Risk Assessment Summary

for

NSN 19662: CTX001

(For use as an investigational gene and cell therapy drug for treatment of transfusion-dependent beta-thalassemia and sickle-cell disease)

Introduction

Under the *Canadian Environmental Protection Act,* 1999 (CEPA), animate products of biotechnology (i.e. “living organisms”) not listed on the Domestic Substances List (DSL) are considered “new” to Canada. Information and data prescribed by the *New Substances Notification Regulations (Organisms*) [NSNR(O)] in regards to the new organism must be submitted before that new organism is manufactured or imported in Canada. Environment and Climate Change Canada (ECCC) and Health Canada (HC) must assess that information and data to determine if the new organism has potential to harm human health and the environment. Under these Regulations, live human cell lines are considered ‘microorganisms’ and ‘harm to human health’ is assessed as the potential to cause harm to humans thorough an environmental exposure (the efficacy of the substance as well as its safety through the direct exposure to patients are assessed under the *Food and Drugs Act*).

CTX001 is a population of genetically modified, autologous human cells that were proposed to be imported for use in human clinical trials of an investigational gene therapy and were assessed according to the requirements for Schedule 1 of the NSNR(O), which applies to “manufacture or import of new microorganisms for introduction anywhere in Canada” (which is the appropriate Schedule for human clinical trials). Living organisms notified under this schedule may be eligible for addition to the Domestic Substances List (DSL).

Regulatory decision

Based on the assessment described below, import of CTX001 is not considered to be harmful to human health or the environment for the intended use as an investigational gene therapy for treatment of transfusion-dependent beta-thalassemia (TDT) and sickle-cell disease (SCD). As CTX001 is not entering the environment in a quantity or under conditions that pose a danger to the environment or humans, no further action under CEPA is recommended as a result of this assessment. After August 31, 2018, the import of CTX001 could proceed in Canada. This substance is eligible to be added to the DSL.

Background

CTX001 is a population of genetically modified human hematopoietic cells (i.e. precursors of blood cells) that are isolated from a select group of patients. The cells are subjected to genome editing using CRISPR-Cas9 to introduce specific changes in the genome of the cells. Following modification, CTX001 cells will be re-introduced into to the patient from whom they were isolated, where further differentiation and gene expression will lead to increased production of fetal haemoglobin in the study subjects. That effect is intended to improve the clinical signs of TDT and SCD in those patients.

Hazard considerations

The human and environmental hazard potential of CTX001 is considered to be low for the following reasons:

- There are no antibiotic or antiviral resistance genes, or genes of unknown function present in CTX001.

- Genetic modifications in CTX001 are well-defined and stable. They are not known or likely to result in any pathogenic or toxic properties.

- Results of tests conducted by the notifier to determine the effects of the notified organism on experimental animals produced no observable adverse effects, toxicity or mortality.

- CTX001 is the product of the CRISPR-Cas9 gene editing technique. The cells are modified outside of their human hosts where the reagents decay quickly. Subsequent transfer of modified genetic material to other cells is therefore unlikely.

Exposure considerations

The environmental and human exposure potential from import of CTX001 for investigational use is considered to be low for the following reasons:

- For the purposes of the investigational study, small quantities of CTX001 will be transported in secure containers. CTX001 will be administered to a maximum of eight adult patients in a single dose under controlled conditions in a single Canadian healthcare facility.

- During the course of the clinical study, a limited number of properly trained health care professionals may be exposed to CTX001. Protocols are in place to limit exposure including use of personal protective equipment, proper handling, etc.

- Autologous human hematopoietic cells are specific to the individual from whom those cells were obtained and cannot survive in another human body due to immune rejection. The modification brought about by this use of genome editing is not expected to change this.

- Wild-type human hematopoietic cells require specific physiological conditions inside the human body to survive. As such, they are not able to persist or proliferate outside of the human body. The genetic modification used to generate CTX001 cells is not expected to change the survival of those cells in the environment.

- Clinical trial protocols and contingency plans for accidental spills are expected to adequately contain CTX001 and prevent its release to the environment. The general population will therefore not be exposed to it.

- CTX001 is intended as an investigational gene and cell therapy product for treatment of TDT and SCD. No other potential use for it has been identified. Should CTX001 be commercialized as a gene and cell therapy product for TDT and SCD, protocols to be followed are expected to be similar to those used during the clinical trial. As a result, exposure to humans and the environment would not be expected to significantly change despite an increase in the quantity of CTX001 being imported into Canada.

- CTX001 is not manufactured in Canada. If it were, exposure of Canadians through environmental exposure would not significantly increase as the process controls currently in place for manufacture would effectively prevent releases of the notified organism into the environment.

Risk assessment conclusion

Risk is typically described as the probability of an adverse effect occurring based on hazards and a particular scenario of exposure (Environment Canada and Health Canada, 2011). Exposure scenarios can be described based on intended and any potential uses. In the present case, CTX001 will be imported and used as an investigational gene therapy or as an approved and commercialized drug.

With respect to the environment (as an investigational gene therapy)

Given the low potential environmental hazard and the low potential environmental exposure, the environmental risk associated with the use of CTX001 as an investigational gene and cell therapy drug is considered low.

With respect to human health (as an investigational gene therapy)

Given the low potential human health hazard and the low potential human exposure, the human health risk associated with the use of CTX001 as an investigational gene and cell therapy drug is considered low.

With respect to environment and human health (as an approved and commercialized drug)

Should CTX001 be approved and commercialized for use in Canada for treatment of TDT and SCD, the environmental and indirect human exposure is not expected to change significantly, and so would not significantly increase environmental or human health risks.

References

(excluding proprietary information or references provided by the notifier)

Environment Canada and Health Canada (2011). Framework for Science-Based Risk Assessment of Micro-organisms Regulated under the Canadian Environmental Protection Act, 1999. (viewed in January 2019).

NEW ENGLAND BioLabs® Inc. (2014). CRISPR/Cas9 & Targeted Genome Editing: New Era in Molecular Biology. (viewed in January 2019).

NIH. (2018). U.S. National Library of Medicine, Genetic and Rare Diseases Information Centre: pages for beta-thalassemia and sickle cell anemia. (viewed in January 2019).