3 June 2019

Dr. Michael Baker

Michael.Baker@uhn.ca;

Dear Michael:

Thank you for meeting with us on Friday May 31. We understand that further to planning over the last five months next month an Inquiry into Patient Care at UHN will be undertaken, specifically to review the administration of unlicensed deferiprone between 2009 and 2015. Arising from our conversation on Friday, we have serious concerns related to this process.

We write to place on the record our view that the process of review, as planned, will produce few meaningful and relevant findings and, as in the case of so many other such reviews,[1] may eventually require to be supplanted by another legal or ethics-based review that may require intervention of a body outside UHN.

We appreciate that your co-reviewer may have limited time, and/or demonstrate a lack of a willingness to examine these records in the necessary detail, but it is important to not subvert the real questions to be answered, and to undertake meaningfully to examine the data, as we did over many years, without short cuts. **Simply stated, our concerns raised serious questions about safety and medical oversight at UHN and the use of an unlicensed drug that threatened patient safety, led to serious clinical complications and death, and possibly impacted these patient's future health.** These concerns deserve more than a quick review.

Our concerns relate to the following:

(i) New information that emerged about the extent of the use of unlicensed deferiprone at UHN from 2009 to 2015.

As per the recent paper by Ward and Kuo,[2] not 41 patients, but 71 patients, were switched to

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[1] The Naimark Report of 1998 was commissioned by The Hospital for Sick Children's Administration in response to public protest about the Apotex/deferiprone controversy at that Hospital. Arnold Naimark, and his paid colleagues, relied heavily upon testimony from Gideon Koren, and others supported by The Hospital for Sick Children's Administration, primarily to facilitate the referral of Dr. Olivieri to the CPSO in an attempt to rescind her medical license. This approach ultimately backfired. The CPSO rejected this demand ruling Dr. Olivieri's conduct "commendable"; the following week, *The Olivieri Report* (Lorimer 2001) the definitive history of the matter up to that time which had been commissioned by the Canadian Association of University Teachers in response to The Naimark Report, was published, revealing the malfeasance of some members of The Hospital for Sick Children Administration and of course, Gideon Koren. (The ultimate disgrace of Dr. Koren and his supporters at The Hospital for Sick Children is now a matter of public record).

[2] Attached: Binding A, Ward R, Tomlinson G, Kuo K. Deferiprone exerts a dose dependent reduction of liver iron in adults with iron overload. doi: 10.1111/ejh.13244. Note that these authors disclose that "Binding's fellowship was partially funded by an unrestricted education grant [sic] from Apopharma Inc. and Novartis Pharma." This reference to Novartis is gratuitous: no Novartis drug is promoted in this article, and Novartis did not support this work. This statement is provided only, as it often is, to present an illusion of 'balance', that is: to convey that the authors accept money from other, even competing companies and not only from ApoPharma and therefore that this conflict of interest did not influence the conclusions of this work. Curiously, although unrestricted educational grants (as obtained under Freedom of Information) were provided to these physicians exclusively from ApoPharma,, the authors do not disclose that funding.

deferiprone at UHN from 2009 to 2015.[3] This new information raises profound concerns, including about research integrity, which we will address in another forum. However, this information is also relevant to the discussion of your Inquiry as follows:

There is now an even higher burden of proof required to support the claim that 71 patients (about 50% of locally-transfused patients of the UHN Program) required treatment with unlicensed deferiprone between 2009 and 2015. In our view, it defies credulity that, from March 2009 after Dr. Ward was hired up to 2015, 71 patients required deferiprone under Health Canada's Special Access Program (the mechanism under which it was prescribed by Ward *et al* in collaboration with Apotex which, as below requires all patient to have failed *both* licensed, first-line therapies) although very few patients had required deferiprone prior to 2009. As you know, Health Canada's Special Access Program is one under which the treating physician must confirm "*conventional therapies have failed, or are unsuitable or unavailable",* which provides access to a drug which should "*be limited in duration and quantity to meet emergency needs only."*

Are we really to understand that both standard, licensed first-line therapies *were unsuitable or unavailable,* and/or had "failed" in 71 patients?

Whatever the outcome of your Inquiry as to the effect of deferiprone in these patients, a fundamental question that remains is whether truthful information was provided to Health Canada.

(ii) Analysis of treatment intervals to prevent obfuscation of deferiprone effects

In our view, based on experience with the UHN EMR in our research, it will be impossible for you or your co-reviewer to undertake meaningful review of these additional 30 patients, **unless you are prepared to isolate and analyze treatment intervals during deferiprone exposure.** This time-consuming process, outlined in PLoS, was necessary because Dr. Ward *et al* had frequently accidently or purposefully altered regimens of treatment in the same patient *without assessments of baseline and follow-up endpoints*. By contrast, we avoided erroneous attribution of effectiveness or toxicity to any drug or drug combination by evaluating *treatment intervals*, evaluable if (i) bracketed by baseline and follow-up liver iron concentration and/or cardiac T2*, and (ii) throughout the interval, one drug or combination had been prescribed with no interruption longer than one month.

To be clear, a frequently-observed process undertaken in the prescribing of deferiprone by Dr. Ward and colleagues at UHN (evident in review of the full data set in our 2019 publication) was that patients started on deferiprone monotherapy were, after a variable period (depending how long it took for evidence of problematic body iron increases to emerge), removed from deferiprone and prescribed licensed therapy. Even more commonly, licensed therapy at variable doses was *added* to deferiprone, but deferiprone was continued, despite the acknowledged 3-fold increased incidence of toxicity during combination therapy and despite clear demonstration of both failure of effectiveness and of toxicity. Subsequently, and often quickly, regimens would often be changed again: licensed drugs -- having corrected the elevations of body iron arising during deferiprone exposure -- would be stopped, and deferiprone would re-prescribed as monotherapy, often at increasing doses. Then, after increases in body iron burden again became evident during deferiprone monotherapy, deferiprone would be re-combined with a licensed drug, often a different licensed drug, at variable doses.

The point is that during such exposure, the relevant endpoints of treatment (liver iron and cardiac T2*) we re not assessed at the time of changes in regimen. **This common practice in the UHN**

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3 As you know we were in possession of the consent of only a sub-group of 41 deferiprone patients who had consented to my REB approved study; therefore in the PLoS paper data are presented on only 41 patients who received deferiprone.

clinic had the effect of obfuscating the poor performance of deferiprone. Indeed, the *Binding et al* publication reporting on the same patients that we evaluated, contains no patient-specific details. This is in sharp contrast to the specific details recorded for each of the 41 patients we reported, not means and medians but the *specific* liver iron concentrations and T2* values measured at all relevant points in each patient's treatment regimen (***Supplementary published data***). Unless you and your colleague undertake the same painstaking review of the additional 30 patients as we did of our 41 consented patients, your inquiry may learn, and reveal, nothing, because reviewing the charts without addressing treatment intervals will yield nothing and indeed continue to conceal the harm of deferiprone.

(iii) Obfuscation by addition and removal of other drugs between courses of deferiprone

Another serious concern is that findings in many patients may be reported in a misleading and false way. To fully illustrate these concerns, we attach a file: **"Patient 30"** in our manuscript[4]. (In passing, we note that exposure to deferiprone in Patient 30 illustrates that the patient was able be prescribed *full doses of both deferoxamine and deferasirox* with excellent compliance over five years; hence the claim (to Health Canada) that Patient 30 could not take standard licensed therapy, and required prescription of deferiprone under the terms of Special Access Program, was patently false). Importantly, we anticipate that the course of this patient might be presented as follows by UHN physicians to your reviewer:

"The patient received deferiprone from November 2010 to July 2015 in various combinations with other drugs. Liver iron concentration remained in ideal range (6.1 mg/g to 4.1 mg/g) during this period."

This would be a false representation of the findings. A genuine review of the data would show that during repeated extended periods of deferiprone monotherapy over several of those five years, Patient 30 sustained substantial elevations of liver /body iron concentration, which placed her at risk of cardiac disease and early death. Was Patient 30 informed about these extended periods of dangerously inadequate control? Why was deferiprone continued at all, after clear and repeated failures? What information did Health Canada received about the 'deferiprone response' in this patient?

Possibly, Health Canada was provided with a summary as follows:

"The patient received deferiprone from November 2010 to July 2015 sometimes in various combinations with other drugs. Liver iron concentration remained in ideal range (6.1 mg/g to 4.1 mg/g) during this period."

Similarly, a parallel claim made by UHN physicians might be: "T2* increased (improved) from 8.1 msec in 2010 to 13.7 msec in 2015 during ongoing deferiprone."

As you will see detailed in the attached documentation from the EMR of Patient 30, both these claims about liver iron concentration and about cardiac iron, would be false. It would be important for your Inquiry to determine what was presented to Health Canada, because false representation to a federal agency constitutes fraud.

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[4] Olivieri NF, Sabouhanian A, Gallie BL. Single-center retrospective study of the effectiveness and toxicity of the oral iron chelating drugs deferiprone and deferasirox. PLoS One. 2019;14(2):e0211942.

(iv) Did patient preference explain why 71 UHN patients we re prescribed deferiprone?

Another concern is that the prescribing clinicians could claim as an explanation for why 71 UHN patients were prescribed deferiprone that many patients "requested" deferiprone. But our patient summaries (arising from archives of several years of clinical notes from the UHN EMR) record a different story. How would such a claim by the prescribing UHN clinicians be verified under the planned approach of the "Review"?

As an example we attach a file **"Patient #19."**

Patient 19

Efforts to start this young mother on deferiprone began very shortly after Richard Ward arrived at UHN in early 2009. The clinical notes record (quote): *"deferasirox is not sufficiently good at removing such heavy iron deposition as [the patient] has".* (Note, that there is no evidence in the literature for this statement and, as ultimately observed, deferiprone tragically failed to reduce body iron, leading to death; deferasirox controlled body iron less than optimally because Dr. Ward prescribed it at lower-than-recommended doses, as detailed below). Despite Ward's encouragement, the patient wisely opted initially to continue licensed deferasirox (which Ward inexplicably, accidentally or purposefully, prescribed at only 66% of the dose recommended for her level of body iron which, consequently, remained at unacceptable levels). There was no question that this failure to prescribe the correct dose was related to deferasirox "intolerance," because although claims of "bloating" were advanced by Ward (without investigations recorded), other clinic notes confirm that the patient tolerated deferasirox *"with minimal GWE complications, and does not miss any doses"*. The balance of evidence (aside from Ward's notes), therefore, indicate that she was tolerating deferasirox well; indeed, for two months (January to March 2012) deferasirox was further *increased,* to 85% of recommended dose: the only period during which a close-to-recommended, albeit still less than indicated, dose of a chelating agent was prescribed. Then, after those two months without re-assessment of liver iron concentration (see above: ***Analysis of treatment intervals to prevent obfuscation of the effects of deferiprone)*** deferiprone was added to deferasirox. The indications for deferiprone were not recorded in the EMR. The patient was recorded in clinic notes as willing to take deferasirox with IV deferoxamine (both licensed drugs) and, as above, had been *"tolerating deferasirox [with] no missed doses"* before she was switched to deferiprone.

Richard Ward himself acknowledged in the EMR: "Due to a lack of information about deferiprone, she would be happiest to combine IV deferoxamine with deferasirox". Ward also acknowledged: "There is very little evidence for this combination [deferasirox + deferiprone] (which he prescribed this until her death a year later) <u>although it is something we are doing more often</u>. She has signed consent forms today. We will reduce deferasirox."

Sadly, over the last year of this patient's life, deferasirox (the only licensed agent prescribed to the patient) was indeed progressively reduced to homeopathic doses -- so that the patient's only remaining full-dose therapy was deferiprone. These decisions resulted in tragic consequences, but the records document that these we re not decisions requested **<u>by the patient</u>**.

(Your planned Inquiry will have great difficulty in identifying these notes although they are in the UHN EMR).

(v) Could the prescribing clinicians claim that "other drugs were not working?

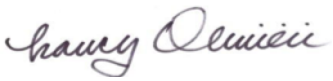
The UHN physicians may indicate that the reason for switching to deferiprone was that "the other drugs were not working optimally." As our PLoS paper showed, in a large number of patients, both deferoxamine and deferasirox were administered at lower-than-recommended doses for the patients' body iron burden. Will your Inquiry examine the doses of the standard licensed agents prescribed before the patient was switched to deferiprone to confirm, or refute, this claim?

For example, in 31% of 13 patients in whom pre-deferiprone liver iron concentrations were greatly elevated (while cardiac T2*s we re acceptable), liver iron had *already* (during deferoxamine or deferasirox) declined (by a mean of 100%) while T2* had improved. However, many of these and other patients, for unknown reasons, were being prescribed doses of deferoxamine or deferasirox well below those recommended for these levels of body iron burden: for example, in these 13 patients, deferoxamine was prescribed at a mean of less than 70% recommended dose and deferasirox was prescribed at a mean of 65% of recommended dose. **Few experts would claim that the failure of iron to decline during lower-than-recommended doses of proven licensed therapy (that is, accidental or purposeful underdosing, which is inadequate treatment) represents a genuine indication for substitution of an unlicensed drug.**

Finally again we re-attach the questions (**"Appendix 2 Final Dr. Olivieri and Gallie to Dr. Baker 9-4-19"**), which will need to be addressed if your Inquiry is to examine the concerns in any robust, meaningful way.

Unless the Inquiry addresses and answers these questions, it can have no relevance, because it will have failed to address the critical issues impacting on patient safety at UHN.

Yours sincerely,



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