CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125011

PHARMACOLOGY REVIEW(S)

Nonclinical Pharmacology and Toxicology Review of 131-I Tositumomab

STN 125011\0

Product: Tostitumomab (Bexxar)

Sponsor: Corixa

Study SB-G99054, Repeat Dose Intravenous Toxicity Study in Cynomolgus Monkeys. This study used Cynomolgus monkeys given Anti-B1 Antibody given 0, 7.5 or 75 mg/kg/dose (3/sex/group) on days 1 and 8. The duration of the study was 12 weeks. Antibody manufactured at BI Pharma (lot 5712054B) was injected iv (10.7 ml/kg of 14.1 mg/ml solution containing 10% maltose, 145 mM sodium chloride, 10 mM phosphate at pH 7.2). Monkeys were followed for 3 months at which time a complete necropsy was performed. The following endpoints were assessed: clinical observations, body weight, body temperature, ECG, ophthalmology, hematology, hemostasis, clinical chemistry, urinalysis, serum immunoglobulins, lymphocyte subsets, antibody response to Anti-B1 antibody, peripheral blood mitogen response, lymph node biopsy, toxicokinetics, organ weights, immuno-histochemistry of lymph node and spleen, gross and microscopic anatomy.

Although pharmacological effects were observed, no frank adverse effects were observed in any toxicity endpoint. Mean absolute lymphocyte counts were decreased by 40% to 55% on day 6 for animals given 7.5 or 75 mg/kg. The mean absolute CD20+ lymphocyte counts were decreased 85% to 100% from 24 hours post dosing through day 10 for monkeys given 7.5 mg/kg or 75 mg/kg of antibody as compared to day 1 baseline values. Full recovery occurred in males by day 84 with 100% after 7.5 mg/kg and 88% after 75 mg/kg in males; in females only 62% and 65% of baseline values were achieved. Analysis of lymphocytes from lymph nodes on day 30 found CD20+ and CD40+ B cells were decreased 33% to 69% for monkeys given 7.5 or 75 mg/kg. By day 98 to 100, levels of CD20+ lymphocytes were comparable to concurrent controls. All monkeys given anti-B1 antibody developed anti-mouse IgG antibodies. Titers of anti-mouse antibody decreased by day 28. Anti-mouse antibody decreased exposure to anti-B1 antibody at the time of the second dose to approximately 61% of the first dose. The elimination half-life ranged from 44 to 69 hours.

Three tissue cross-reactivity studies using a full complement of tissues were performed with various versions of Tositumomab. These studies are cited as IM298 (unlabeled antibody from Lonza and Coulter), IM404 (labeled and unlabeled antibody from Lonza) and IM 427 (unlabeled antibody from BI Pharma and Lonza). All tissue cross-reactivity studies used concentrations of 1 and 10 ug/ml and human tissues. All studies revealed binding to mononuclear cells in mantle and germinal center regions of follicles in spleen, lymph node, mucosal-associated lymphoid tissue and lymphoid cells in a variety of tissues. No differences were observed in the nature or extent of binding due to labeling or source of manufacture.

The following pharmacokinetic and biodistribution studies were performed to assess potential differences due to changes in manufacture or type of radiolabeling (central versus site): B1-PT-019, BI-PT-002, B1-PT-001, 3-F44 and 3-K06. All studies were conducted as single dose iv administrations using a dual label approach (both 131-I and 125-I were co-administered) with the exception of B1-PT-001, which used 131-I only. Cold loading and radiolabeled follow-on dosing was used in through out the studies. Besides pharmacokinetic analysis the radioactive content of various tissues including blood, liver, spleen, kidneys, heart, lungs, femur and muscle were determined. No meaningful differences in pharmacokinetics or biodistribution were found.

Study	Purpose	Species	N/sex/group	Dose, unlabeled/labeled
B1-PT-019	Central vs on-site label	Mouse	6/F; 6 groups	0.1 mg/0.001 to 0.002 mg
B1-PT-002	Repeat of B1-PT-019	Mouse	5/F; 5 groups	0.1 mg/0.001 mg
B1-PT-001	Change HSA to povidone	Mouse	6/F;2 groups	0.1 mg/0.002 mg
3-F44	Lonza vs Coulter	Monkey	3/M; 2 groups	7.5 mg/kg/0.3 mg
3-K06	BI Pharm vs Lonza	Monkey	3/M; 2 groups	7.5 mg/kg/0.3 mg

Table of pharmacokinetic and biodistribution studies performed using Swiss-Webster mice and Cynomolgus monkeys.

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