Dragon, Karen E. (CDC/NIOSH/EID)

From:	droman@rdg.boehringer-ingelheim.com
Sent:	Thursday, September 20, 2007 3:52 PM
To:	NIOSH Docket Office (CDC)
Cc:	mmcconne@rdg.boehringer-ingelheim.com
Subject:	Boehringer Ingelheim Pharmaceuticals, Inc. Comments on NIOSH Docket Number 105
Importance:	High
Follow Up Flag:	Review
Due By:	Thursday, September 20, 2007 12:00 AM
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Attachments:	NIOSH Docket Number 105 Boehringer Ingelheim Pharmaceuticals Comment 9.20.07.pdf

Dear Ms. Miller:

Attached please find comments on NIOSH Docket Number 105 from Boehringer Ingelheim Pharmaceuticals, Inc. If you have any questions, please do not hesitate to contact me at (203) 228-0287 or my colleague Mary McConnell-Meachen at (203) 798-5075.

Best regards, Donna

Donna Lyn Roman
Director, Government Affairs & Public Policy
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Boehringer Ingelheim
Pharmaceuticals, Inc.

SUBMITTED VIA MAILAND E-MAIL to niocindocket@cdc.gov

September 20, 2007

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Re: Boehringer Ingelheim Pharmaceuticals, Inc. Comments on DHHS (NIOSH) Publication No 2004-165 [NIOSH Docket Number 105]

Dear Ms. Miller:

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) welcomes the opportunity to comment on the public documents noted above that are under review by the National Institute for Occupational Safety and Health (NIOSH) and its peer-review panel of experts. We request that you remove Spiriva® Handihaler® and Viramune® from the Hazardous Drug Alert and provide scientific risk-based explanations supporting our request below. We have also included some general comments on the Drug Alert and the process for updating it for your consideration.

BIPI, based in Ridgefield, CT, is a member of the Boehringer Ingelheim group of companies. The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 144 affiliates in 45 countries and nearly 36,000 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel products of high therapeutic value in the areas of cardiovascular health, respiratory, HIV/AIDS and diseases of the central nervous system. BIPI is the company's worldwide center of excellence in immunology and inflammatory and cardiovascular disease research. The company also represents the primary U.S. clinical research and marketing arm for products developed by other Boehringer Ingelheim companies around the world.

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Request Spiriva® Handihaler® De-listing from the NIOSH Hazardous Drug Alert

BIPI believes Spiriva Handihaler is inappropriately included on the "Alert for Hazardous Drugs." The proposed inclusion of Spiriva in the list of drugs considered hazardous is based entirely on reproductive toxicity findings reported in non-clinical toxicology studies in animals. BIPI believes that Spiriva HandiHaler does not warrant listing in the NIOSH alert for hazardous drugs in health care settings because the observations in the animal studies only occurred in situations where there were clear signs of maternal toxicity, while the exposure to health care workers can only be minimal due to the nature of the compound and its mode and frequency of administration to the patient.

The Spiriva drug product consists of a hard gelatin capsule dosage form containing a dry powder formulation of tiotropium bromide monohydrate for oral inhalation using a hand held device (HandiHaler). The capsules are dispensed in a blister pack to the patient. Each capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) as the pharmacologically active ingredient blended with an inert lactose carrier (5.5 mg), and is placed unopened in the HandiHaler device. Tiotropium is a synthetic quaternary ammonium compound with a high specificity for muscarinic receptors and a long duration of action. Tiotropium is also referred to as an anti-cholinergic. In the airways, tiotropium exhibits pharmacological effects by inhibiting a muscarinic smooth muscle receptor that results in bronchodilation. The bronchodilation following inhalation of tiotropium is predominantly site specific. Spiriva HandiHaler is indicated for once daily treatment of patients with chronic obstructive pulmonary disease (COPD). Tiotropium is delivered to the patient following mechanical puncture of the hard gelatin capsule within the enclosed HandiHaler device. Following the once daily treatment the device is opened and the punctured capsule tipped directly into the trash and the mouthpiece rinsed and dried for subsequent use according to the instructions in the package insert supplied for the information of the patient and health care worker.

Tiotropium is formulated as a powder in a hard gelatin capsule contained within a blister pack. Thus, up to the stage of actuating the HandiHaler device there is no possibility of inadvertent exposure to the patient or the health care provider (e.g., pharmacist, nurse). It is only after use in the HandiHaler that the potential for exposure may exist. The majority of any powder remaining in the intact but punctured capsule will be the inert excipient lactose. However, to avoid even a remote chance of inadvertent exposure to the active ingredient, the Package Insert specifies instructions for use of the HandiHaler, including disposal of the used capsule. The used capsule can be tipped directly from the HandiHaler into the trash without the need to handle it. Thus, there is no actual direct physical contact of the health care provider with any tiotropium residue remaining within the capsule. It is estimated that between 5.5 and 8.0 mcg of tiotropium remains adhered to the inner surface of the used capsule due to its sticky physical attributes. It is also estimated that a further 0.5 to 1.0 mcg remains in the device itself after actuation, this amount is removed and diluted by the rinsing procedure described in the package insert. In the highly unlikely event there is transfer of the tiotropium from the device to the gloves worn by the health care provider or directly to the skin, as a quaternary ammonium compound, no glove penetration or

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dermal absorption of the dry powder is expected. Further, if the powder is transferred from the hands to the mouth and swallowed, oral bioavailability is very low (2-3%). In addition, the likelihood of inhaling any residue that somehow becomes airborne during the disposal process is considered negligible due to it adhering to the inside of the used capsule or it being in an aqueous liquid form. Should the health care worker be inadvertently exposed to tiotropium, the early warning signs of dry mouth and inhibition of saliva occur at doses far below those associated with reproductive toxicity seen in animal studies (see details below).

The potential of tiotropium to induce reproductive toxicity has been studied in a comprehensive set of repeat-dose studies in mice, rats, rabbits and dogs. In repeat-dose studies of up to 2 years duration in rats and mice (highest dose in 2-year carcinogenicity 0.7 mg/kg/day and 0.18 mg/kg/day respectively) and 52 weeks in dogs (highest dose 0.45 mg/kg/day) there was no evidence of any adverse effects in the reproductive organs. The results of the specific reproductive toxicity studies showed that the treatment with tiotropium resulted in neither impairment of fertility in male and female rats, nor was it teratogenic in rats and rabbits. However, at supratherapeutic doses resulting in maternal toxicity the drug was embryo- and feto-toxic in rats at an inhalation dose of 2.0 mg/kg/day and in rabbits, the drug was abortifacient at an oral dose of 100 mg/kg/day and embryocidal and fetotoxic at an inhalation dose of 0.5 mg/kg/day. These supratherapeutic doses were associated with maternal toxicity typified by a reduction in body weight gain a well known consequence of the exaggerated pharmacological activity of high doses of anticholinergic drugs. The reproductive toxicity findings are provided in the package insert and abstracted below.

The PRECAUTIONS section of the Spiriva HandiHaler Package Insert includes a section entitled PREGNANCY. It is within this section that reproductive toxicity information on tiotropium is summarized. The exact language in the PREGNANCY section is noted below:

"*No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m^2 basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation of tiotropium doses of ≥0.078 mg/kg/day (approximately 35 times the RHDD on a mg/m^2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m^2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in inhalation studies. There are no adequate and well-controlled studies in pregnant women. Spiriva should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.*"

The above-captioned section of the Package Insert captures the following concepts. It is clear that tiotropium does not result in structural malformation in rats or rabbits. In other words, tiotropium is not teratogenic in rats or rabbits. Tiotropium does result, however, in fetotoxicity in rats and rabbits. The doses at which fetotoxicity occurs in rats and rabbits is 35 times and 360 times the

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recommended human daily dose (RHDD), respectively. As noted, the ratio of 35 and 360 times the RHDD is conservatively based on mg/m^2 (body surface area) rather than a mg/kg (body weight) basis. It is also reasonable to express the ratio of fetotoxic doses of tiotropium to the RHDD on the basis of mg/kg exposure. Using widely accepted conversion factors, the ratio (when based on mg/kg) increases to 210 and 1,080, for the rat and rabbit versus human, respectively. It is also useful to recalculate the 4- and 80-fold margins of safety based on doses that do not result in fetotoxicity in rats and rabbits. When based on mg/kg exposure, the safety margins in rats and rabbits increase to 24 and 240 times the RHDD, respectively.

The animal studies clearly show that there are sufficient dose multiples between animal and the human clinical dose to assure reasonable safety in patients treated with a nominal dose of 18 mcg tiotropium. In the worst case scenario in which the health care worker is exposed by inhalation to the 0.5 to 1.0 mcg of tiotropium remaining in the device meaning the dose multiples above are increased by a factor of 18 which further emphasizes the safety of health care workers handling tiotropium. For each patient treated with tiotropium the exposure to a health care worker under the worse case scenario would be 0.02 μg/kg (50 kg individual) which is 5,000 times less than the dose in rats (100 μg/kg) that results in maternal toxicity (below which no adverse embryo-fetal effects were seen). Using the principles and uncertainty factors for extrapolating from animal exposures to man outlined in the EPA's "Guidelines for Reproductive Toxicity Risk assessment" tiotropium does not constitute a reproductive risk to humans at the exposures likely to be experienced by health care workers.

In conclusion, based on lack of reproductive health risk, the Spiriva HandiHaler (tiotropium) does not meet the criteria established by NIOSH for inclusion in its Hazardous Drug Alert. Considering the dosage form and route of administration, use and/or handling of the Spiriva Handihaler capsules and the HandiHaler device does not constitute a human health risk to health care workers.

Request Viramune® De-listing from the NIOSH Hazardous Drug Alert

NIOSH has included Viramune (also referred to as nevirapine) for inclusion on its list of new FDA drugs that fit the NIOSH Hazardous Drug Alert criteria. NIOSH based the listing decision on the Package Insert. Specifically, NIOSH has designated cancer, reproductive toxicity, and organ toxicity as the bases for its nevirapine Alert listing. BIPI believes that nevirapine does not warrant listing in the NIOSH alert and provides a scientific risk-based explanation below.

Viramune is formulated as a 200 mg tablet and an oral suspension (50 mg/5 mL). The active drug substance, nevirapine, is a non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type (HIV-1). Nevirapine is structurally a member of the dipyridodiazepinone class of compounds. Nevirapine binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent polymerase activities by causing disruption of the enzyme's catalytic site. Human DNA polymerases α, β, δ, or γ are not inhibited by nevirapine. Viramune is indicated in combination with other antiretrovirals for the treatment of HIV-1 infection.

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The Viramune Package Insert contains a Black Box warning for organ toxicity. Hepatotoxicity, severe, in some cases life-threatening, and in some cases fatal, is mentioned in the Black Box warning as well as severe, life-threatening skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. In addition, hypersensitivity reactions characterized by rash, constitutional findings and organ dysfunction are also mentioned. The WARNINGS section of the Package Insert also focuses on hepatotoxicity, skin reactions, and hypersensitivity reactions providing greater detail.

The PRECAUTIONS section of the Viramune Package Insert includes sections entitled **Carcinogenesis, Mutagenesis, Impairment of Fertility** and **Pregnancy**. It is within these sections that cancer and reproductive toxicity information on nevirapine is summarized. The exact language in the Carcinogenesis, Mutagenesis, Impairment of Fertility section and additional information from the Pregnancy section are noted below.

Carcinogenesis, Mutagenesis, Impairment of Fertility: "Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375, or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 3.5, 17.5 or 35 mg/kg/day for two years, an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies were lower than that measured in humans at the 200 mg BID dose. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames: Salmonella and E.coli), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity for nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine treated mice and rats is not known. In reproductive toxicology studies, evidence of impaired fertility was seen in male rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of VIRAMUNE."

The above-captioned section of the Package Insert captures the following concepts. Nevirapine is carcinogenic in both mice and rats. However, nevirapine is not genotoxic. As such, the relevance of the rodent findings to humans is unknown. In addition, the fact that nevirapine is not genotoxic clearly implies a non-genotoxic mechanism for the hepatic neoplasms in rodents and the presence of a threshold dose below which neoplasms resulting from nevirapine will not occur. Thus, the risk of cancer to nevirapine in humans is not evident. A nevirapine hazard profile is incomplete without mentioning the findings of reduced fertility in male rats.

The **Pregnancy** section of the Nevirapine Package Insert characterizes the reproductive hazard associated with nevirapine. NIOSH lists the Pregnancy Category C for nevirapine. However, this is incorrect and out of date. In fact, nevirapine is assigned a Pregnancy Category B by the FDA.

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Nevirapine is not teratogenic in both rat and rabbit teratogenicity studies. Any fetal toxicity in developing rat or rabbit offspring is attributed to maternal toxicity.

It is reasonable to conclude that the hazard profile for nevirapine includes organ toxicity (liver, skin, hypersensitivity reactions), cancer, and fertility effects. However, NIOSH incorrectly attributes reproductive toxicity to nevirapine. It is not a teratogen.

The hazard profile in animal studies provides only a partial explanation for potential human health risks to health care provider. It is also important to consider the potency and exposure. The Package Insert establishes the doses used clinically. Viramune is administered at an initial dose of 200 mg/day for 2 weeks which is escalated to 400 mg/day. As such, Viramune is not considered to be a potent drug at the doses administered. In the absence of exposure, there is no adverse human health risk. Nevirapine is formulated as a 200 mg tablet and an oral suspension. Handling of these dosage forms does not result in exposure to the patient or the health-care provider (e.g., pharmacist or nurse). There is essentially no product handling and no reconstitution of a lyophilized powder. This there is negligible exposure and hence, essentially no risk to health care providers from handling of nevirapine.

In conclusion, Viramune containing nevirapine is not a reproductive hazard and does not meet the Hazardous Drug Alert criteria as established by NIOSH. Use and/or handling of the Viramune tablets and oral suspension does not constitute a human health risk to health care providers. We appreciate your consideration of our request to remove Viramune from the Hazardous Drug Alert.

Support NIOSH Decision to Exclude Aptivus® from Hazardous Drug Alert

NIOSH has designated Aptivus (also referred to as tipranavir) for inclusion on its list of new FDA drugs that **DO NOT FIT** the NIOSH Hazardous Drug Alert criteria. NIOSH based the listing decision on the Package Insert. BIPI supports the NIOSH decision that Aptivus does not fit the NIOSH criteria. The comments below provide further support for this reasoned and appropriate decision by NIOSH.

Aptivus is formulated as a 250 mg soft gelatin capsule for oral administration. The active drug substance, tipranavir, is a non-peptidic protease inhibitor with activity against Human Immunodeficiency Virus Type (HIV-1). Tipranavir inhibits virus-specific processing of polyproteins in HIV-1 infected cells, preventing formation of mature virions and inhibits replication of HIV-1. Aptivus is indicated in combination with ritonavir for the treatment of HIV-1 infection.

The toxicology data for tipranavir is summarized herein. Long-term carcinogenicity bioassays with tipranavir have been completed recently. The administration of tipranavir at dose levels of 30, 100, and 300 mg/kg/day did not produce any evidence of a direct carcinogenic effect. The slight increased incidence of benign tumors of the liver and thyroid gland were unsurprising in rats, based on the known effects of tipranavir on drug metabolizing enzymes systems. There is no evidence of mutagenicity or clastogenicity in a battery of five *in vitro* and *in vivo* tests (Ames, unscheduled DNA synthesis, mammalian cell gene mutation, chromosome aberration in cultured human cells,

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and micronucleus assay in mice). Tipranavir had no effect on fertility or early embryonic development in rats at dose levels up to 1000 mg/kg/day. No teratogenicity was detected in rats or rabbits at doses up to 1000 mg/kg/day and 150 mg/kg/day, respectively. In pre- and post-development studies in rats, tipranavir showed no adverse effects at 40 mg/kg/day, but caused growth inhibition in pups and maternal toxicity at a dose level of 400 mg/kg/day. No post-weaning functions were affected at any dose level. The FDA has assigned a Pregnancy Category C for tipranavir.

It is always important to consider exposure when assessing risk to a given population (e.g., health-care providers/workers). In the absence of exposure, there is no adverse human health risk. Tipranavir is formulated as a 250 mg soft-gelatin capsule. Handling of this dosage form does not result in exposure to the patient or the health-care provider (e.g., pharmacist or nurse). There is essentially no product handling and no reconstitution of a lyophilized powder. Thus, there is no exposure and hence, no risk to health-care providers from handling of tipranavir.

In conclusion, BIPI agrees with NIOSH that Aptivus containing tipranavir does not meet the NIOSH criteria for a hazardous drug because use and/or handling of the Aptivus capsules does not constitute a human health risk to health care providers.

General Comments

The utility of the NIOSH Hazardous Drug Alert will be lost if the list covers drugs which do not carry a significant and practical occupational risk, and we therefore encourage NIOSH to carefully re-evaluate the list. We believe that it is critical for NIOSH to consider dose-response and bioavailability of a drug as well as mechanisms of action in its hazard assessment process, and also to incorporate weight-of-evidence considerations.

A clear and transparent peer-review system for adding/deleting or updating information on drugs approved by FDA on a periodic basis (e.g., quarterly) is essential to ensure the effectiveness of the NIOSH Hazardous Drug Alert. In order to reduce any unnecessary risk to healthcare professionals/employees, we suggest development of a publicly available repository for this information, preferably available via a web-based link through which the healthcare community can easily access the most up-to-date information. We also strongly encourage NIOSH to share the criteria used to select the NIOSH Alert Committee/Panel of Experts to demonstrate its balanced representation of the healthcare community and support the credibility of its process. In addition to these comments, BIPI is aware of and supports the comments submitted by PhRMA and strongly encourages NIOSH to adopt their recommendations.

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Conclusion

Thank you for this opportunity to comment on the Hazardous Drug Alert. As always, we are pleased to work with NIOSH to protect the safety of the healthcare community. If you have any questions on our comments or recommendations, please feel free to contact me at (203) 798-5075.

Sincerely,

Mary McConnell-Meachen

Mary McConnell-Meachen, CIH, CSP
Executive Director Environmental Affairs & Safety
Environmental Affairs & Safety