Health Canada / Santé Canada

Health Products and Food Branch / Direction générale des produits de santé et des aliments

NOTICE OF COMPLIANCE

AVIS DE CONFORMITÉ

Sponsor / Manufacturer / Promoteur / Fabricant:

Sanofi Therapeutics Research Limited
Peter Street, Unit G04
Adelaide Chambers
Dublin 8, Ireland

Date:

DEC 2 0 2017

Submission Number / Numéro de présentation: 211495

Product Name / Nom du produit: HepaGam B

Medicinal Ingredient(s) / Ingrédient(s) médicinal(aux): Hepatitis B Immune Globulin (Human) / Immunoglobuline humaine anti-hépatique B

Reason for Submission / Raison pour présentation: Administrative – Transfer of Drug Identification Number (DIN)

Administratif – transfert de DIN

Drug Identification Number(s), Route(s), Form(s), Strength(s) / Identification numérique de(s) drogue(s), voie(s), forme(s), dosage(s): 02290979, IM / IV, SOL, 312 IU/mL

This is to notify you that the above new drug submission complies with the requirements of sections C.08.002 and C.08.005.1 of the *Food and Drug Regulations*. Pursuant to section C.08.004 of the *Food and Drug Regulations*, this Notice of Compliance is issued.

Ceci est pour vous aviser que la présentation de drogue nouvelle citée en rubrique est conforme aux exigences des articles C.08.002 et C.08.005.1 du *Règlement sur les aliments et drogues*. Cet avis de conformité est délivré conformément à l'article C 08.004 de ce règlement.

You have undertaken to conduct timely, well designed studies to verify the clinical benefit of this drug. You have also undertaken to provide appropriate educational material and comply with any post-market surveillance commitments and advertising, labeling and distribution requirements placed on the drug. Failure to comply with any one or all of these undertakings may be interpreted as suggesting, inter alia, the possibility of insufficient evidence, at that time, to establish the effectiveness of the drug for the purposes recommended. Accordingly, consideration will be given to regulatory action, removing the product from the market under the authority of the Food and Drug Regulations.

Vous avez pris l'engagement d'effectuer dans les meilleurs délais des études bien conçues afin de confirmer le bénéfice clinique du médicament. Vous avez également pris l'engagement de fournir des documents d'information appropriés, de satisfaire à tout engagement en matière de surveillance après la commercialisation et de respecter toute exigence en matière de publicité, d'étiquetage et de distribution applicable au médicament. La non-observation partielle ou totale de ces engagements pourra être interprété comme suggestion à l'alléna, la possibilité de témoignage insuffisant, à ce moment, pour établir l'efficacité du médicament pour des raisons recommander. Par conséquent, considération sera donnée aux actions régiementaires, pour le retrait du médicament du marché en application de la Loi sur les aliments et drogues et de son Règlement.

Catherine Parker
Director General / Directrice générale
Biologics and Genetic Therapies Directorate / Direction des produits biologiques et thérapies génétiques

Enclosures:
- Product Monograph – cover page
- Certified Product Information Document (CPID) – cover page
- Letter of Undertaking

Pièces jointes:
- Monographie de Produit – page couverture
- Document certifié d'information sur le produit (DCIP) – page couverture
- Lettre d'engagement

Canada

Digitally signed by Chirtoacă Iurie
Date: 2021.09.12 20:42:35 EEST
Reason: MoldSign Signature
Location: Moldova

PRODUCT MONOGRAPH

HepaGam B®

Hepatitis B Immune Globulin (Human) Injection
Liquid >312 IU/mL
Standard: World Health Organization (WHO) International Reference Preparation
Passive Immunizing Agent

HepaGam B®, indicated for the prevention of hepatitis B recurrence following liver transplantation, has been issued marketing authorization with conditions pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

Saol Therapeutics Research Limited
Dublin, Ireland

Distributor (in Canada): Emergent BioSolutions Canada Inc.,
a subsidiary of Emergent BioSolutions Inc.

Control No.: 211495 Date of Approval: December 20, 2017

Health Canada Santé Canada

November 17, 2017 Saol Therapeutics Research Limited

Certified Product Information Document (Schedule D Drugs)

(CPID (Schedule D Drugs)) in the CTD Format

INTRODUCTION

Submission File #9427-C1449/1-28

NDS Approval Date and Control #: January 19, 2007; Control # 089393

CPID Revision Date and Control #: 17 November 2017

Proprietary Name: HepaGam B®

Non-proprietary name or common name of the drug substance: Hepatitis B Immune Globulin (Human)

Company Name: Saol Therapeutics Research Limited

Name of Canadian Distributor: Emergent BioSolutions Canada, to Canadian Blood Services and Héma-Québec

Therapeutic or Pharmacological Classification: Passive Immunizing Agent

Dosage form(s): Sterile Solution

Strength(s): >312 IU/mL (5%)

Route(s) of Administration: Intravenous or Intramuscular

Maximum Daily Dose: Liver Transplant: maximum daily dose 70 mL

Post Exposure Prophylaxis: no maximum daily dose (single dose only)

New Active Substance (NAS)? Not Applicable

Control: 211495 **Date of Approval:** December 20, 2017

SAOL THERAPEUTICS
Saol Therapeutics Research Limited
Peter Street, Unit G04
Adelaide Chambers
Dublin 8, Ireland

November 17, 2017

Re: Letter of Undertaking - HepaGam B® [Hepatitis B Immune Globulin Intravenous (Human)]
DIN: 02290979 - >312 IU/mL (1 and 5 mL vials)
Control # 089393, Notice of Compliance with Conditions (NOC/C), issued 19January2007
File Number 9427-C1449/1-28
eCTD Reference Number e137614

Reference is made to the above-mentioned submission in which a Letter of Undertaking was originally signed by Cangene Corporation as a result of the NOC/C issued for the prevention of hepatitis B recurrence following liver transplantation in adult patients with hepatitis B who have no or low levels of HBV replication. A Letter of Undertaking was subsequently signed by Aptevo BioTherapeutics LLC in 2016 upon transfer of the DIN from Cangene Corporation to Aptevo BioTherapeutics.

The above-mentioned DIN for HepaGam B is to be transferred from Aptevo BioTherapeutics LLC (Aptevo) to Saol Therapeutics Research Limited (Saol). As such, Saol is providing this revised Letter of Undertaking as required. A copy of the originally signed Letter of Undertaking (2007) and its Amendment (2010) are attached for ease of reference.

Listing of Confirmatory Studies

As per the Notice of Compliance with Conditions (NOC/c) Policy, we hereby agree to accept an NOC/c for HepaGam B® (Hepatitis B Immune Globulin [Human] Injection), indicated for the prevention of hepatitis B recurrence following liver transplantation, in adult patients with hepatitis B. We also agree, as the condition for authorization of HepaGam B® to submit to Health Canada, a Supplemental New Drug Submission – Confirmatory (S/NDS-C) which will include:

a. **The final study report for the phase 3 clinical trial HB-005, Hepatitis B immune globulin (NP-002) for prevention of graft re-infection in hepatitis B related liver transplant patients.**

   Status: Study completed. Final study report was submitted as "post-clearance data" on 08April2010.

b. **The final study report of the 1-year extension study to HB-005, study HB-006.**

   The final study report was submitted as "post-clearance data" on 08April2010.

c. **The final study report for the HB-009 study, examining the safety, pharmacokinetics and efficacy of HepaGam B in combination with antiviral therapy in the first year post-transplant.**

   Cangene Corporation submitted a CTA for HB-009 protocol in February 2007 for which a No Objection Letter was issued in March 29, 2007. A CTA-A was filed with Health Canada for the latest HB-009 protocol (version 3.1) in October 2009. Health Canada issued a No Objection Letter for the CTA-A in December 7, 2009. For the efficacy endpoint, the combination of HepaGam B and antiviral therapy will be compared to a statistically justified reference rate for antiviral therapy alone in a superiority analysis as agreed between Cangene and Health Canada. The sample size for this study will be at least 30 patients. Cangene consulted with Health Canada on the design and conduct of this study, and incorporated all CTA-A review comments from Health Canada.

SAOL THERAPEUTICS
Saol Therapeutics Research Limited
Peter Street, Unit G04
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Dublin 8, Ireland

The proposed time lines for the HB-009 study at the time of original Letter of Undertaking were as follows:

- Submit CTA-A in October 2009 for HB-009 protocol version 3.1 (status: completed)
- Re-Initiate study sites and start screening in January 2010
- Complete recruitment by August 2011
- Complete study report by January 2014

Cangene committed to provide an interim report including safety and efficacy data when at least 15 patients have completed the HB-009 study.

The progress of the study will be reported annually and the final study report will be submitted as soon as it is available.

On 25November2011, a meeting was held with Health Canada where the challenges with recruitment for HB-009 were discussed. It was agreed by Health Canada that Cangene should continue recruitment up until August 2012. Health Canada understood that the pre-defined sample size of 31 patients was considered unlikely but encouraged Cangene to file as much data as possible from the HB-009 study, acknowledging that statistical significance may not be achieved.

In May 2013, a Clinical Development Update plan was provided to Health Canada confirming that the recruitment for HB-009 would be halted with a total of 11 patients recruited.

We commit to completing studies HB-005 and HB-006 and submitting the S/NDS-C for these two studies within 5 years following issuance of NOC/c.

Status – Complete.

We commit to completing study HB-009 and submitting the S/NDS-C for this study within 7 years following issuance of NOC/c (i.e. January 2014) or to communicate with Health Canada regarding its status and assessment plan.

Status – Submission pending.

Post-Marketing Surveillance Commitments

a. All serious Adverse Drug Reactions occurring in Canada and all serious unexpected ADRs occurring outside of Canada will be reported within 15 days to The Marketed Health Products Directorate in accordance with the current Guidelines for Reporting Adverse Reactions to Marketed Drugs and the Guidance for Industry, Notice of Compliance with Conditions (NOC/c).

b. Periodic Safety Update Reports (PSUR-Cs) to be submitted semi-annually until the conditions have been removed from the NOC/c by Health Canada. PSURs will be prepared in accordance with ICH guidelines.

Shayen Hamm, PharmD, RPh
Regulatory Agent

21 Nov 2017
Date