

Pharmacology / Toxicology Review

Memorandum - Wilate, September 11, 2007

Date: 9-11-2007
From: Paul W. Buehler
Through: Abdu Alayash, Basil Golding and Susan Abbondanzo
Supervisor signature: I approve this memo as LBVB Lab Chief but not as an expert in the field.
To: Franklin Stephenson, Pauline Cottrell and Tim Lee
Subject: BLA STN: 125251/0
Sponsor: Octapharma Pharmazeutika Produktionsges.m.b.H.
Product: Coagulation Factor VIII/von-Willebrand Factor Complex (Human)
Short Summary: For the treatment -----(b)(4)----- of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease (vWD), and in mild and moderate vWD where use of DDAVP treatment is ineffective or contra-indicated. -----(b)(4)-----

Final Review: 9-11-2007

Final Recommendation: After review of the pharmacology and toxicology sections of BLA 125251/0 there are no issues which would prevent approval of Coagulation Factor VIII/von-Willebrand Factor Complex (Human) from the perspective of non-clinical safety.

Background:

Octapharma has completed several studies primarily focusing on solvent detergent residuals (TNBP and Triton-X 100) in the Coagulation Factor VIII/von-Willebrand Factor Complex (Human). All of the studies presented indicated an acceptable margin of safety for exposure which would occur in patients receiving Coagulation Factor VIII/von-Willebrand Factor Complex (Human).

Vial Sizes: -(b)(4)- IU and -(b)(4)- IU vWF potency to be reconstituted in 5 mL water for injection + polysorbate 80 at 0.1% -(b)(4)- IU and -(b)(4)- IU is reconstituted in 10 ml WFI + polysorbate 80 at 0.1%.

Dosages:

Minor hemorrhages: loading dose 20-40 IU/kg, maintenance dose 20-30 IU/kg every 12-24 hours.

Major hemorrhages: loading dose (b)(4)-60 IU/kg, maintenance dose 20-(b)(4) IU/kg every 12-24 hours.

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

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

Note: contains TNBP < 2.8 ug/kg, Triton X 100 < 5.6 ug/kg and Polysorbate 80 = 0.56 mg/kg.

Release specifications after reconstitution with 0.1% polysorbate 80 are as follows:

Parameter	Test Specification	Test Method
-----------	--------------------	-------------

Parameter	Test Specification	Test Method
----(b)(4)-----	White, pale yellow powder	--(b)(4)--
--(b)(4)--	----(b)(4)-----	--(b)(4)--
----(b)(4)-----	----(b)(4)-----	--(b)(4)--
----(b)(4)-----	----(b)(4)-----	--(b)(4)--
Protein	----(b)(4)-----	--(b)(4)--
----(b)(4)-----	----(b)(4)----- ----(b)(4)-----	--(b)(4)--
Moisture	----(b)(4)-----	--(b)(4)--
FVIII activity	----(b)(4)-----	--(b)(4)--
----(b)(4)----- -----	----(b)(4)-----	
vWF R:Cof	----(b)(4)-----	--(b)(4)--
Glycine	----(b)(4)-----	--(b)(4)--
Sucrose	----(b)(4)-----	--(b)(4)--
Sodium	----(b)(4)-----	--(b)(4)--
Calcium	----(b)(4)-----	--(b)(4)--
Citrate	----(b)(4)-----	--(b)(4)--
Chloride	----(b)(4)-----	--(b)(4)--
TnBP	--(b)(4)--	--(b)(4)--
Triton-X 100	--(b)(4)--	--(b)(4)--
Endotoxin	--(b)(4)--	--(b)(4)--
Sterility	sterile	21 CFR 610.12
General Safety	Pass	21 CFR 610.11

Summary of non-clinical safety studies:

Single Dose toxicology of TNBP and Triton X-100

Study 7724/92: Acute toxicity study of TNBP + Triton X-100 (--(b)(4)--) by i.p. administration to ----(b)(4)----- rats

Summary of findings:

The first observation of intolerance for the (-(b)(4)-) mixture of TNBP:Triton X-100 occurred at 46.5 mg/kg, human (70kg) equivalent of 3255 mg (-(b)(4)-) per dose with TNBP = -(b)(4)- mg and Triton X-100 = -(b)(4)- mg. Neurological symptoms consisting of ataxia and loss of muscle tone defined the primary intolerance to the mixture in this study using i.p. administration. The NOAEL was defined as 21.5 mg/kg (-(b)(4)-) per dose or 1505 mg human (70kg) equivalent per dose with TNBP = -(b)(4)- mg and Triton X-100 = -(b)(4)- mg. The lowest lethal dose was lower in female rats (100 mg/kg) than male rats (215 mg/kg).

Study 7725/92: Acute toxicity study of TNBP + Triton X-100 (--(b)(4)--) by i.p. administration to Newborn ---(b)(4)--- rats

Summary of findings:

Very similar to Study 7724/92, the first observation of intolerance in newborn rats for the (-(b)(4)-) mixture of TNBP:Triton X-100 occurred at 46.5 mg/kg, human (70kg) equivalent of 3255 mg (-(b)(4)-) per dose with TNBP = -(b)(4)- mg and Triton X-100 = -(b)(4)- mg. Neurological symptoms consisting of ataxia and loss of muscle tone defined the primary intolerance to the mixture in this study using i.p. administration. In addition cyanosis accompanied this dose in newborn rats. The NOAEL was defined as 21.5 mg/kg (-(b)(4)-) per dose or 1505 mg human (70kg) equivalent per dose with TNBP = -(b)(4)- mg and Triton X-100 = -(b)(4)- mg. The lowest lethal dose was lower in male

newborn rats (46.5 mg/kg) than female male newborn rats (147 mg/kg). This is opposite the findings in adult rats.

Study 5123/88: Examination of the acute toxicity of TNBP by i.p. administration to

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

Summary of findings:

The first observation of intolerance in mice (18-23 g) dosed with TNBP (0.0453 g/kg, 0.144 g/kg, 0.453 g/kg, 0.549 g/kg, 0.665 g/kg, 0.806 g/kg and 0.977 g/kg) via the i.p. route occurred at 0.144 g/kg, human (70kg) equivalent of 10 g/kg per dose with TNBP. Neurological symptoms consisting of ataxia and loss of muscle tone defined the primary intolerance to TNBP this study using i.p. administration. In addition dyspnoea accompanied this dose in mice. The lowest lethal dose of TNBP in mice was 0.549 g/kg.

**Study 6344/90: Acute toxicity study of TNBP by i.v. administration to -----(b)(4)-----
- rats (only reliable study)**

Summary of findings:

The first observation of intolerance in rats dosed with TNBP (2.15 mg/kg, 4.64 mg/kg, 10 mg/kg, 21.5 mg/kg and 46.4 mg/kg) via the i.v. route occurred at 4.64 mg/kg, human (70kg) equivalent of 324.8 mg per dose with TNBP. Neurological symptoms consisting of ataxia and loss of muscle tone defined the primary intolerance to TNBP this study using i.v. administration. In addition dyspnoea accompanied this dose in rats. The lowest lethal dose of TNBP in rats was 21.5 mg/kg.

Study 5126/88: Examination of the acute toxicity of TNBP by i.p. administration to -----(b)(4)----- rats

Summary of findings:

The first observation of intolerance in rats dosed with TNBP (0.0453 g/kg, 0.144 g/kg, 0.453 g/kg, 0.549 g/kg, 0.665 g/kg, 0.806 g/kg and 0.977 g/kg) via the i.p. route occurred at 0.144 g/kg human (70kg) equivalent of 10.1g per dose with TNBP. Neurological symptoms consisting of ataxia and loss of muscle tone defined the primary intolerance to TNBP this study using i.v. administration. In addition dyspnoea accompanied this dose in rats. The lowest lethal dose of TNBP in rats was 0.549 g/kg.

Repeat-Dose Toxicity:

Study 5568/1/89: 13 week subchronic toxicity of TNBP + Triton X-100 (-(b)(4)-) by intravenous administration to -----(b)(4)----- rats

Study 5569/1/89: 13 week subchronic toxicity of TNBP + Triton X-100 (-(b)(4)-) by intravenous administration to ---(b)(4)--- Dogs

Summary:

Neither study indicates that TNBP or Triton X-100 are inducing toxicity.

Genotoxicity:

**Study 11586: TNBP -----(b)(4)-----assay in vitro in -----(b)(4)-----
----- cells**

Summary:

No significant findings at all concentrations evaluated in the presence and absence of metabolic activators.

Study 122486: ----(b)(4)---- test with TNBP on ---(b)(4)--- cells of ---(b)(4)--- mice.

No mutagenic properties could be detected following dosing levels of 5, 10 and 20 mg/kg in ----(b)(4)---- mice.

Carcinogenicity:

Not performed

Immunogenicity:

Not performed

Reproductive Studies:

Study 6086/90: The influence of TNBP and Triton X-100 on the pregnant rat and fetus following intravenous injection

Summary:

The lowest expected dose level of TNBP to produce toxicity in the pregnant female is approximately 300-600 mg/kg. The lowest expected dose level of TNBP to produce toxicity in the embryo or fetus is above 900 mg/kg.

Study 6087/90: The influence of TNBP and Triton X-100 on the pregnant rabbit and fetus following intravenous injection

Summary:

The lowest expected dose level of TNBP to produce toxicity in the pregnant female, embryo and fetus is approximately 150-450 mg/kg.

Polysorbate 80: Polysorbate 80 is safe via the IV route at a dose of 20 mg/kg (Expert panel of CIR, 1984). Patients receiving Wilate will be exposed to approximately 0.625 mg/kg polysorbate 80. Accumulation of polysorbate 80 would not be expected at dosing intervals of greater than 4 hours given a half-life of 0.61 hours in humans. Polysorbate 80 has not been reported to be genotoxic in vitro or in vivo.

Total product (single and repeated dose toxicology):

Have not be presented within the submission

Acceptable rationale for this is based on the fact that this is a human plasma derived product used as a replacement therapy. Additionally, the complex can only be dosed in single dose toxicology studies, which are of limited value without accompanying longer term dosing studies. Coagulation Factor VIII/von-Willebrand Factor Complex (Human) can not be successfully dosed repeatedly in animals due to neutralizing antibody response to Factor VIII/von-Willebrand Factor complex demonstrated by the sponsor. As a result long term toxicology data would be of no value.