Miller, Diane M. (CDC/NIOSH/EID)

From: Cuozzo, Michael [CNTUS] [MCuozzo1@its.jnj.com]
Sent: Tuesday, June 30, 2009 10:41 AM
To: NIOSH Docket Office (CDC)
Subject: 105a - Haz Drug Appx A Rev
Attachments: NIOSH Hazardous Drugs _comment.doc

Dear Sir(s),

Please find attached comments relating to "Updating the List of Hazardous Drugs for the NIOSH Alert: Additions and Deletions to the NIOSH Hazardous Drug List (NIOSH-105A)". The comments contained within specifically support the removal of REMICADE® (infliximab) from the hazardous drugs list. I welcome the opportunity to discuss any of the material contained within this letter and thank you, in advance, for your consideration.

Kind regards,
Michael

<<NIOSH Hazardous Drugs _comment.doc>>

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June 29, 2009

NIOSH Docket Office
Robert A. Taft Laboratories
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Cincinnati, OH 45226

Dear Sir(s):

Thank you for the opportunity to comment on the draft document entitled "Updating the List of Hazardous Drugs for the NIOSH Alert: Additions and Deletions to the NIOSH Hazardous Drug List (NIOSH-105A)" as requested by the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control (CDC). The comments contained within specifically support the removal of REMICADE® (infliximab) from the hazardous drugs list.

REMICADE is a chimeric IgG1 monoclonal antibody that binds specifically to and neutralizes the activity of human tumor necrosis factor alpha (TNFα). REMICADE is approved to treat several medical conditions, including moderately-to-severely active rheumatoid arthritis, active psoriatic arthritis, active ankylosing spondylitis, severe psoriasis, moderately-to-severely active adult and pediatric Crohn's disease, and moderately-to-severely active ulcerative colitis.[i]

Each vial of REMICADE contains 100 mg as lyophilized concentrate requiring reconstitution with 10 mL of Sterile Water for Injection. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP and subsequently infused intravenously over a period of no less than two hours. REMICADE is dosed in a weight-based manner, with patients receiving 3-5 mg/kg once every 6-8 weeks, depending on the therapeutic use.[i]

NIOSH defines a hazardous product as any drug identified by at least one of the following six criteria (see http://www.cdc.gov/niosh/review/public/105-A/pdfs/ResponsetoPublic.pdf): carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low doses in humans or animals, genotoxicity, or new drugs that mimic existing hazardous drugs in structure or toxicity. As described in the following portions of the approved package insert for REMICADE, an analogous compound to REMICADE demonstrating similar biologic activity in mice has not demonstrated carcinogenic, tumorgenic, or mutagenic activity in mouse models. In addition, maternal toxic, embryotoxic, and teratogenic effects were not observed in developmental mouse models. REMICADE is classified as pregnancy category B.[i]

Carcinogenesis, Mutagenesis and Impairment of Fertility

A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. cV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.[i]

Pregnancy Category B
Since infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed.[i]

According to the document "NIOSH Summary of All Comments and NIOSH Hazardous Drug Committee" (see http://www.cdc.gov/niosh/review/public/105-A/pdfs/ResponsetoPeer.pdf), the addition of REMICADE to the Hazardous Drugs List-Appendix A was proposed due to warning language pertaining to lymphoma and overall malignancy risk in the REMICADE package insert. Importantly, patients receiving REMICADE who developed malignancies in clinical trials or the post-marketing setting were exposed to the therapeutic doses of REMICADE. Therapeutic blood levels of REMICADE can only be achieved and maintained when REMICADE is administered via intravenous infusion over several hours at doses of 3-5 mg/kg (or higher) every 6-8 weeks. In addition, patients developing malignancies frequently received other immunosuppressive and in some cases, known mutagenic therapies (i.e. azathioprine). These patients also had medical conditions (i.e. rheumatoid arthritis, Crohn's disease, psoriasis) that predisposed them to develop certain types of malignancies, including lymphomas. As a result of these confounding clinical factors, the package insert states that "the role of TNF blocking agents in the development of malignancies is not known."[i]

Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. All reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients received

treatment with azathioprine or 6-mercaptopurine concomitantly with REMICADE at or prior to diagnosis.[i]

In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.[i]

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately 4-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.[i]

In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking,. Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD.[i]

Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients with previous phototherapy.[i]

The potential role of TNF-blocking therapy in the development of malignancies is not known. Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE.[i]

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With regard to occupational exposure, unlike the prescribing information for numerous antineoplastic/anti-cancer agents,[ii,iii] the prescribing information for REMICADE contains no cautionary statements regarding the risk of dermal exposure or safe handling instructions (i.e. use of impervious gloves, washing/flushing instructions following exposure, risk of extrasavation, etc).[i]

As described in a letter from the Biotechnology Industry Organization to NIOSH in January 2008 (visit http://www.bio.org/reg/20080130.pdf), high molecular weight protein therapeutics such as REMICADE pose an extremely low risk of penetrating skin, gastrointestinal and pulmonary barriers due to their molecular weight and overall chemical structure. With a molecular weight of 149 kDa,[i] REMICADE significantly exceeds the molecular size 0.5 kDa, which has been suggested as the threshold for drug penetration into the outer layer of the epidermis.[iv] Penetration of high molecular weight protein therapeutics such as REMICADE into the lungs following inhalation is also extremely unlikely, due to the proteins' large aerodynamic diameter (10 μm). To reach the alveoli of the lungs, particles must be < 2.5 μm.[v,vi,vii] Similarly, given its complex protein structure and high susceptibility to denaturing, the acidic environment in the gastrointestinal system provides an effective barrier to systemic exposure of REMICADE.

Thank you for your consideration of our comments. Given the information provided above-namely that REMICADE has not been demonstrated to be carcinogenic, mutagenic, or teratogenic, coupled with the extremely low likelihood of occupational penetration of skin, respiratory and gastrointestinal barriers, as well as the need for parenteral administration over prolonged periods to achieve therapeutic serum concentrations, please consider the removal of REMICADE from the list of hazardous drugs (Appendix A) of the NIOSH Alert on Antineoplastic and Other Hazardous Drugs in Health Care Settings. We welcome the opportunity to discuss any of the material contained within this letter and thank you, in advance, for your consideration. You may reach me at (215) 325-7264.

Sincerely,

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[i] REMICADE (infliximab) current prescribing information.
[ii] CYTOXAN (cyclophosphamide) current prescribing information.
[iii] TAXOL (paclitaxel) current prescribing information.
[iv] Bos, JD, Meinardi MM. The 500 dalton rule for the skin penetration of chemical compounds and drugs. *Experimental Dermatology*. 2000;9(3):165-9.
[v] Hext PM. Inhalation toxicology, In General and Applied Toxicology. 2nd Ed. Ballantyne B, Marrs T, Syversen T. Vol. 1, Grove's Dictionaries. New York. 587-601.
[vi] Newman SP, Steed KP, Hardy JG, et al. The distribution of an intranasal insulin formulation in healthy volunteers: effect of different administration techniques. *J Pharm Pharmacol*. 1994;46(10):657-60.
[vii] Newman SP, Steed KP, Hooper G, et al. Scintigraphic assessment of the oropharngeal and nasal depositions of fusafungine from a pressurized inhaler and from a novel pump spray device. *J Pharm Pharmacol*. 1995;47(10):818-21.