Health Canada Santé Canada

Biologics and Genetic Therapies Directorate
200 promenade Tunney's Pasture Driveway
Address Locator 0702C
Ottawa, Ontario
K1A 0K9

File No.: 9427-O0484/1-22
Control No.: 150026
Document No.: 720220

May 17, 2012

[employee name removed]
Senior Director, Regulatory Affairs / Quality Assurance
Osiris Therapeutics, Inc.
7015 Albert Einstein Drive
Columbia, MD 21046

NOTICE OF COMPLIANCE WITH CONDITIONS - QUALIFYING NOTICE

Dear *[employee name removed]*:

This Notice of Compliance with Conditions Qualifying Notice (NOC/c-QN), issued in accordance with the Health Canada NOC/c Policy, is to advise you that information submitted in support of the New Drug Submission for Prochymal (remestemcel-L), Control Number 150026, for the indication of acute Graft versus Host Disease (aGvHD), qualifies to be considered for authorization under the NOC/c Policy. In keeping with the provisions outlined in the NOC/c Policy, the following additional information is required to complete the assessment:

1. A letter, signed by the Chief Executive Officer or designated signing authority of Osiris Therapeutics, Inc., indicating that you agree to have this submission considered under the NOC/c Policy. Please be reminded that in agreeing to accept an NOC under the NOC/c Policy, Osiris Therapeutics, Inc. consents to the posting of the NOC/c-QN on Health Canada's website.

2. A draft Letter of Undertaking signed by the Chief Executive Officer or designated signing authority of Osiris Therapeutics, Inc., having a form and content satisfactory to Health Canada, as indicated in the *Guidance for Industry: Notice of Compliance with Conditions*, including commitments to supply the following:

Confirmatory Studies

   a. As per the Expert Advisory Panel Report Recommendations Osiris Therapeutics, Inc. must develop a strong clinical trial design that will demonstrate efficacy of Prochymal in the pediatric or steroid refractory GvHD population. This could take the form of **either** a randomised clinical trial comparing Prochymal versus the best standard of care (Option 1

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from the report) **or** a properly conducted case control study with appropriately matched concurrent or historical controls (Option 2 from the report). Osiris Therapeutics, Inc. must commit to provide substantial data that show statistical significance in the efficacy of Prochymal in a GvHD patient population that is steroid refractory. Osiris must provide the final study report as a Supplemental New Drug Submission - Confirmatory (SNDS-c) by June 2016. This date needs to be stated in the Letter of Undertaking. Provide the draft protocol for the clinical study with the response to Qualifying Notice.

b. As per the Expert Advisory Panel Report Recommendations, Osiris Therapeutics, Inc. must develop a formal long-term registry to monitor the safety of Prochymal. The registry would also facilitate traceback, lookback activities and help gather information on patient populations excluded from the trials (and/or those in whom Prochymal was used off-label). In specific cases where patients are autopsied, the lungs should be screened to look for the potential presence of residual Prochymal cells.

Post Market Safety Monitoring Studies

c. Report of all serious Adverse Reactions (AR) that occur in Canada and all serious unexpected ARs that occur outside of Canada should be forwarded, within 15 days, to Health Canada. One copy is provided to the Marketed Health Products Directorate and another copy to the Office of Regulatory Affairs, Biologics and Genetic Therapies Directorate (BGTD) in accordance with current regulations and guidelines.

d. Submit Periodic Safety Update Reports for NOC/c Products (PSUR-Cs) for Prochymal (remestemcel-L) on an annual basis until such time as conditions associated with the market authorisation are removed. PSUR-Cs should be prepared in accordance with the E2C International Conference on Harmonisation (ICH) Guideline, including format and content, as per Section 3.4.2 of the *Guidance for Industry, Notice of Compliance with Conditions (NOC/c).*

e. Implement the Risk Management Plan (RMP) in Canada with the following recommendations and provide an updated RMP:

i. The Product Monograph needs to be updated to reflect the potential for risks identified within the RMP submitted.

ii. Consideration should be given to including pregnant or nursing women in the RMP as a potential safety concern for which safety information is missing.

iii. The possibility of off-label use is always present, especially after issuance of the NOC. Consideration should be given on how any off-label use will be monitored and reported. The population size for which the authorized indication is being requested is small resulting in a limited safety database. Therefore, it is expected that rare, potentially significant signals would not have been detected prior to the

issuance of the NOC pursuant to the NOC/c policy. The possibility of detecting new signals or adverse events (AEs) when a larger population is involved is increased and, therefore, a better indication for level of safety can be elucidated.

iv. It was indicated that donor suitability will be assessed according to the United States Food and Drug Administration (FDA) Donor suitability Guidance. Details regarding donor screening should be provided in a revised RMP to demonstrate how these criteria are aligned with those in Canada.

v. *[commitment e(v) removed, as it was not included in the Letter of Undertaking]*.

vi. As also noted by the Expert Advisory Panel, you should clarify how the potential late development of ectopic tissue will be followed longer-term.

f. As per the Expert Advisory Panel Recommendations please address in your Letter of Undertaking how Osiris Therapeutics, Inc. will limit the distribution of Prochymal to only pediatric blood and marrow transplant centres in Canada as Prochymal will only have an indication for acute GvHD in children.

Additional Information

3. A draft of the "Dear Health Care Professional Letter" detailing the issuance of a Notice of Compliance under the NOC/c Policy for Prochymal for the indication of acute Graft versus Host Disease.

4. A draft of the Product Monograph that is consistent with the requirements outlined in Section 5.2.1 of the *Guidance for Industry: Notice of Compliance with Conditions*. Please note that, if applicable, a boxed text must appear on the cover page and at the beginning of each major section of the Product Monograph (Parts I, II, and II) disclosing the nature of the authorization granted for Prochymal and the need to conduct confirmatory studies. The Product Monograph should be revised and updated taking into account the recommendations made by the Expert Advisory Panel and include the following revised indication:

> "Prochymal is indicated in the management of acute Graft versus Host Disease (aGvHD) in pediatric patients. Acute GvHD should be refractory to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents. Prochymal may be used for Grades C and D of the disease in any organ. Prochymal may also be used in the management of Grade B aGvHD involving any visceral organ, including the gastro-intestinal (GI) tract and the liver, but excluding skin."

5. Provide a complete and up-to-date listing of ongoing clinical trials related to Prochymal, appended to the draft Letter of Undertaking, as per Section 4.5 of the *Guidance for Industry: Notice of Compliance with Conditions*.

6. Provide copies of any marketing authorisations or other regulatory actions for Prochymal from any other regulatory authority as per Section 4.6 of the *Guidance for Industry: Notice of Compliance with Conditions*.

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I wish to advise you that this Qualifying Notice is being issued in accordance with Health Canada's guidances and policies on the *Management of Drug Submissions* and *Notice of Compliance with Conditions*, respectively. Sponsors are instructed to submit a complete response (refer to the *Guidance for Industry; Notice of Compliance with Conditions*) to the outstanding information within 30 calendar days of the date of this letter. It is highly encouraged to consult the BGTD before subsequent submission filings.

In order to facilitate and to ensure proper processing, please include a revised Submission Certificate with your response, quote the product name and control number, and address all correspondence to:

Submission and Information Policy Division
Therapeutic Products Directorate
Health Canada
Finance Building Address Locator 0201A1
101 Tunney's Pasture Driveway,
Ottawa, Ontario
K1A 0K9

Sincerely,

[employee name removed]
Director General