HIND WING CO., LTD.

UNIT 1103B, 11/F., BLOCK B,
SEAVIEW ESTATE, 2-8 WATSON ROAD,
NORTH POINT, HONG KONG.
E-mail: info@hindwing.com

PO BOX NO. 35325
KING'S ROAD POST OFFICE
HONG KONG
Tel. No.:(852) 2541 0909
Fax:(852) 2854 0695

香港北角屈臣道二至八號
海景大廈B座一一零三B室

顯榮行有限公司

To: Chairman, Health Services Panel

LC Paper No. CB(2)2368/10-11(01)

Legislative Council
Legislative Council Building
8 Jackson Road
Central, Hong Kong

Date: July 7, 2011

Re: Options for thalassemia patients in Hong Kong

Dear Chairman,

This letter addresses matters raised in the letter by Mr. Leung KF, Chairman of The Thalassaemia Association of Hong Kong, dated June 3, 2011. Mr. Leung expresses his gratitude for the allocation of an increased budget of HK$10M by our government for the iron chelator deferasirox and hopes to persuade the LegCo for more funding to allow the use of the same drug for patients older than 6 years old. While applauding any increased allocation of funds to meet the patients' needs, at the same time, I trust that our Government would explore solutions to these needs that may be cost effective in these times of fiscal restraint.

Hopefully, my comments will provide some alternative perspective on the views that have been expressed to you by very briefly updating relevant information on oral chelators and addressing the reality of thalassemia treatment in Hong Kong. In particular, we would hope that as part of the consideration to allot a further increase in funding to supply deferasirox, due consideration would be given to the availability of deferiprone, the first oral chelator in Hong Kong, to meet the need. Yet, no information was provided on deferiprone in Mr. Leung's letter. When considering matters of increasing the budget, it would be imprudent to ignore an alternative with greater cost-effectiveness, especially considering that deferiprone has a long established safety profile, not only by the Hong Kong Hospital Authority, but world-wide.

We strongly believe in the need for evidence-based medicine when making decisions that affect allocations of new money. This is particularly true when dealing with medicines that are designed to decrease morbidity and mortality, not simply reduce iron loads. However, even if one is simply considering the reduction of iron in the heart, there is a need for evidence of clear effectiveness, compared to deferiprone or deferoxamine. While there are uncontrolled and/or non-randomized studies that report a decline in cardiac iron concentrations (MRI T2*) in thalassemia patients treated with deferasirox, there are no data to determine if that effect is better or worse than with deferoxamine or deferiprone. More importantly, there are absolutely no published data demonstrating any reduction in heart disease or reduced mortality with deferasirox, even though its first approval was 6 years ago in the US. This is in contrast to deferiprone, where randomized controlled trials with deferiprone as monotherapy (Pennell, 2006)

or in combination with deferoxamine (Tanner, 2007) have demonstrated superior reduction in cardiac iron compared to deferoxamine alone. More recently, a cross sectional comparison of a very large number of patients in Italy has revealed that mean concentrations of cardiac iron were lowest in patients put on deferiprone, compared to either deferoxamine or deferasirox, and the best performance of left ventricular ejection fraction was also seen with deferiprone in these patients (Pepe 2011). Similar results were reported in Greece (Berdoukas, 2009). Since heart disease is the primary cause of death in thalassemia patients, the importance of these matters is paramount.

Most importantly, within 3 years of the marketing of deferiprone, the first publication reporting decreased heart disease had been published (Piga, 2003) and within 6 years, the first large scale studies reported extensive reduction in heart disease and mortality in deferiprone treated patients, either in monotherapy or in combination with deferoxamine (Borgna-Pignatti, 2006; Telfer, 2006). Today, there are at least 6 studies that report reduced heart disease and/or increased survival in deferiprone-treated patients, while there are none that report such effects with deferasirox.

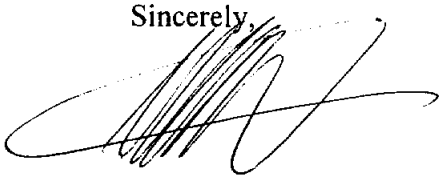
In addition to the cardiac benefits seen from deferiprone as monotherapy or in combination with deferoxamine, there is growing evidence that the combination is able to preserve or restore the function of endocrine organs including the thyroid, pancreas and gonads in iron overloaded thalassemia patients (Farmaki, 2010).

In the case of serious adverse events, agranulocytosis remains a target for monitoring while on deferiprone, with a world-wide incidence of rate of 0.28 per 100 patient years of exposure, 80% of which appears in the first year. However, from a chelator perspective, this is offset by the need for monitoring for drug-induced liver and kidney disease in patients with deferasirox. The risk of renal toxicity with deferasirox is increasingly becoming a concern. This is no longer limited to simply an increase in serum creatinine, but includes Fanconi's syndrome in thalassemia (Baum, 2010). Indeed, MedWatch in the U.S.A. has noted a very large number of suspected deaths in 2009 associated with deferasirox use, ranking second in most frequent suspected drugs related deaths in that year, after rosiglitazone, a drug that has later been removed from the market due to an increase of adverse events.

In spite of controlling liver iron concentrations in many patients, the lack of comparative clinical evidence of reduction in morbidity and mortality, combined with the growing concern of deferasirox toxicity, must be a reason to give pause to approving programs aimed at encouraging an even greater use of deferasirox, especially at costs that greatly exceed the costs of deferiprone as an alternative. You may be aware that concerns regarding cost-effectiveness of deferasirox has already been raised in a published Health Technology Assessment in the UK (McLeod, 2009). In our opinion, deferiprone remains a viable cost-effective, life-saving option in treating thalassemia patients, and one for which there is extensive evidence to support the claim.

Based on the above information, we would hope that the authorities would be able to allocate any additional funds that are available for treating patients with thalassemia to aspects where a *bona fide* need truly exists.

Sincerely,



Wilson Lun., PharmD
Marketing Manager, Ethical Division

On behalf of
Hind Wing Co. Ltd. &
ApoPharma, Canada

Cc:
Members of Health Services Panel,
Your Honorable Dr. York Chow, GBS, JP, Secretary for Food and Health
Professor Gabriel M Leung, JP, Under Secretary for Food and Health
Miss Gloria Lo, Principal Assistant Secretary for Food and Health
Dr. Leung Ka Lau, Health Services, Deputy Chairman
Dr. Joseph Lee Kok Long, Legislative Council Member, Health Services Constituency
Dr. Leung Pak Yin, Chief Executive, Hospital Authority
Dr. Cheung Wai Lun, Director (Cluster Services), Hospital Authority
Ms. Anna Lee, Chief Pharmacist, Chief Pharmacist's Office
Mr. Benjamin Kwong, Senior Pharmacist, Chief Pharmacist's Office

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ApoPharma Inc.

Dennis Tam Yeuk Sze
Manager, Hospital Products Division
Hind Wing Co. Ltd.

July 8, 2011

Dear Dennis:

Re: Questions Regarding Ferriprox® Utilization

Thank you for your enquiry regarding Ferriprox status in various markets around the world. My letter to you will deal with two key questions that you posed to ApoPharma. We will address the uptake of Ferriprox, the first oral iron chelator, a key component of treatment in major markets with a high prevalence of Thalassemia major. We will also provide information regarding agranulocytosis and its clinical consequences, revealing that problems are rare when cases are managed according to the labeled instructions for Ferriprox.

As you know, Ferriprox was the first oral iron chelator approved in the developed world with approval from EMEA (now EMA) in 1999. In addition to the ApoPharma sponsored clinical trials, there are now numerous investigator led studies published and over 12 years of post marketing experience with Ferriprox. During this time no new serious unexpected adverse events have been reported that were not listed in the original SmPC. As you know this is unusual and reflects the cautious development program that was used for Ferriprox.

Agranulocytosis was noted early in the development of Ferriprox and although this concern was prominent at one time, long-term experience reveals that it is easily managed in most patients. The recommendation to monitor patients has been included in the prescribing information in every country. Appropriate monitoring and interruption of therapy at signs of infection or neutropenia are the most important measures to avoid serious clinical consequences as the event is reversible on discontinuation of the drug. The data supporting this view are presented below.

In the ApoPharma-sponsored clinical trials, agranulocytosis was defined as a confirmed absolute neutrophil count (ANC) of less than 0.5×10^9/L (in clinical practice this is often referred to as "severe" neutropenia, with agranulocytosis being defined as an absence of neutrophils). The rate of agranulocytosis ($<0.5 \times 10^9$/L) in clinical studies corresponds to 0.8 per 100 patient-years of exposure. In this group of closely monitored clinical trial patients all episodes of agranulocytosis resolved with discontinuation of deferiprone. No residual adverse effects were observed as a result of these episodes of agranulocytosis.

The rate of agranulocytosis during post-marketing surveillance is approximately 0.28 reports per 100 subject-years of exposure given an estimated 33,725 subject-years of deferiprone exposure.

Thirteen fatal cases (four males and nine females) have been reported during the post-marketing experience with Ferriprox since 1999. The last case of agranulocytosis with fatal outcome reported to ApoPharma was in 2008. The information available to ApoPharma indicates that adequate monitoring of the neutrophil count and/or adequate management of the agranulocytosis was not performed in the majority of the fatal cases. Infection was associated with all 13 cases. In three cases, signs of infection were confirmed to occur before the official diagnosis of agranulocytosis. In only three of the 13 cases was Ferriprox discontinued within a few days after the onset of neutropenia. Apart from one report, there was no evidence that the patients had their WBC counts monitored on a weekly basis prior to the first sign/symptom of neutropenia.

To emphasize the recommendations concerning monitoring of blood cell counts and early discontinuation of Ferriprox at the first sign of neutropenia, a Dear Health Care Professional Letter (DHCPL) was distributed to the specialists treating these patients to remind them of the importance of following the Ferriprox product monograph on the prevention and treatment of agranulocytosis. The available data indicate a decline in the rate of fatal cases of agranulocytosis from 0.07 to 0.02 episodes/100 patient-years, which coincided with the implementation of these risk minimization activities.

We can now deal with the second question regarding the utilization of Ferriprox.

When evaluating the utilization of iron chelation therapy the fairest way to assess whether the drug is a standard of care or treatment of choice is to determine the proportion of patients who take that therapy. This can be expressed as a patient market share and has the advantage of eliminating bias based on cost of therapy if measures such as revenue is used to calculate share. Over the last 12 years, ApoPharma has developed a database of the number of chelated patients in the major Thalassemia markets of the world. This number is used as the denominator in the patient share calculation. Off-label use is not taken into consideration.

The data from such calculations are provided in Figures 1 and 2. These data demonstrate that Ferriprox is included in the treatment of the majority of patients in the European Union (Figure 1). The major reason for this exceptional market share is the proven cardiac benefits of Ferriprox which have been documented in numerous publications, and which is now an official part of the SmPC in the EU.

In regions of the world where Ferriprox has been launched more recently it continues to gain market share (Figure 2). In markets in the same geographic region as Hong Kong only Australia and Indonesia stand out as markets with less than 50% market share. However, Ferriprox continues to improve its position in these markets. In Indonesia, Ferriprox had its first full year of sales in 2008 and has gained share every year since. Based on market research from these markets Ferriprox use is increasing for three key reasons: 1) its overall ability to reduce iron

stores, 2) its benefit in reducing cardiac iron burden, with the benefit of improved survival and, 3) cost effectiveness versus other available chelators.

The market share data is provided here for your reference and use as you see fit. We have previously provided copies of the published data supporting the efficacy of Ferriprox and the Health Technology Assessment performed by NICE. Should you require additional copies please let me know.

FIGURES:

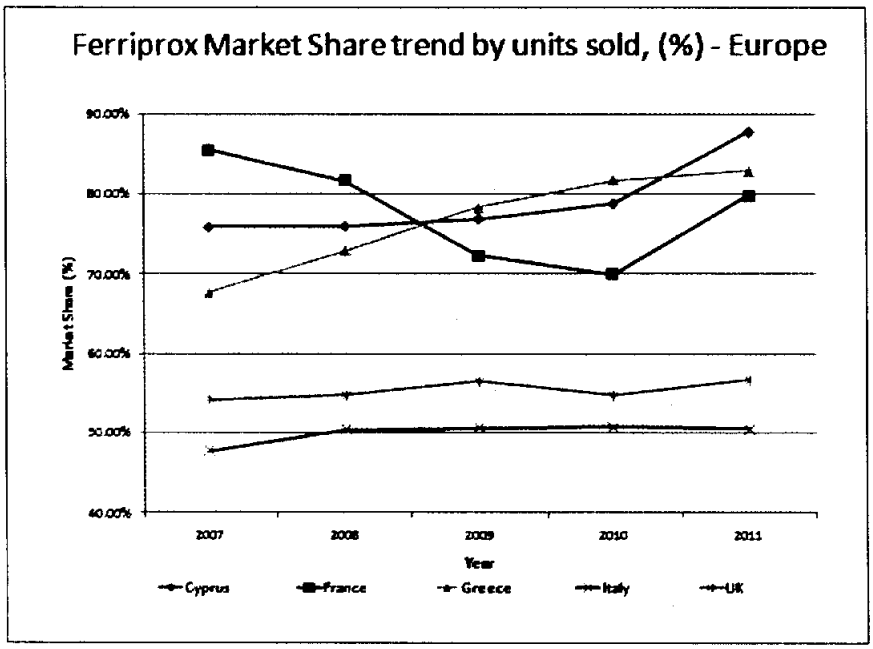

Figure 1

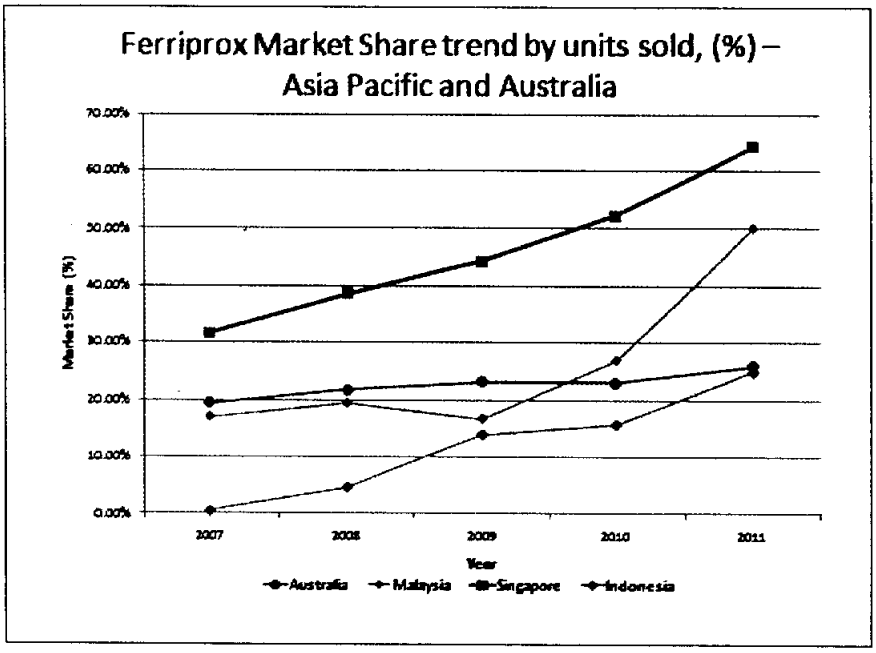

Figure 2

Should you have any further questions please feel free to contact me.

Yours truly,

Mike Woolcock
Director, Sales, Marketing & Business Development

MW/lm