



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

To: BLA STN 125350/0

Cross Reference: IND -(b)(4)-

From: Evi Struble, Ph.D.

Through: Dorothy E. Scott, M.D.

CC: Pratibha Rana, RPM, HFM-370

Applicant: CSL Behring AG

Product: IgPro20, Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid

Subject: Memo, Nonclinical Pharmacology/Toxicology

Brief Description of BLA Submission

IgPro20 is a new ready-to-use 20% protein liquid formulation of human immunoglobulin G (IgG) preparation for subcutaneous application (SCIG). The sterile 20% IgG solution is formulated with 250 mmol/L of L-proline at pH 4.8. IgPro20 also contains a nominal amount of 20 µg/mL polysorbate 80.

Proposed indication:

IgPro20 is indicated for the treatment of primary immunodeficiency (PI).

Proposed Dose:

The dose will be individualized based on the patient's clinical response to IgPro20 therapy and serum IgG trough levels. The highest dose used in the clinical trials did not exceed 400 mg/kg.

Conclusions

There are no issues to prevent this BLA from being approved.

Letter ready comments for IR:

1. In study no. -(b)(4)- 01/06, titled "Effects of Sandoglobulin, IgPro10 and IgPro20 on blood pressure in rats" in the conclusions section you state that "...lot number

2. Please include names of the responsible personnel in “Legacy Study Report Bacterial Stress Gene Assay Zen-0995” signature page (pg 2).

Studies performed with IgPro 20

- 1) Local tolerance studies
 - a. IgPro20 administered in rabbits s.c. up to volumes corresponding 7 times the maximum volumes applied to humans per infusion site and kg body weight caused erythemas and edemas.
 - i. Erythema development after IgPro20 administration was comparable to that of the marketed SCIG product Beriglobin P, and to IgPro18.
 - ii. The frequency and intensity of edema was higher for IgPro 20 than the Beriglobin P control and it increased with the increasing IgG dosing. The frequency of edema was higher for proline than saline controls.
 1. Healing was observed during the three day observation period.
 - iii. No histological abnormalities were detected after s.c. infusion of IgPro20.
 - b. IgPro20 applied to rabbits via intravenous (i.v.), intra-arterial (i.a.) and paravenous (p.v.) routes of administration to assess local reactions after correct and incorrect application.
 - i. Erythema and edema formation induced by test article and saline injection were slight and similar in incidence and severity after i.v. and i.a. application.
 - ii. Well defined erythemas and moderate to severe edemas were observed after p.v. administration of IgPro20.
 1. Healing was observed during the three day observation period.
 - iii. There were no drug related macroscopical or histopathological findings after i.v., i.a. or p.v. application.
- 2) Pharmacokinetic studies
 - a. Pharmacokinetics of IgPro20 in rats was investigated after repeated s.c. dosing on five consecutive days and relative bioavailability was assessed in comparison to IgPro10 (Privigen) administered intravenously. The overall bioavailability was 57% with 90% confidence interval of 49-67%.
 - b. Single dose pharmacokinetic study in rabbits showed that the bioavailability of IgPro20 is 80% of the bioavailability of Vivaglobin.
- 3) The pharmacodynamic effect of IgPro20 was evaluated in hemodynamic safety pharmacology study after i.v. bolus administration in rats.
 - a. IgPro20 caused moderate hypotension which was in the same range as for the marketed products IgPro10 (Privigen) and Sandoglobulin.

Safety of Excipients

The excipients are L-proline and polysorbate 80 and the main impurity is octanoic (caprylic) acid.

Octanoic acid is a naturally occurring medium chain fatty acid and has been used in similar amounts in other Ig products such as Gamunex (IGIV 10%). In albumin solutions is used up to concentration of 4 mmol/L (5% albumin) and 25 mmol/L (25% albumin).

Table 1: Exposure to the Excipients/Impurities

	IgPro 20		Flebogamma 10%		Gamunex 10%	
	Conc.	Dose#	Conc.	Dose^	Conc.	Dose^
Polysorbate 80	30 mg/mL	60 mg/kg	200 mg/mL	1600 mg/kg		
Octanoic (Caprylic) Acid	-(b)(4)- -----	-(b)(4)- -----			1.3 mmol/L	10.4 μmol/kg

#Calculated using a dose of 400 g/kg

^Calculated using a dose of 800 g/kg

L-proline is used as a stabilizer in a concentration of 250 mmol/L IgPro20 (= 28.75 g/L). L-proline is present as an excipient in the licensed biologic Privigen (human IGIV preparation) and aminoacid mixtures intended for parenteral nutrition such as 8.5% FreAmine® III, B. Braun Medical Inc.

The acute exposure to L-proline from IgPro20 use in the clinic will result to approximately 58 mg/kg bw L-proline once weekly. This amount is lower than with the “parent” IVIG IgPro10 (i.v. doses of 287.5 mg/kg L-proline with IgG doses of 1g/kg) and lower than the doses for parenteral nutrition intended for sub-chronic administration. For example up to 255 mg/kg/day L-proline are given to healthy and 348 mg/kg to malnourished or traumatized infants with 8.5% FreAmine® III, B. Braun Medical Inc.

Table 2: Maximum human doses of IgG and L-proline administered with IgPro20 and approved products formulated with L-proline

Product	Route of Administration	Maximum daily dose: IgG (mg/kg bw)	Maximum daily dose: L-proline (mg/kg bw)
IgPro20	s.c.	400*	58
IgPro20	s.c.	1000^	145
IgPro10 (Privigen)	i.v.	1000	288
8.5% FreeAmine® III#	i.v.	n.a.	255-348

*The highest dose used in clinical trials

^Theoretical maximal dose, not likely to be used in the clinic

#Labeled “For short-term use in adult patients”; also used in infant and pediatric populations.

Results from the animal studies performed with L-proline are summarized below.

- 1) Repeat-dose toxicity studies were conducted with L-proline in two species, rats and dogs.
 - a) In rats, the No Observed Adverse Effect Level (NOAEL) was set at the high-dose of 1449 mg/kg/day. Slight reductions in body weight gain and reduced food consumption was observed at this in the 28-day high dose male group. There was no other treatment related changes in all dose groups.
 - b) In dogs, the NOAEL was 4350 mg/kg/day, the highest dose used. In the 4-week study, clinical signs such as emesis were noted for several animals in the highest dose group. A reduction in food consumption was seen for animals during treatment with the highest dose; the weight gain was considered normal.
- 2) L-proline was not genotoxic when used in combination with nicotinamide and L-isoleucine using the Ames test, in vitro cytogenicity assay, a bacterial stress gene assay and a bone marrow micronucleus assay in mice.
- 3) L-proline was not teratogenic when administered i.v. at a dose of 1449 mg/kg/day during days 6 to 17 of gestation. At this dose, there was no indication of maternal or embryo-toxicity, and the dose tested was No Observed Effect Level (NOEL).
 - a) The impact of L-proline on fertility, early embryonic development and peri-natal development has not been assessed. L-Proline is a naturally occurring amino acid and these studies are not considered necessary.
- 4) L-proline was not neurotoxic in a neurotoxicity studies in rats.
 - a) L-proline did not significantly affect the behavior of rats during or after infusion for 5-days whereas minor to moderate effects were seen with glycine. Cumulated doses of L-proline and glycine induced slight statistically significant increases in body temperature after 5 days of infusion when compared to control groups.
 - b) L-proline caused no neurological effects in rats when administered s.c. at a dose of 2 g L-proline/kg bw.
- 5) L-proline was not neurotoxic when investigated in juvenile rats.
 - a) In an acute neurotoxicity and a Morris water maze task study in juvenile rats, L-proline administered at doses 1500-2000 mg L-proline/kg on days 9-13 or on days 9, 16, and 23 was shown not to have any negative effects in short and long term memory and in the nervous system development in rats.
- 6) In published research, juvenile rats injected s.c. with high doses of L-proline from birth to day 28 displayed short and long term memory loss in standard tests.
- 7) Pharmacokinetic studies with L-proline were performed using intravenous infusion to rats and dogs, as well as s.c. and i.p. injection in rats.
 - a) In rats L-proline administered s.c. and i.p. at a dose of 2.0 or 4.0 g /kg bw respectively was eliminated quickly from the serum with a half-life of L-proline s.c. 1.5 h and baseline levels reached at 8 h after injection for most animals.
 - b) Plasma levels after a single s.c. administration of 1.9 g/kg bw L-proline to juvenile rats were about 15 mmol/L L-proline 15 minutes after application and declined to about 16% of this concentration 4 hours after injection. Thus, elimination from plasma in juvenile animals was slower compared to adult rats.
 - c) In rats L-proline administered i.v. up to a dose of 1449 mg/kg/day for 5 or 28 consecutive days showed no accumulation of L-proline in the serum. The total

- d) In dogs, L-proline administered i.v. at a dose 2170 and 4350 mg/kg for 7 or 28 consecutive days showed no accumulation of L-proline in the serum; less than 5% of the infused L-proline dose was excreted with urine.
- 8) Sponsor has performed no distribution study and only limited excretion studies with L-proline. The following has been derived from the studies performed by the sponsor and the published literature.
- a) L-proline is a naturally occurring amino acid and present in plasma at a concentration of 266–35 $\mu\text{mol/L}$. It is tubularly reabsorbed in kidneys uses the same transporter as glycine and hydroxyproline and thus not secreted in the urine of healthy individuals.
 - i) In studies performed by the sponsor, L-proline administered i.v. in dogs and rats was not accumulated in plasma and only a limited amount is excreted in urine, namely 5 and 2% respectively.
 - b) L-proline injected into muscle tissue is rapidly transported to the liver and to a lesser degree the intestine where it is used for protein synthesis and also converted to L-glutamine.
 - c) L-proline passes the blood-brain barrier (BBB) where it acts as a low potency member of the class of excitatory amino acids. In adults it is effluxed by the amino acid transporter ATA2, the orphan transporter v7-3 (solute carrier 6a15, or B0AT2), and the PROT transporter. One or some of these transporters may not be well developed in young children.