



Department of Health and Human Services
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Center for Biologics Evaluation and Research

To: File, BLA 125810/0

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Applicant: Biotest AG

Product: Immune globulin intravenous, human – dira, 10% liquid (YIMMUGO)

Indication: For primary humoral immunodeficiency (PI) in patients 2 years of age or older

Subject: Nonclinical Pharmacology/Toxicology Review

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Introduction

This BLA has been filed to obtain marketing authorization for a 10% immunoglobulin (Ig) G product from pooled US source plasma from healthy donors. The proprietary name for the product is YIMMUGO, also called IgG Next Generation and BT595 throughout the submission. These names will be used interchangeably in this review.

YIMMUGO contains (b) (4) human immunoglobulin ($\geq 96\%$ IgG, all subclasses are represented) and (b) (4) of Ig of other classes. The product was tested as IgG replacement therapy for Primary Immunodeficiency Disorders (PID) when administered every 3 to 4 weeks at a dose of (b) (4) to 800 mg/kg.

Pharmacology and Toxicology

Pharmacology

Primary pharmacodynamic studies were performed to assess Fab- and Fc functions of YIMMUGO. (b) (4)
(b) (4)

The results of these studies demonstrate functionality of YIMMUGO and its potential to be efficacious in the PID indication.

Toxicology

One single-dose toxicity and safety pharmacology study was performed in Sprague Dawley rats with YIMMUGO. In this study, 2 g/kg BT595 was given as an intravenous infusion and the animals were assessed one and fourteen days after infusing for systemic and local toxicity. No unexpected toxicities were observed in this study.

Toxicity of excipients was assessed via a literature review. There are no safety concerns related to potential toxicity of excipients and other impurities in the final formulation of YIMMUGO.

Main Findings

There are no pharmacology and toxicology issues that would prevent YIMMUGO from being approved.

Complete Review

Toxicology

Single Dose Intravenous Infusion Toxicity Study in the Sprague Dawley Rat

Study Number S56588

Performing Laboratory: (b) (4)

Aim: A GLP general toxicity study of BT595 infused in Sprague Dawley rats

Design: Three groups of 8M (203-232 g) and 8F (172-218 g) rats received intravenous infusion of test article BT595 or positive control (Gamunex) at 2000 mg/kg (20 mL/kg), or negative control (formulation buffer) at 20 mL/kg. n=4/sex/group were sacrificed on Day 2 and the rest on Day 15.

Outcome measures: Clinical signs /local tolerance on day and days 2, 8 and 15; weekly food consumption; body weights on day 1, 8, 14 and 15; body temperature prior to dosing, 6 hours post-dosing and prior to sacrifice; functional observation battery (grip strength, locomotor activity) prior to dosing, post-dose on day 1, and on day 15; hematology, coagulation, blood biochemistry and urinalysis on day 1 and 15; complement activation (C3); gross pathology and histopathology.

Results

Swollen areas (limbs and snout) in groups receiving test article and the positive control; n=2 females receiving BT595 showed a hunched back (sign of pain/discomfort), with one of them having unsteady gait and only partial response in the proprioception reflex on day 1. It is unclear what the reasons were for this sign, and there were no findings for this animal in the other outcome measures.

Changes in red blood parameters on day 1 for Gamunex and BT595 consistent with RBC hemolysis, expected following IGIV administration at high doses in rats. The reduction in RBC and hematocrit was larger for BT595 compared to Gamunex. A trend to recovery was observed on day 15 for both groups. An

increase in C3 levels was seen in Gamunex and BT595 on day one but returned to baseline on day 15. There was no change in body temperature.

At necropsy, an increase in spleen weights was noted at 24 hours after dosing for animals in all animals receiving BT595 and males receiving Gamunex. No findings were noted on histopathology.

Conclusions

BT595 had a comparable tolerability profile to Gamunex at doses that are at least 2.5 times higher than the highest human dose for the PID indication. The transient differences between these two articles noted in some parameters such RBC, could be due to higher serum concentrations following administration of BT595 compared to Gamunex.

Formulation

The formulation of YIMMUGO contains glycine and PS80 at the levels shown in Table 1.

Glycine is used in the formulation of other IgG products at similar levels. The estimated highest exposure to glycine via IgG Next Generation (BT595) at a dose 2 g/kg (assuming 70 kg individual) would be (b) (4) g/day. Moreover, several approved human immunoglobulin drug products contain glycine as a stabilizer (b) (4) at similar concentration used in the IgG Next Generation (BT595) (b) (4) - 0.33 M). The exposure to glycine through these drug products ranged from (b) (4) further supporting the safety of glycine in IgG Next Generation (BT595).

Polysorbate 80 is a commonly used excipient with a highest exposure (b) (4) to polysorbate 80 from drug product IgG Next Generation (BT595) when used at 2 g/kg dose.

The EMA has determined the threshold for cardiovascular effects as (b) (4) mg/kg/day and for hepatic effects (enzyme elevation) as (b) (4) mg/kg/day (intravenous). The estimated exposure is lower than these threshold values. The intravenous permitted daily exposure (PDE) for polysorbate 80 was established as (b) (4) mg/day. The estimated exposure of (b) (4) mg/day is (b) (4) fold lower than the intravenous PDE.

Table 1. Formulation

Material	Specification drug product
Glycine	(b) (4) (270-330 mmol/l)
Polysorbate 80	(b) (4)