those levels in both my heart and liver. It was the Deferiprone that succeeded where the other two failed.

My quality of life since I have been on Deferiprone has dramatically improved. I take my pills without a second thought. My results speak for themselves, but what they don't describe is the peace of mind I have now, something I couldn't have pictured two years ago. I no longer worry that I will die before the end of each day. With Desferal, I had pain from the injections, swelling where the needle was. The alternative was to have a permanent IV or catheter in my arm, affecting my ability to play with my kids and always a reminder of the Thalassemia. With Deferiprone, I have no side-effects and no discomfort.

In the last 2 years, I've had to face my own mortality more than anyone my age should have to. I can say without an instant or a shred of doubt that Dr. [REDACTED] and Deferiprone have saved my life and are the reason why I am alive today. Deferiprone was made available to me on a compassionate basis, but the truth of the matter is that I should never have come as close as I did to a cardiac failure and the thought that I could have died and left my boys fatherless, when Deferiprone exists and has been used elsewhere for decades, angers me. Any individual who is threatened with iron overload deserves to be on Deferiprone, without being near death to have access to it. The context of "compassionate basis" should be to allow someone to live a life of both quality and quantity, not to wait until they are on the brink of death and endure difficult and painful treatments as Desferal has proven to be in the meantime.

Please allow those who need Deferiprone to have access to it. You are not just affording them an alternative treatment. You are affording them a chance at a life that everyone deserves.

Thank you,

[REDACTED]

[REDACTED]

From: [REDACTED]
Sent: Friday, August 26, 2011 5:32 AM
Subject: Re: Patient feedback on Deferiprone

To Whom It May Concern,

My name is [REDACTED] and I am a 37 year old Thalassemia major patient in Toronto currently on combination therapy with IV Desferral and Deferiprone.

I have been on this treatment regime for 8 months now and have already seen some very promising results.

Prior to being able to take Deferiprone I have tried using IV desferal compliantly for a number of years (4+ years) on it's own and I have not been able to successfully reduce my liver iron levels. I also tried the highest dose of Exjade possible for approx. 3 years with similar results.

Before I started using Deferiprone in combination with Desferal my liver iron levels as measured by Ferriscan were >43 and my ferritin was in the 8000 to 10000 range. After only 4 months on this combination therapy with Deferiprone my Ferriscan result was 29 and my recent ferriscan results are approx 5000. Although it is still too early to tell how successful this therapy will be in the longer term, the preliminary results give me much hope and promise which I have not felt for a long time.

I am also hopeful that if I can bring my iron levels to reasonable levels on combination therapy, I can move to taking only an oral chelator (Deferiprone) to maintain these levels. This would give me greater flexibility and enhance my quality of life so that I can continue to spend quality time with my husband and two children and continue to excel in my career and other life endeavours.

I thank you in advance for your consideration of a patient's perspective. I truly believe that it is in the best interest of all patients to have as many treatment options as possible so that together with our health professionals we can decide the best treatment option for us as individuals.

Like our counterparts around the world I hope that US and Canadian patients will soon have the benefit of having Deferiprone as an approved drug as a treatment option.

Warm regards,

[REDACTED]

[REDACTED]

From: [REDACTED]

Sent: Friday, August 26, 2011 12:05 PM

Hello my name is [REDACTED] & I am definitely for the use of L1 in north america. I have had the privilege of using this drug several times in my life. During each time, I found it helpful, convenient & an asset to use in my lifestyle. I have not experienced any adverse side effects or reactions. Unlike deferral-which has left me with permanent scars (that I've had plastic surgery on to try to correct), L1 has yet to leave my arms or legs in any altered condition. I am someone who travels often which made deferral cumbersome to use. In addition when I was using desferal via port I ended up with lone sepsis, & a pulmonary embolism. Both of these issues are potentially life threatening. Currently I use exjade, though also convenient the price is astronomical. I am lucky to have medical coverage from my husbands work however, if he were to lose his job I should not be able to afford exjade. I hope the use of L1 is reconsidered. It makes no sense that a drug can be used world wide but is not accessible here, makes one speculate the politics behind the pharmaceutical industry. Kind regards, [REDACTED]



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August 22, 2011

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Dear Dr. Briggs,

The following are the comments I plan to make at the September 14, 2011 FDA meeting on deferiprone.

My name is Dr Thomas Coates. I have been the Section Head for Hematology and Director of the Hemoglobinopathy Program at the Children's Center for Cancer and Blood Diseases at the Children's Hospital Los Angeles since 1991. We have over 120 children and adults with on chronic transfusion for thalassemia, sickle cell disease and other red cell disorders. All are on iron chelation therapy. We established measurement of cardiac and liver iron by MRI in 2002 and currently monitor about 200 sickle cell and thalassemia and patients per year from our own program and other programs throughout the United States.

By way of disclosure, I am currently on the Novartis speakers bureau and have consulted for them. I have had funding in the past from ApoPharma.

I am speaking here today on behalf of my patients with severe iron overload and am not representing any organization or entity.

We have eight patients in Los Angeles on deferiprone through the ApoPharma compassionate use program. Three of these patients have life-threatening iron cardiomyopathy. Because of the difficulty in obtaining the medication, we have restricted its use only to patients that have evidence of cardiac dysfunction secondary to iron overload.

There are three concerns that I wish to discuss today:

1. In my opinion, it is critical that deferiprone be approved for use in the United States for the following reasons: 1) it is clear from the literature and the substantial experience with the use of this drug in the other parts of the world over many years that deferiprone is the drug of

choice for patients with iron related cardiac disease. Deferiprone protects cardiac function in the face of severe cardiac iron loading to a much greater extent than desferrioxamine or deferasirox. It is also clear that the safety profile of this drug is acceptable when drug is properly monitored and prescribed by physicians who are familiar with its toxicities. 2) It is critical that the patients in the United States have more options for iron chelation. The biggest obstacle to proper chelation is poor adherence to treatment. Exjade and desferrioxamine are not well tolerated. We must have additional treatment options so that we can properly tailor chelation regimens to the patient's lifestyle, maximize effect and minimize toxicity.

2 I would like to relate three very brief case histories: The first patient is a chronically transfused 27-year-old woman with sickle cell anemia. She developed severe iron cardiomyopathy with a cardiac T2* less than 7.8 ms indicating severe cardiac iron loading. Her ejection fraction by MRI was only 45%, consistent with significant cardiac left ventricular dysfunction. She had signs of overt clinical heart failure, in spite of combination treatment with ExJade and desferrioxamine. She could not lie flat on the exam table for more than a minute, had bilateral pedal edema, rales, and hepatosplenomegaly. Within four weeks of starting deferiprone, she was completely asymptomatic and was taken off of all cardiac medications. Within 7 months, her cardiac T2* had improved significantly to 11.8 ms and her ejection fraction had normalized to 56%. She remains in good health with no cardiac symptoms. The second patient is a transfused 32-year-old sickle cell patient with severe cardiac iron overload. Her cardiac T2* was less than 4.8 ms and she had iron-induced arrhythmias. She was not compliant with Exjade or desferrioxamine. She has been intermittently compliant with deferiprone for about a year. Since she has been on deferiprone, her cardiac arrhythmias have stopped and her ejection fraction remains normal at 72%. The third patient has beta thalassemia and had anaphylaxis to desferrioxamine. He has severe cardiac iron loading as evidenced by a cardiac T2* between 2.8 and 7.8 ms on 8 measurements since 2003. He has been intermittently compliant with chelation with deferiprone since 2004. Kirk's data, published in *Circulation* in 2009, predicts heart failure in 47% of patients within 1 year of a T2* < 10 ms. This patient's cardiac function has remained normal in spite of persistent severe cardiac iron loading.

In my opinion, these three patients, two of whom have sickle cell disease, are alive today solely because they are on deferiprone. The drug has been well tolerated in all eight of our patients and we have seen no neutropenia, although, the number of patients we have followed is small. The limited experience I have recounted here is entirely consistent with the more extensive European experience.

3 Lastly I would like to comment on toxicity. Agranulocytosis is a serious complication that occurs in 1-2% of patients on deferiprone. In my opinion, the danger from neutropenia and agranulocytosis with this medication has been exaggerated. Hematologists use many drugs that predictably cause profound and prolonged neutropenia, yet we use them safely. There is no reason whatsoever that there should be any deaths from agranulocytosis long as the patients seek medical attention the moment they develop any kind of fever or mouth ulcers. Hematologists have far more experience managing neutropenia than they do severe iron overload and protocols for management of fever and neutropenia are standard practice.

Frequent monitoring of blood counts is essential. However, the treating physician should be the one who decides whether or not the drug should be continued in the face of noncompliance with safety monitoring. I again point out that poor adherence to chelation is the major cause of life threatening cardiac iron overload and death in thalassemia. The patients with life-threatening iron cardiomyopathy are in fact the most non-adherent patients. Having to obtain blood counts on a weekly basis is a significant impediment to taking this drug. At a minimum, blood counts are being obtained every two to four weeks at the time of their transfusions.

Withholding deferiprone because of lapse in CBC monitoring is more likely to be fatal for this subset of patients than sepsis from agranulocytosis.

In summary, there is extensive evidence showing the efficacy and safety of Deferiprone in humans based on years of use and many published results from outside the United States. Because of its proven efficacy, its ability to protect the heart from iron related dysfunction, and an acceptable toxicity profile that differs from existing chelators, we feel it is a critical medication for the management of iron overload.

Sincerely,



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