



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research**

To: To File (BLA STN 125350/0)

From: Douglas J. Frazier, Biologist, CBER/DH/LPD/HFM-345

Through: Dorothy Scott, MD, Chief, CBER/DH/LPD/HFM-345

CC: Pratibha Rana, RPM, HFM-380

Applicant: CSL Behring AG

Product: Immune Globulin Subcutaneous (Human), 20% Liquid
Trade name (proposed): HIZENTRA™

Subject: Final Review

Recommendation

This BLA is recommended for approval.

Background Summary

The pharmaceutical company CSL Behring AG, located at Wankdorfstrasse 10, CH-3000 Berne 22, Switzerland (US License 1766) (CSLB), has submitted a Biologics License Application for a new immune globulin product, Immune Globulin Subcutaneous (Human), 20% Liquid. CSL Behring AG is a company of CSL Behring L.L.C., headquartered in King of Prussia, Pennsylvania, USA. CSL Behring L.L.C. is a wholly owned subsidiary of the biopharmaceutical company CSL Limited based in Melbourne, Australia.

This new IG product is termed by CSL as “IgPro20” with a proposed trade name of “HIZENTRA™”, and is supported by BB-IND -(b)(4)-. The pivotal clinical study (Study ZLB04_008CR) is a Phase 3 open-label, prospective multicenter study on efficacy, tolerability, safety, and pharmacokinetics in PID patients.

The proposed indication for IgPro20 is treatment of patients with primary immunodeficiency. IgPro20 is a liquid, sterile, 20% protein solution, with an IgG purity of NLT 98%, pH 4.6 – 5.2, and contains 210 – 290 mM L-proline and 10 – 30 µg/mL polysorbate 80, with “trace amounts of sodium” and < 50 µg/mL IgA. No preservative is included. IgGPro20 is to be provided in fills of 5, 10, -(b)(4)-, and 20 mL, in -(b)(4)- glass vials. The proposed storage condition is 2 – 25 °C, protected from light, for up to -(b)(4)-.

CSL submitted summary reports for their validation studies; the ones relevant to this submission are evaluated below:

Study subject	Report no.	Module 3 ref.	Section (below)
Manufacture of IgPro20 bulk in -(b)(4)- from -----(b)(4)-----	05002.03.PVR.003	3.2.P.3.5, Att. 1	1
Manufacture of IgPro20 bulk in -(b)(4)- using -----(b)(4)-----	07092.03.PVR.002	3.2.P.3.5, Att. 2	2*
Manufacture of IgPro20 bulk in -(b)(4)- from -----(b)(4)-----	07056.04.PVR.002	3.2.P.3.5, Att. 3	3
Uniformity of IgPro20 final bulk in -(b)(4)-	05002.04.PVR.005	3.2.P.3.5, Att. 4	4
Manufacture of IgPro20 bulk in -(b)(4)- from -----(b)(4)-----	07056.03.PVR.001	3.2.P.3.5, Att. 5	5
Aseptic filling of IgPro20 on filling line -(b)(4)- and visual inspection	05027.51.PVR.004	3.2.P.3.5, Att. 6	ND [†]
------(b)(4)-----	02085.14.QQB.006	3.2.P.3.5, Att. 7	ND [†]
------(b)(4)-----	07041.02.PVR.001	3.2.P.3.5, Att. 8	ND [†]
Process simulations (media fills, filling line -(b)(4))	05027.54.PVR.001	3.2.P.3.5, Att. 9	ND [†]
Sterile filter filtration	04048.06.PVB.001	3.2.P.3.5, Att. 10	ND [†]
Final bulk stability	PHAD 1554	3.2.P.3.5, Att. 11	ND [‡]
Comparability of IgPro10 from -(b)(4)-----: process parameters	02085.11.PVR.007	3.2.P.3.5, Att. 12	ND**
Comparability of IgPro20 with IgPro20 m ^f red using --(b)(4)-- and w/IgPro20 from -(b)(4)-- -----	05002.05.PVR.001	3.2.P.3.5, Att. 13	6
------(b)(4)-----	VSR # C30523	3.2.S.2.5, Att. 1	7
Comparison ------(b)(4)----- Processed w/Modified Process Parameters to Intermediates From Current Licensed Process	Doc. No. SR-460r	3.2.S.2.5, Att. 2	8
Comparison of ------(b)(4)----- Processed With Modified Parameters to Material From The Current Licensed Process	Doc. no. SR-468Ar	3.2.S.2.5, Att. 4	9

* also reviewed under STN 125201/148

** previously reviewed under STN 103955/5230 and STN 125201/149

† reviewed by DMPQ

‡ reviewed by DH

1. **Manufacture of IgPro20 bulk in -(b)(4)- from (b)(4)-----** (Study no. 05002.03.-(b)(4)-.003; Section 3.2.P.3.5, Att. 1)

------(b)(4)-----

------(b)(4)-----

18 Pages to be Determined to be Non-Releasable: (b)(4)