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

From: Schwartz, Chuck [Chuck.Schwartz@pfizer.com]

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To: NIOSH Docket Office (CDC)

Subject: NIOSH Docket #105 - HazDrug Update Comments

Attachments: GEODON (ziprasidone) comments - Proposed NIOSH Hazardous Drug Alert Listing.doc; LYRICA (pregabalin) comments - Proposed NIOSH Hazardous Drug Alert Listing.doc; CHANTIX (varenicline) comments - Proposed NIOSH Hazardous Drug Alert Listing.doc

Attached are three documents that outline and support Pfizer Inc's position that neither CHANTIX (varenicline), nor GEODON (ziprasidone), nor LYRICA (pregabalin) meet the definition of "Hazardous Drug" as it appears in Appendix A of NIOSH Publication No. 2004-165, *Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings*.

We have also reviewed our data and concur with NIOSH's position that ERAXIS (anidulafungin) and MACUGEN (pegaptanib sodium) also do not meet the definition.

We appreciate the opportunity provided by NIOSH to contribute to the process of updating the list of hazardous drugs in the Alert. Additional detail on the information discussed in the attached abbreviated summaries, along with relevant references, can be made available to NIOSH and its expert panel of peer reviewers upon request.

Chuck Schwartz, Ph.D., DABT
Director, Toxicology and Hazard Communication
Global EHS Operations
Pfizer Inc
235 E. 42nd St
New York, NY 10017

Phone: (212) 733-7317
Fax: (646) 383-9029
Cell: (917) 601-6465

NIOSH HAZARDOUS DRUG LIST

GEODON (ziprasidone) Response

Pfizer believes that ziprasidone, an antipsychotic agent with dopamine (D_2) and serotonin receptor antagonist activity, does not meet the definition of Hazardous Drug as outlined in Appendix A of NIOSH Publication No. 2004-165. Specifically, Pfizer believes that ziprasidone presents no credible genotoxic or carcinogenic hazard of occupational or clinical relevance. No significant target organ toxicity was observed at occupationally-relevant doses and ziprasidone does not present a reproductive or developmental toxicity hazard.

Regarding the assessment for genotoxic potential, ziprasidone was tested for mutagenic activity at the gene and chromosomal level in several *in vitro* and *in vivo* assays. In the bacterial mutagenicity assay (Ames test), there was a slight increase in mutation frequency in a single strain, and only at the highest concentration tested. This increase was not considered significant, however, as it occurred only at or near insoluble levels of the drug, and did not meet established criteria for a true significant mutagenic response (>3-fold increase in mutation frequency as compared to concurrent vehicle control). The *in vitro* mouse lymphoma assay for gene mutation activity and *in vitro* human lymphocyte chromosomal aberration assay for clastogenicity were also both negative. Two *in vivo* micronucleus assays, the first after oral administration to mice and the second after intramuscular dosing to rats, for the detection of chromosomal aberrations were negative. Based on these data, Pfizer concluded that ziprasidone is not mutagenic or clastogenic.

To definitively determine the carcinogenic potential of ziprasidone, two-year in-feed studies were conducted in rats and mice. In rats, no treatment-related clinical signs were seen and there was no effect on survival over the 24 months of the study. There was no evidence of an increased incidence of tumors in treated animals of either sex as compared to controls. Given the pharmacology of the drug (dopamine receptor antagonism in the pituitary can result in hyperprolactinemia), serum prolactin concentrations were measured and shown to be unaffected by treatment. It was concluded from this study that there was no evidence of a carcinogenic potential in male or female rats as a result of ziprasidone administration at its maximum tolerated dose.

In a similar carcinogenicity study in mice, no treatment related clinical signs were seen and, again, there was no effect on survival over the 24 months of the study. However, there was a statistically significant increase in the incidence of mammary gland adenocarcinomas and pituitary adenomas in females only. In the pituitary, there was also a positive trend for focal/diffuse hyperplasia and increased incidences of mammary gland lobular hyperplasia and galactocoele. Pituitary proliferative lesions were shown by immunohistochemistry to be prolactin producing. There was no other increase in tumor incidence in treated animals, as compared to controls. Regressive changes in the ovaries and uterus were also found; these were considered to be secondary consequences of increased prolactin production.

In a separate 1-month study in mice, serum prolactin levels were increased in females only, consistent with the immunohistochemistry results obtained in the carcinogenicity study.

The hyperprolactinemia and pituitary and mammary gland proliferative lesions are effects also reported in rodents with other antipsychotic compounds with D_2 receptor antagonist activity. Dopamine receptor antagonism stimulates prolactin producing cells in the pituitary gland. The resulting increase in serum prolactin exerts a trophic effect on the mammary gland leading to hyperplasia and adenomas while inhibiting ovarian function. Therefore, the changes observed in the 2-year mouse study are a predictable consequence of treatment of mice with a D_2 receptor antagonist, and similar findings have been reported for several other dopamine receptor antagonists.

In the clinic, ziprasidone, as with other drugs that antagonize dopamine D_2 receptors, has caused an increase in serum prolactin concentration in some patients; however, these levels returned to normal ranges in most patients without cessation of treatment. Importantly, the increase in serum prolactin concentration was only detected in ziprasidone-treated female mice, and not observed in male mice or rats of either sex. While the increased prolactin concentrations correlated with a dose-related increase in the incidence of mammary gland and pituitary tumors in female mice in the carcinogenicity study, there is no evidence that prolactin plays a significant role in human mammary carcinogenesis, and patients with induced or spontaneous hyperprolactinemia have not been shown to be at a higher risk than the normal population.

Collectively, the carcinogenicity studies in rats and mice demonstrated that ziprasidone produces no occupationally-relevant toxicity and is not a genotoxic carcinogen.

(Additional detail on the information discussed herein, along with relevant references, is available upon request.)

NIOSH HAZARDOUS DRUG LIST

LYRICA (pregabalin) Response

Pfizer believes that pregabalin does not meet the definition of Hazardous Drug as outlined in Appendix A of NIOSH Publication No. 2004-165. Specifically, Pfizer believes that there is no hazard to humans related to the species-specific hemangiosarcomas found in mice and that the risk of adverse reproductive or developmental events is negligible. No significant target organ toxicity was observed at occupationally relevant doses and pregabalin was not genotoxic *in vitro* or *in vivo*.

Hemangiosarcoma Formation

Pregabalin was not carcinogenic in rats at exposure up to 24 times the mean human exposure at the maximum recommended human dose, but the incidence of hemangiosarcomas (tumors of the blood vessels) was increased in mice given pregabalin at 5000 mg/kg/day for 2 years. Hemangiosarcomas are spontaneously-occurring tumors in the particular strain of mouse used in this study (B6C3F1 mice). The induction of a single tumor type in a single species, along with a lack of genotoxicity (pregabalin was not mutagenic when tested in several bacterial and mammalian cell assays, did not cause chromosomal aberrations *in vitro* and was negative on both the *in vivo* unscheduled DNA synthesis and micronucleus assays in rats and mice), are together characteristics of epigenetic carcinogens. Because such carcinogens are unlikely to pose a carcinogenic hazard to humans, the epigenetic mechanism resulting in hemangiosarcoma formation was extensively investigated. In these studies, the relationship between increases in platelet activation, bone marrow and splenic megakaryopoiesis (differentiation of hematopoietic stem cells in the bone marrow into mature megakaryocytes, a precursor of platelet formation in the blood), circulating and tissue levels of endothelial growth factors (PDGF and VEGF, respectively), endothelial cell proliferation, and incidence of hemangiosarcomas was established in mice at carcinogenic and noncarcinogenic doses. The temporal relationship between these changes and increased endothelial cell proliferation is consistent with a causal association. Results of studies in rats, monkeys, and humans indicate that the mode of action responsible for tumor formation in mice is specifies specific. Therefore, the tumor findings in mice are not relevant to humans and pregabalin does not represent a carcinogenic risk to humans.

Reproductive / Developmental Effects

Although estrus and estrus stages were prolonged at doses of 1250 and 2500 mg/kg, no effects on fertility were observed in female rats given 500 to 2500 mg/kg prior to mating with untreated males. In male rats, pregabalin administration resulted in decreased sperm motility and decreased fertility at exposures of 250 mg/kg/day, but only at doses that were toxic to the rat; the effects were also seen to be reversible. There were no compound-related effects on sperm parameters in monkeys treated for 69 weeks with doses up to 500 mg/kg/day. Finally, pregabalin did not produce detrimental effects on human reproductive function of healthy male subjects given 600 mg/day for 3 months, based on semen analysis and other secondary parameters, when compared to controls.

Pregabalin induced maternal toxicity in embryo-fetal development studies in rats at ≥500 mg/kg and rabbits at ≥250 mg/kg; toxicity to the developing fetus was not seen until doses of 2500 mg/kg (rats) and 1250 mg/kg (rabbit) were administered. Pregabalin was not teratogenic in mice (doses up to 2500 mg/kg/day), rats (up to 1250 mg/kg/day), or rabbits (up to 500 mg/kg/day). In a prenatal-postnatal toxicity study in rats, pregabalin induced offspring developmental toxicity at ≥250 mg/kg/day, but only in the presence of significant maternal toxicity (significant maternal toxicity at ≥100 mg/kg/day, with minor maternal effects also seen at 50 mg/kg/day). No signs of developmental toxicity were seen at 50 mg/kg/day.

As reproductive / developmental effects were seen only at maternally toxic doses and at levels that clearly exceed the dose cut-off appearing in the Alert (1 mg/kg/day), pregabalin does not represent a reproductive / developmental hazard to workers in the healthcare setting.

(Additional detail on the information discussed herein, along with relevant references, is available upon request.)

NIOSH HAZARDOUS DRUG LIST

Abbreviated CHANTIX (varenicline) Response

Pfizer believes that varenicline does not meet the definition of Hazardous Drug as outlined in Appendix A of NIOSH Publication No. 2004-165. Specifically, Pfizer believes that the risk to humans that varenicline could cause the type of highly unusual tumors of the brown adipose tissue (BAT; hibernomas) seen in a 2-year study in rats is negligible. This belief is based upon differences between BAT-related development and physiology in rats and humans, data that indicate that varenicline is not genotoxic, and the high doses relative to potential for occupational exposure at which this effect was observed in the rat 2-year study (1-mg tablets (clinical dose: ~0.014 mg/kg/day) vs. lifetime dosing at 5 and 15 mg/kg/day). No significant target organ toxicity was observed at occupationally-relevant doses and varenicline does not present a reproductive or developmental toxicity hazard.

Hibernoma Formation

The presence of BAT has been confirmed in almost all mammals. In smaller mammals, such as rodents, BAT is present at birth and develops rapidly after; it is important throughout the rodent lifetime in thermogenesis. In contrast, BAT is present in humans in the fetus, with the maximal amount present at birth. Soon after birth, human BAT becomes devoid of mitochondria and loses it thermogenic capacity, and is present as only vestigial remnants in the adult.

Varenicline was not mutagenic or clastogenic in a battery of genetic toxicology assays: Ames bacterial mutation, CHO/HGRPT mammalian cell mutation test, human lymphocyte cytogenetics *in vitro* assay, or rat micronucleus (cytogenetics) *in vivo* study. Further, no hibernomas were seen in female rats, and a parallel carcinogenicity study in mice did not indicate any carcinogenic potential for humans.

Mechanistically, nicotine is known to increase stimulate the sympathetic nervous system through an increase in norepinephrine levels. In rats, norepinephrine stimulation is considered the most important factor in regulation of BAT-induced thermogenesis. However, norepinephrine stimulation of BAT also results in increased production of free oxygen radicals and decreased apoptosis, which can result in tumorogenesis in rats. The hibernomas seen in the rat study are, therefore, thought to have been an effect secondary to the exaggerated pharmacological stimulation of the nicotinic receptor.

Varenicline, a nicotine receptor agonist, may have triggered this mechanism in male rats, but would present little to no risk of such a cascade in humans. Despite extensive abuse of nicotine in the human population, there are no links between nicotine and hibernoma formation in humans. Indeed, there have been fewer than 200 cases of hibernoma identified in humans and all been benign in nature.

(Additional detail on the information discussed herein, along with relevant references, is available upon request.)