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Sent:	Wednesday, January 13, 2010 5:25 PM
To:	NIOSH Docket Office (CDC)
Subject:	NIOSH Hazardous Drug List Update; Docket Number NIOSH 105-A
Importance:	High
Attachments:	NIOSH Comts Docket 105-A.pdf

Attached are Biogen Idec's comments on the NIOSH Hazardous Drug List Update published in the April 29, 2009 *Federal Register.* Our comments address the proposed inclusion of Avonex (interferon beta-1a) in the updated "Appendix A. Drugs Considered Hazardous".

If you have any questions regarding these comments or require additional information, please contact us.

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NIOSH Docket Office
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Re: NIOSH Hazardous Drugs List Update; Federal Register Volume 74, Number 81 Pages 19570-19571; 29 April 2009; Docket Number NIOSH-105-A

Dear Sir or Madam:

Biogen Idec wishes to submit comments on the NIOSH draft document entitiled "updating the List of Hazardous Drugs for the NIOSH Alert: Additions and Deletions to the NIOSH Hazardous Drug List" published in the April 29, 2009 Federal Register. This document updates the "NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings", DHHS Publication No. 2004-165 (2004). The handling of hazardous drugs is an important issue for healthcare workers, healthcare organizations and manufacturers, and Biogen Idec supports NIOSH efforts to routinely update the Hazardous Drugs List. We also support NIOSH in assuring that this information is both current and appropriate. To that end, we are providing the following comments regarding the proposed inclusion of AVONEX® (Interferon beta-1a) in the updated "Appendix A. Drugs Considered Hazardous".

AVONEX® is approved for the treatment of patients with relapsing forms of multiple sclerosis (MS) to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

AVONEX® is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of AVONEX® is identical to that of natural human interferon beta (1). Interferons are cytokines that mediate antiviral, antiproliferative and immunomodulatory activities in response to viral infection and other biological inducers. AVONEX® is non-genotoxic, and does

not interfere with cell growth or proliferation or with DNA synthesis. AVONEX® is administered weekly, at a dose of 30 micrograms, by intramuscular injection. AVONEX® is available as a lyophilized formulation and as a liquid formation in a pre-filled syringe, and is predominantly self-injected in the home setting. Parenteral administration is required to achieve a therapeutic response.

Biogen Idec offers the following points to support removal of AVONEX® from the list of drugs under consideration for addition to the Hazardous Drug Alert list:

1. Absorption Requires Parenteral Administration

Occupational exposure traditionally focuses on three exposure pathways: dermal, oral, and inhalation. The skin, pulmonary, and gastrointestinal systems are effective barriers to absorption of high molecular weight proteins, a fact which is demonstrated by the requisite parenteral administration of these therapeutic products. In general, it is thought that compounds with molecular weights greater than 500 Daltons cannot penetrate the stratum corneum. AVONEX®, in contrast, has a large predicted molecular weight of 22,500 Dalton. Research has shown that specialized formulations and inhalational devices are required to achieve substantial systemic absorption through the lung (ref). Thus, it is very unlikely that AVONEX® will be absorbed systematically through the lung by droplets from inadvertent aerosolization of the product in the occupational setting. In addition, based on internal feasibility testing and published literature, AVONEX, like other high molecular weight proteins is too large for absorption through intact skin (2). All other non-injection routes of delivery (including buccal, oral and nasal) have been shown to be virtually impenetrable to macromolecules unless penetration enhancers are used (3). Thus, in the absence of accidental injection, the occupational exposure of AVONEX® is expected to be minimal.

2. Extensive Person-years of Experience Without Accidental Occupational Exposure

AVONEX® was approved in the US in May 1996 (International Birth Date; IBD). Since the IBD to October 2009, it is estimated that 382,350 MS patients have been treated with AVONEX® in the therapeutic setting, resulting in approximately 1,303,500 person years of exposure. Of these patients, approximately 254,600 are from the US and 127,750 are from the EU member states and other countries in which the drug is currently marketed. Despite significant patient utilization of AVONEX®, Biogen Idec has not received any reports of adverse events pertaining to incidental occupational exposure to AVONEX®.

3. Reproductive Data in Animals

AVONEX® was well tolerated in non-clinical studies conducted in Rhesus macaques and was not associated with any organ toxicity. No teratogenic effects or effects on fetal development were observed in studies conducted in Rhesus macaques treated with 33 mcg/Kg of Interferon beta-1a (100 times the recommended weekly human dose of AVONEX®) administered

repeatedly sc (8-15 injections) to pregnant and non-pregnant animals over 16-30 days. This dosing regimen resulted in anovulatory and abortifacient effects which correlated with decreased serum levels of progesterone as measured in both studies. We note that the NIOSH Response to Peer Review Comments dated April 6, 2009 posted in docket 105-A incorrectly characterizes the exposure to interferon beta 1A in this study. This document inaccurately states that the exposure is "3X the human dose equivalent". The FDA approved US full prescribing information states that the exposure in this study is 100 times the recommended human dose. The conclusion presented in this document suggesting that abortifacient effects were observed at low doses in monkeys is erroneous.

4. Human Experience relevant to NIOSH-defined Reproductive toxicity at Therapeutic Doses

AVONEX® is not known to be teratogenic and does not impair fertility in treated patients. Following the approval of an intramuscular injection of AVONEX® at a dose of 30 mcg/week for the treatment of relapsing MS, Biogen Idec has systematically collected and followed-up cases of pregnancy reported during post-marketing experience, and a formal prospective pregnancy registry (the AVONEX® Pregnancy Exposure Registry Study) was initiated. The study is designed to monitor pregnant subjects and fetuses inadvertently exposed to AVONEX® and to detect any potential increase in the risk of major birth defects. It is also designed to detect any potential increase in the risk of spontaneous fetal loss The data from the registry are reviewed on a regular basis by an external panel of experts, the AVONEX® Pregnancy Registry Advisory Committee.. To assure good reporting to the registry, it has been widely publicized through promotional materials and the package insert. In addition, the availability of the registry was incorporated in a Dear Health Care Professional Letter announcing an unrelated safety update to the AVONEX® Full Prescribing Information in 2005. As a result of these efforts, enrollment in the AVONEX Pregnancy Registry increased substantially, allowing prospective evaluation of pregnancy outcomes for a cohort of patients. Through November 2009, the registry currently includes a total of 264 pregnancies, with outcomes available on 231 of the 264 enrolled pregnancies, and the AVONEX® Pregnancy Registry Advisory Committee's conclusion was that the overall rates of defects that are considered major or serious were not increased, nor were there malformations or groups of malformations that were over-represented in the registry data. The Committee found no public health issue or concern regarding AVONEX®-related birth defects (4).

Cumulatively, up to November 2009, Biogen Idec has received a total of 2,295 reports of pregnancies in patients exposed to therapeutic doses of AVONEX®, including the 264 from the AVONEX® Pregnancy Registry. Of these 2,295 reports, 849 pregnancies were reported prospectively and 1,446 were reported retrospectively. The frequency of major and minor malformation using all available AVONEX® prospective pregnancy outcome data are consistent with the CDC's MACDP background rate of major and minor congenital malformations. Thus,

there is no signal of teratogenic or mutagenic effects of AVONEX® in pregnancy. In addition, for the spontaneously reported prospective pregnancy exposures, the rates of spontaneous losses including early pregnancy loss at less than 20 weeks gestation per CDC guidelines, do not exceed the expected rate within the US general population of 10% to 25% (5,6).

In retrospectively reported cases, the rates of spontaneous pregnancy losses appear to be somewhat higher than expected for the US general population. This is not unexpected, since there is an inherent bias toward reporting cases with a negative outcome after the outcome is known. In addition, it is inappropriate to calculate rates of outcomes from retrospective cases, since the denominator for retrospective reports is unknown. Thus, a direct comparison with background rates in the US general population cannot be made.

Published literature does not support teratogenic or mutagenic effects resulting from exposure to AVONEX® during pregnancy. Although some reports indicated possible low birth weight, it is acknowledged that MS itself may result in otherwise normal, low birth weight neonates. Two recent (2009) publications, whose conclusions are commensurate with the cannon of literature on this subject as a whole, are discussed in the following paragraphs.

In the first publication, the authors discussed pregnancy management challenges for physicians and their MS patients in Brazil. Brazilian databases from 9 MS clinical research units were examined and completed data on 47 women (49 pregnancies) were assessed. Seventeen patients included in this analysis had exposure to Interferon beta, one pregnancy resulted in a low birth weight neonate, and 2 were premature births. Of the 17, one patient who received Interferon beta-1a (22mcg, 3 times per week) and corticosteroids at the start of pregnancy had delayed intrauterine growth (7).

The second study concerned assessment of Interferon (IFN) beta-1a, Interferon (IFN) beta-1b and glatiramer acetate (GA) during pregnancy. A prospective observational cohort was performed with patients enrolled through a drug risk assessment by the Teratology Information Service (TIS) in Berlin from 1996-2007. Pregnancy outcomes for 4 groups of women were compared: two exposed groups (IFN, n=69: GA, n=31), MS patients without exposure to any studied agent (n=64), and a healthy comparative group (n=1556). Results revealed spontaneous abortion rates were in the normal range for all groups including IFN beta-1a. The small subgroup exposed to IFN-beta-1b (n=21), experienced 28% of spontaneous abortions. There were 2 major birth defects in the GA group and none in the IFN-beta-1a cohort. Preterm delivery was not significantly different between exposed cohorts and healthy controls. The adjusted mean birth weight was normal range in all groups (>3200g), but newborns exposed to IFN had a significantly lower birth weight. The authors concluded that neither GA nor IFN constitutes a major risk for prenatal developmental toxicity (8).

In summary, data from pre-clinical studies clinical trials, the Pregnancy Registry, post-marketing surveillance, and published data concerning the use of Interferon Beta during

pregnancy suggest no signal for teratogenicity or mutagenicity for cases inadvertently exposed to AVONEX®. Further, the rate of abortions from prospectively reported pregnancy reports in patients exposed to AVONEX® is consistent with the background rate in the general population.

AVONEX® has been used in over 382,000 patients, resulting in approximately 1,303,500 patient-years of exposure. Despite this significant utilization, Biogen Idec has not received any adverse events reports associated with occupational exposure to AVONEX®. Based on this, and the reasons discussed above, Biogen Idec considers inclusion of AVONEX® on the Hazardous Drug Alert list to be inappropriate from a safety perspective. We appreciate NIOSH's consideration of these comments pertaining to AVONEX® and respectfully ask that NIOSH reconsider the inclusion of AVONEX® on the Hazardous Drug Alert.

Sincerely yours,

Mariska Kooijmans-Coutinho, MD, PhD
Acting Head, Drug Safety and Risk Management
Biogen Idec Inc.

References available upon request:

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