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From: Nancy_Bower@eisai.com
Sent: Thursday, September 29, 2011 2:42 PM
To: NIOSH Docket Office (CDC)
Subject: Submission of comments to NIOSH Docket 190
Attachments: NIOSH rufinamide response_Eisai Inc.doc

NIOSH Docket Office:

Eisai Inc. wishes to submit comments on the NIOSH draft document entitled: "Additions and deletions to the NIOSH Hazardous Drug list"; published in the August 2, 2011 Federal Register. NIOSH Docket 190. This document updates the "NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Health Care Settings."(2004). These comments are contained in the attached Microsoft Word file.

Sincerely,

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NIOSH Docket Office
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Re: NIOSH List of Antineoplastic and Other Hazardous Drugs in Health Care settings 2012: Additions and deletions to the NIOSH Hazardous Drug list; Federal Register Volume 76, Number 148, Page 46299: August 2, 2011

Docket Number: NIOSH-190

Dear Sir or Madam:

Eisai Inc. wishes to submit comments on the NIOSH draft document entitled: "Additions and deletions to the NIOSH Hazardous Drug list"; published in the August 2, 2011 Federal Register. This document updates the "NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Health Care Settings."(2004)

Eisai Inc. recognizes the critical importance of assuring the appropriate identification of hazardous drugs and products used in healthcare settings, and the provision of detailed guidelines for the handling of such products. Eisai also supports NIOSH in assuring that this information is both current and appropriate. To that end, Eisai is providing herein the following comments regarding the proposed inclusion of rufinamide in the updated list of drugs considered hazardous.

Sincerely,

Nancy Bower, MS, DABT
Director, Global Regulatory Affairs – Nonclinical
Eisai Inc.

REGULATORY SUBMITTAL TO THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH) TO REQUEST THAT NIOSH NOT LIST RUFINAMIDE (CAS #: 106308-44-5) AS A HAZARDOUS DRUG

Eisai Inc. (Eisai) recognizes the critical importance of assuring the appropriate identification of hazardous drugs and products used in health care settings, and the provision of detailed guidelines for the handling of such products. Notifying employers and workers in the health care industry of potentially hazardous drugs is important so that appropriate steps can be taken to safely handle these products. There is also a need for a robust process for the identification of hazardous active pharmaceutical ingredients (APIs) and products, to assure the usefulness and applicability of listings of APIs and products that are considered hazardous.

The purpose of this communication is to assess the available data and provide an objective evaluation of the proposed inclusion of rufinamide in the listing of APIs fitting the NIOSH criteria for hazardous drugs. For the reasons outlined within this document, Eisai believes that rufinamide does not meet these criteria, and requests that it be excluded from this list. An overview of the relevant supporting scientific data and rationale is provided.

EXECUTIVE SUMMARY

Rufinamide (the active ingredient in the drug product Banzel®) has been proposed by the National Institute for Occupational Safety and Health (NIOSH) as a hazardous drug, to be added to a list of hazardous drugs previously published in the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings 2004 (NIOSH Alert, 2004).

Eisai does not believe that the scientific data support the listing of rufinamide as a hazardous drug because of the following:

- Rufinamide does not possess the primary characteristics of a hazardous drug, as described in the NIOSH Alert (2004). It does not exhibit carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity, or genotoxicity.
- Rufinamide is well absorbed orally and is given at relatively high doses (as much as 1600 mg/dose, equaling 3200 mg/day) with an acceptable adverse effects profile in patients taking the drug. It therefore does not have organ toxicity at low doses.
- Rufinamide does not have structural or toxicologic characteristics that mimic the compounds currently listed, which are almost entirely cytotoxic anticancer drugs, antivirals, hormonal agents, and immune system modulators.
- When considering rufinamide as a "hazardous drug", the basis provided by NIOSH was that rufinamide may have potential to be a developmental or reproductive toxicant. There have been eight studies evaluating the reproductive and developmental toxicity of rufinamide. The conclusion of these studies is that effects were only observed at doses >20 mg/kg/day in rats or >30 mg/kg in rabbits and were associated with or attributed to maternal toxicity. The human equivalent dose to the no adverse effect dose (NOAEL) in the most sensitive species (i.e., rats) is approximately 230 mg total for a 70 kg human (when normalized to body

surface area). The dose causing developmental toxicity in rats was five-fold higher (equivalent to 1150 mg for a 70 kg human). When extrapolated to the occupational setting, these toxic doses are not relevant to the risk of handling rufinamide in an occupational health care settings as the potential to achieve airborne levels resulting in an exposure to the 1150 mg/day needed to elicit general toxicity that was associated with reproductive or developmental toxicity are unlikely to occur. For example, exposure to a dust concentration of 5 mg/m^3, which is high enough to be visible to the naked eye, for an entire work day would result in inhalation of 50 mg of a material, assuming 10 m^3 of air are breathed in an 8-hour work day in moderate work. The calculated Occupational Exposure Limit (OEL) for rufinamide is 3 mg/m^3. Based on the extreme circumstance described above, the OEL for rufinamide would, for an entire work day, result in inhalation of 30 mg of a material, assuming 10 m^3 of air are breathed in an 8-hour work day in moderate work. This exposure delivers a dose that is approximately 8- and 38.5-fold lower than the extrapolated NOAEL and toxic dose, respectively, for developmental toxicity. In an occupational health care setting, 3200 mg per day is the maximum recommended dose either as an oral suspension or as coated tablets that can be crushed or divided (an option as per prescribing information) to facilitate administration. Approximately 7% of the daily dose would have to be inhaled on repeated days by the health care worker to theoretically achieve the extrapolated NOAEL for developmental toxicity; however, there is no evidence that rufinamide has a long residence time in tissues (Perucca et al., 2008). Therefore, there is a reasonable margin of safety (8-fold minimum) from the dose that does not cause reproductive or developmental toxicity (NOAEL) to the amount that could be breathed in an occupational health care setting under conditions of maximum exposure to inhalable material.

- The potential for exposure to health care workers is reduced by the dosage form of the drug. The NIOSH Alert describes conditions for exposure in the handling of hazardous materials, with a focus on handling of liquid, powdered or lyophilized drugs where spills or inhalation may contribute to accidental exposure. With respect to solid oral dosage forms, specific concern is noted for handling of uncoated tablets. The primary dosage form of rufinamide is a coated tablet. The maximum prescribed dose of rufinamide is 1600 mg BID, equating to four 400 mg tablets BID. An oral suspension is also marketed as an alternative to crushing or dividing tablets for those patients who have difficulty swallowing a tablet. Eisai specifies in the prescribing information controlled conditions to reduce potential exposure of health care providers who prepare the suspension. Exposure through handling with these dosage forms is therefore significantly less than other dosage forms such as uncoated tablets.
- Eisai has developed an OEL for rufinamide developmental toxicity using current and scientifically defensible approaches to establishing these values, which are equivalent to NIOSH Recommended Exposure Limits (RELs) and OSHA Permissible Exposure Limits. This OEL for reproductive and developmental toxicity, based on a conservative no-effect dose for maternal toxicity in humans, was calculated to be 3 mg/m^3. Therefore, to reach a threshold level of concern, occupational exposure to rufinamide would have to reach levels 300 times greater than the standard OEL (i.e., 10 $\mu g/m^3$) used by NIOSH to define a "hazardous drug".

The scientific data summarized within this document supports Eisai's position that rufinamide does not meet the criteria established by NIOSH for a "hazardous drug". Eisai requests that NIOSH not list rufinamide with other much more significantly potent and toxic drugs in the

NIOSH Alert, so that adequate precautions are taken for true hazards of more relevant concern to occupational health care workers.

INTRODUCTION

The NIOSH criteria for defining a hazardous drug is the following (NIOSH Alert, 2004):

1. Carcinogenicity
2. Teratogenicity or other developmental toxicity [††]
3. Reproductive toxicity [††]
4. Organ toxicity at low doses [††]
5. Genotoxicity [‡‡]
6. Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria.

[††]All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses. For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg per day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 $\mu g/m^3$ after applying appropriate uncertainty factors [Sargent and Kirk 1988; Naumann and Sargent 1997; Sargent et al. 2002]. OELs in this range are typically established for potent or toxic drugs. Under all circumstances, an evaluation of all available data should be conducted to protect health care workers.

The following will review the clinical and nonclinical data for rufinamide and determine its applicability to the NIOSH definition of a "hazardous drug" which is described above.

SUMMARY OF HUMAN AND NONCLINICAL TOXICITY DATA

General Toxicity Profile

In the United States, rufinamide is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). LGS is a rare and severe form of epilepsy (FDAa, 2011). Consequently, rufinamide was approved by FDA as an orphan drug, which by definition is intended to treat less than 200,000 people in the United States (approximately 0.06% of the US population). The recommended starting dose in adults is 200 to 400 mg/day BID, (400 to 800 mg/day), given orally, which is then increased every other day until a maximum daily dose of 1600 BID (3200 mg/day) (FDAa, 2011).

Rufinamide is an antiepileptic agent that is structurally distinct from other marketed drugs of this class (Kluger, 2009). Although the precise mechanism of action is unknown, results of in vitro studies suggest that it exerts its effects through modulation of sodium channels in neurons (FDAa, 2011). This prolongs their inactive states and limits their firing frequency.

Rufinamide is well absorbed after ingestion, though the extent of absorption decreases with increasing dose (FDAa, 2011; Perucca et al., 2008). Absolute systemic bioavailability after a single dose of 600 mg is 85%, and peak plasma levels are achieved within 6 hours post-dosing. A high degree of interindividual variability has been reported (Cheung, 1995). Rufinamide is extensively metabolized to inactive metabolites and is excreted almost entirely via urine, with an elimination half-life of 6 to 10 hours (FDAa, 2011). There is no evidence that rufinamide has a long residence time in tissues (Perucca et al, 2008). No data are available on inhalation absorption but it is assumed to be similar to oral absorption for the purposes of determining occupational health risk. This is important for assessing risk as the doses causing significant effects in laboratory animals and humans are moderate to high. Since absorption and inhalation absorption are both considered to be high, data from oral dosing can be used to determine potential occupational exposure risk without modification due to any differences.

The most commonly observed (≥10%) adverse reactions in rufinamide-treated patients, when used as adjunctive therapy at all doses studied (200 to 3200 mg/day) with a higher frequency than in placebo, were headache, dizziness, fatigue, somnolence, and nausea (FDAa, 2011). Although they occur infrequently, rufinamide use may also cause shortening of the QT interval, hypersensitivity reactions, and exacerbation of suicidal thoughts (FDAa, 2011).

Rufinamide is considered to be well-tolerated in animals after single doses. In the rodent studies, a single oral dose of 3000 or 5000 mg/kg was associated with transient clinical signs, but did not result in deaths. In dogs, a single oral dose of 2000 mg/kg resulted in emesis but did not result in deaths. Thus, the oral LD_{50} in rats and mice would be >5000 mg/kg and >2000 mg/kg in dogs (EMA, 2007).

Repeated-dose toxicity studies in laboratory animals have been conducted in several laboratory species, including non-human primates. In repeated-dose studies in rats up to 52 weeks in duration, orally administered rufinamide up to 600 mg/kg/day resulted in adverse effects that included CNS effects and alterations of liver morphology indicative of species-specific enzyme induction. Effects on rat pituitary and thyroid function that were considered species-specific were also reported (EMA, 2007). The lowest No-Observed-Effect-Level (NOEL) in these rat studies was 20 mg/kg/day.

In dogs given rufinamide orally up to 600 mg/kg/day for up to 12 months, the primary findings were species-specific effects on the bile and the liver. These effects were identified as being associated with increased bile flow associated with increased bile viscosity and the resulting biliary stasis (EMA, 2007). The NOAEL of <20 mg/kg/day, was based on histopathologic findings. Because these histopathologic findings were species-specific, this is not considered the NOAEL for evaluating the toxicity from repeated exposure and extrapolation to effects in humans.

In repeated-dose studies conducted in non-human primates given rufinamide orally up to 300 mg/kg/day for up to 12 months, abnormal crystals were found in the bile and gallbladder wall. These crystals were identified as being comprised of a cysteine-S-conjugate of a hydroxylated metabolite of rufinamide, a metabolite not formed in humans (EMA, 2007).

Therefore, this effect was considered species-specific and the lowest NOAEL for this effect, 20 mg/kg/day, is not considered the NOAEL for evaluating the toxicity from repeated exposure and extrapolation to effects in humans.

In summary, the general toxicity profile of rufinamide is that it exhibits low toxicity, but clinical efficacy, at moderate doses in humans, and low to moderate toxicity in laboratory animals. The spectrum of effects that defined the NOAELs in laboratory animals after repeated dosing were species specific effects, therefore the NOAELs from these studies are overly conservative for extrapolation of the no effect dose to humans. Additionally, the spectrum of effects observed was not typical of many of the compounds on the NIOSH hazardous drug list, which are primarily cytotoxic agents having an effect on rapidly dividing cells, such as those of the hematologic, gastrointestinal and reproductive systems.

Genotoxicity/Carcinogenicity

Rufinamide lacks genotoxic and carcinogenic potential based on the available data. Rufinamide was negative in several short-term screening tests for mutagenicity (FDAa, 2011; Bialer et al., 2001), and did not exhibit clastogenicity in the in vitro or in vivo assays (FDAa, 2011).

Rufinamide was tested in long-term carcinogenicity studies in mice and rats. An increased incidence of benign and malignant liver tumors was observed in mice given 400 mg/kg (FDAa, 2011, EMA, 2007). These liver effects are considered to be a high-dose, rodent-specific effect not relevant to humans (EMA, 2007). In mice given 400 mg/kg, benign bone tumors were observed (FDAa, 2011; EMA, 2007). This effect was hypothesized to be associated with the activation of a mouse-specific virus (as detected by electron microscopy) and therefore not relevant to humans (EMA 2007). An increased incidence of thyroid adenomas in rats was associated with doses $\geq$60 mg/kg/day (FDAa, 2011). This effect was consistent with a rat-sensitive mechanism (UDP-GT induction altering thyroid hormone homeostasis) that has not been associated with a human health risk (Hayes, 2001).

Reproductive/Developmental Toxicity

A comprehensive oral developmental and reproductive toxicity database has been generated for rufinamide.

In a fertility and reproductive toxicity study in rats, the LOAEL identified by FDA was 20 mg/kg (FDAb, 2008). The effects on conception rate, mating index and fertility index in this study noted by FDA in the Pharmacology Review of rufinamide tablets (FDAb, 2008) are within the range of historical control data of the testing facility and do not exhibit any dose-response relationships. Similarly, the preimplantation loss at 20 mg/kg noted in the review documentation should not be considered when establishing the NOAEL in this second study because of the following reasons: a) there was no dose response in this study, b) the control value was near the low end of the historical range for the strain of rat used in the study, c) there was a lack of effects on other fetal parameters at the 20 mg/kg dose, d) the values were all within normal range, and e) there was no obvious effect of dose response in the prior study. Therefore, Eisai considers the NOAEL to be 60 mg/kg (equivalent to 9.7 mg/kg in humans).

Embryo-fetal development was fully investigated in rats and rabbits, with a preliminary study performed in mice. In the main/definitive rat embryo-fetal developmental study at doses of 20, 100, and 300 mg/kg/day, effects on fetal weights and skeletal anomalies and variations due to growth retardation were observed at the doses ≥100 mg/kg. These findings were observed at doses which caused maternal toxicity. The NOAEL was identified as 20 mg/kg (equivalent to 3.2 mg/kg in humans) (FDAa, 2011).

In the main/definitive rabbit embryo-fetal developmental study at doses of 30, 200, and 700 mg/kg/day, similar findings were seen with increased incidences of skeletal variations accompanied by reductions in fetal weights and maternal toxicity at the higher doses. An additional rabbit study in which doses up to 1000 mg/kg/day were examined revealed no clear adverse effect upon embryo-fetal development at any dose level, although maternal toxicity was observed at 1000 mg/kg. The NOAEL was identified as 30 mg/kg (equivalent to 9.7 mg/kg in humans) (FDAb, 2008). No teratogenic potential was observed in any animal species.

Perinatal and postnatal investigations were performed in mice and rats. In mice, there were no adverse effects on dams or pups at up to 500 mg/kg and the NOAEL was 500 mg/kg. However, in rats, decreased F_1 pup survival (lactation Days $0-4$) was observed at all dose levels (15 - 150 mg/kg) (EMA, 2007). This finding was similar to that seen in the fertility study where the same effects were observed at maternally toxic doses. In a follow-up cross-fostering study using a 150 mg/kg dose, the decreased pup survival was indicative of an effect of rufinamide in utero during late gestation. A limited second cross-fostering study with treatment at 150 mg/kg showed reduced survival in pups from treated dams which were cross-fostered to control dams (due to in utero exposure) and in pups from control dams which were cross-fostered to treated dams (due to maternal toxicity). As in the other studies where decreased pup survival was observed, maternal toxicity was seen. A final pre- and postnatal toxicity study described the NOAEL of 30 mg/kg for F_0 females and F_1 offspring (EMA, 2007). No toxicologically significant behavioral or developmental changes were seen in the pups after birth.

As mentioned previously, studies performed for the assessment of reproductive and development toxicity as well as other endpoints are required by current testing guidelines to establish a maximum tolerated dose (MTD), which is operationally defined in toxicology as the highest daily dose of a chemical that does not cause overt toxicity. The MTDs for rufinamide in the reproductive and developmental toxicity studies conducted in mice, rats and rabbits were associated with maternal toxicity and were 50 mg/kg and higher. Despite the presence of maternal toxicity, teratogenicity was not observed. The NOAELs for fetal effects were between 20 and 500 mg/kg across the various reproductive and developmental toxicity studies. The concentrations of aerosolized rufinamide equivalent to these doses would not be achievable in practice in a health care setting for limited handling of tablets or for dispensing a liquid suspension using the controlled conditions specified in the prescribing information.

Occupational Exposure Limit (OEL)

The typical approach for determining an OEL is to identify a no-observed-adverse-effect-level (NOAEL)[1] from animal or human studies and then to apply appropriate uncertainty, or safety, factors, as necessary (Lehman and Fitzhugh, 1954; Sargent and Kirk, 1988; Galer et al., 1992; Naumann and Weideman, 1995, Baird et al., 1996; Dourson et al., 1996). Eisai has used these approaches for determining an OEL for rufinamide. The typical equation used for determining an OEL by this approach is:

$$OEL = [(NOAEL)\ (BW)] / [(SF)_n\ (BR)]$$

where:

NOAEL = no-observed-adverse-effect-level for the most sensitive adverse effect;

BW = body weight of an adult worker, typically assumed by default to be 70 kg;

$(SF)_n$ = a number of safety factors that considers such uncertainties as animal-to-human variability in response, human-to-human variability in response, bioavailability by different routes of exposure, biological half-life, quality of the available data, etc.; and

BR = breathing rate of an adult worker, typically assumed by default to be 10 m^3/8-hour workday.

If an appropriate NOAEL cannot be identified, then an appropriate lowest-observed-adverse-effect-level (LOAEL) may be used. This LOAEL is typically adjusted by a safety factor of up to 10, or even higher, depending on the severity of the adverse effect. For instance, if the LOAEL is for minor liver toxicity, the safety factor used may be 3; if the LOAEL is for developmental toxicity, the safety factor used may be 10. For pharmaceuticals, the low end of the therapeutic dose range sometimes may be used as a surrogate for the LOAEL (Schwartz, 1995; Ku, 2000). If the NOAEL is based on animal data, then a safety factor of up to 10 is typically considered to accommodate for animal-to-human extrapolation. A safety factor up to 10 is considered to accommodate possible human-to-human variability in response. Other issues including the duration of exposure and the quality and robustness of the available data are considered for the determination of the magnitude of this and other safety factors.

Eisai believes that the most appropriate point of departure (i.e., adverse health endpoint) to set an OEL for reproductive and developmental toxicity for rufinamide is the 800 mg/day dose by oral administration given to patients. At this dose, a minimal increase in the incidence of side effects compared to placebo was reported. Therefore, this dose is considered a LOAEL. This point of departure was considered preferable to extrapolation from animal studies given that the reproductive and developmental effects in animals only occurred in the presence of maternal

[1] NOAELs and NOELs are frequently used interchangeably, as are LOAELs and LOELs; these terms are used interchangeably in this submission.

toxicity. It is assumed that humans would be similar to animals in that reproductive and developmental toxicity would only occur at doses that caused adverse effects in the mother.

As rufinamide is considered well absorbed orally based on the available data and assumed to be well absorbed after inhalation exposure, no bioavailability adjustment is needed in estimating an OEL. A safety factor is applied to this LOAEL, dependent on the severity of the adverse effects. In the case of rufinamide, a safety factor of 3 was considered adequate to adjust the LOAEL to a NOAEL, as the identified toxicity endpoints pertain to the central nervous system. A safety factor of 10 is used to accommodate for human-to-human variability in response due to limited studies conducted to date. Then, by taking the typical breathing rate assumption of 10 m^3/8-hour workday for a 70 kg adult, the rufinamide OEL for reproductive and developmental toxicity is:

OEL = (800 mg/day)/[(3)(10)(10 m^3/day)] = 2.667 mg/m^3.

Rounded to one significant figure, the estimated OEL for rufinamide becomes 3 mg/m^3.

Therefore, to reach a threshold level of concern for reproductive and developmental toxicity, occupational exposure to rufinamide would have to reach levels 300 times greater than the standard OEL (10 µg/m^3) used by NIOSH to define a "hazardous drug".

SUMMARY AND RATIONALE FOR NOT LISTING RUFINAMIDE ON NIOSH HAZARDOUS DRUG ALERT

Rufinamide is a pharmacologically active substance used for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, a rare and severe form of epilepsy. Rufinamide was approved by FDA as an orphan drug, which by definition is intended to treat less than 200,000 people in the United States (approximately 0.06% of the US population). Eisai believes that it is not a "potent drug" by industry definitions or a "hazardous drug" by NIOSH definitions (NIOSH, 2004). Rufinamide does not possess significant pharmacologic potency to require special handling by health care employees and lacks the cytotoxic and other properties of most currently listed products.

Specifically for the reproductive and developmental toxicity effects described by NIOSH as nominating it for consideration for listing, the lowest NOAEL for rufinamide is 20 mg/kg in the rat (human equivalent dose of 230 mg based on a 70 kg human). Rufinamide was not teratogenic in the developmental toxicity studies conducted, and the effects observed in the reproductive and developmental toxicity studies do not appear to be caused by direct toxicity to the reproductive organs or embryofetal tissues, but rather most likely occur secondary to maternal toxicity. The human equivalent dose (≥1150 mg based on a 70 kg human) to that which caused findings in animals cannot be achieved occupationally in a health care setting for limited handling of coated tablets or for dispensing a liquid suspension of the product, even if small numbers of the tablets were crushed or divided (an option as per prescribing information) to facilitate administration. Consequently rufinamide is not likely to pose a significant risk of harm to health care workers.

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