23 September 2019

Dr. Kevin Smith Health Network
President & CEO, University
kevin.smith@uhn.ca

Dr. Brian D. Hodges
EVP and Chief Medical Officer
brian.hodges@uhn.ca

Dear Dr. Smith and Dr. Hodges,

Further to our correspondence dated August 20, 2019 with respect to the unilateral appointment of Dr Odame's Review of the Red Cell Program, we again respectfully request that you please send us Dr. Odame's review.

We write now with concerns arising out of the recent publication, Binding A, Ward W, Tomlinson G, Kuo K. Deferiprone exerts a dose dependent reduction of liver iron in adults with iron overload. Eur J Haematol 2019 103:80–7. From the UHN, Binding et al. report *"A single-centered, retrospective, cohort observational study involving 71 patients exposed to deferiprone doses up to 113 mg/kg/day between January 2009 and June 2015 for a median of 33 months"* .

Issues of concern:

1. The UHN patients reported here were exposed to unlicensed deferiprone and their data were used at Health Canada without signing informed consent in a REB-approved study. This point requires a short clarification:

Binding et al. state that this *"retrospective, cohort observational study"* was conducted *"in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki"* [and] *"approved by the local research ethics board".* The citation of the *Declaration* would lead reviewers and readers to the understanding that *exposure* to (unlicensed) deferiprone had been approved by the REB.

However, the study approved by UHN's REB was the *retrospective process* of examining data, *post hoc,* that had already been generated during the *prior* prescribing deferiprone as a first line drug to half the locally-transfused UHN patients, while deferiprone was unlicensed in Canada. Deferiprone remains "last resort" licensing in all jurisdictions worldwide.

We find no evidence that the UHN REB approved the administration of unlicensed deferiprone to these 71 patients.

2. UHN patients were exposed to deferiprone, an unlicensed drug, when other first-line drugs were available.

3. UHN patients were exposed, without REB-approval, to deferiprone in doses in excess of the upper limits imposed by all regulatory bodies and in the drug product monograph.

4. The doses of deferiprone reported in Binding et al. are not supported by the data in UHN patient records.

5. The claims by Binding et al. about deferiprone's "effectiveness" and "safety" are not supported by the data in patient records.

6. Binding et al.'s analysis of liver dysfunction developing during deferiprone is not supported by the data in patient records.

7. Binding et al.'s report of the responsible physicians' management of severe adverse effects developing during deferiprone is not supported by the patient records.

8. We have identified no evidence of compliance of Binding et al. with demands imposed by FDA and Health Canada with respect to the reporting of severe adverse effects of a drug.

9. Binding et al.'s report of bone marrow toxicity developing in deferiprone-exposed patients, and of the responsible physicians' management of this toxicity, is not supported by the patient records.

10. Binding et al.'s report of GI toxicity in deferiprone-exposed patients, and of the responsible physicians' management of this toxicity, is not supported by the patient records.

11. Binding et al.'s report of arthralgias in deferiprone-exposed patients, and of the responsible physicians' management of this toxicity is not supported by the patient records.

12. The description by Binding et al. of the death of a UHN patient is not supported by the data in the patient record.

Several medical care and practice issues arising out of our concerns. We are writing you prior to taking this matter up with institutions concerned with research misconduct, and also anticipate advice from bodies concerned with medical care.

We respectfully request a reply to this letter by Monday September 30, 2019.

Yours sincerely,

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CC: Dr. Michael Baker