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**Sent:** Monday, October 03, 2011 5:23 PM
**To:** NIOSH Docket Office (CDC)
**Subject:** 190 - NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2012: Proposed Additions and Deletions to the NIOSH Hazardous Drug List
**Attachments:** 2011-09-30 NIOSH Request to Not List Televancin as Hazardous Drug.doc

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# REGULATORY SUBMITTAL TO THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH) TO REQUEST THAT NIOSH NOT LIST TELEVANCIN HYDROCHLORIDE (CAS #:560130-42-9) AS A HAZARDOUS DRUG

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 is recognized. It is important that employers and workers in the health care industry are notified and have taken appropriate steps to 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 may be considered hazardous.

The purpose of this communication is to assess the available data and provide an objective evaluation in considering the proposed inclusion of telavancin in the listing of APIs fitting the NIOSH criteria for hazardous drugs. For the reasons outlined within this document, Theravance, Inc. ("Theravance") believes that telavancin 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

Telavancin hydrochloride ("telavancin") (the active ingredient in the drug product **VIBATIV®**) 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).

Theravance does not feel that the scientific data support the listing of telavancin as a hazardous drug because of the following:

- Telavancin does not possess the primary toxicological characteristics of a hazardous drug, as described in the NIOSH Alert (2004). It is not considered to be genotoxic, carcinogenic, or a reproductive toxicant, and does not cause toxicity or pharmacological effects at low doses. It is given at relatively high doses (10 mg/kg administered over 60 minutes by intravenous infusion once every 24 hours for 7 to 14 days or approximately 500 to 700 mg/day to a 50 -70 kg patient) with a relatively low adverse effects profile in patients taking the drug.
- When considering telavancin as a hazardous drug, the basis provided by NIOSH was that telavancin may have potential to be a developmental toxicant. Although the current labeling of the drug product indicates that the compound may be a potential teratogen, further evaluation of the studies conducted in three species indicates that effects were at high doses, are questionable in terms of their conclusion, and occur at very low rates. Established protocols for the conduct of reproductive and developmental studies, as adopted by the FDA and other regulatory authorities

require the highest dose to be a toxic dose, either maternally or to the developing fetus. These toxic doses when extrapolated to the occupational setting are not "occupationally relevant" to the risk in handling televancin in health care settings as the potential to achieve dust or aerosol concentrations that would result in a level resulting in a dose of grams/day are unlikely to occur. For example, exposure to an aerosol or 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, as 10 $m^3$ of air are breathed in a 8-hour work day in moderate work. This would not be achievable in practice in a health-care setting for limited handling of the product. Therefore, there is a considerable margin of safety from the dose that may cause developmental toxicity to the amount that could be breathed in a health-care setting under conditions of maximum exposure to inhalable material.

- Televancin does not have the toxicological characteristics common to the compounds currently listed, which are almost entirely cytotoxic anticancer drugs and sex steroid hormones. Furthermore FDA has not required that the current product labeling contain special handling procedures similar to many of the other compounds on the NIOSH hazardous drug list.
- Televancin's clinical use is as an antibiotic; other antibiotics which cause effects on the developing fetus at high doses are not listed by NIOSH as hazardous drugs, because like televancin, effects observed are at high clinical doses, and are rare. For example "mycin"-compounds such as streptomycin, cause ototoxicity to the developing fetus at high therapeutic doses. Presumably NIOSH has reviewed these compounds and found them not to present the same risks or hazards as the cytotoxic or highly potent drugs currently on the NIOSH list of hazardous drugs as the basic premise of "the dose makes the poison" has been applied to listing of compounds.
- Theravance has developed an Occupational Exposure Limit (OEL) for televancin 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 was determined to be 0.7 $mg/m^3$ as an 8-hour time-weighted average over a 40-hour work week, a value 70 times the criteria described in the NIOSH Alert as being hazardous. The rationale for the OEL is provided in the following document.

The scientific data summarized within this document supports Theravance's position that televancin does not meet the criteria established by NIOSH for a "hazardous drug". Theravance requests that NIOSH not list televancin with other much more significantly potent and toxic drugs in the NIOSH Alert, so that adequate precautions are taken for hazards of more relevant concern to health care workers. The following provides further scientific evidence to support the request that televancin not be listed.

## 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 few milligrams or less). 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 in the pharmaceutical industry. 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 telavancin 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*

Telavancin is indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and –resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius,* and *S. constellatus)*, or *Enterococcus faecalis* (vancomycin-susceptible isolates only) (Astellas, 2009). The recommended dosing for telavancin is 10 mg/kg administered over a 60-minute period in patients ≥18 years of age by intravenous infusion once every 24 hours for 7 to 14 days. This dose is equivalent to 500 mg for an average weight woman (50 kg) and 700 mg for an average weight man (70 kg).

Most common adverse reactions (≥10% of patients treated with telavancin include: taste disturbance, nausea, vomiting, and foamy urine (Astellas, 2009). Increases in serum creatinine to 1.5 times baseline occurred more frequently among telavancin-treated patients with normal baseline serum creatinine (15%) compared with vancomycin-treated

patients with normal baseline serum creatinine (Astellas, 2009). Additionally, it may cause QTc prolongation at clinical doses (Astellas, 2009).

Acute and repeated dose studies indicate a relatively low to moderate degree of toxicity. A single-dose toxicity study in mice found the minimum lethal dose to be 100 mg/kg, with the maximum tolerated dose for males being 50 mg/kg and 35 mg/kg for females (Health Canada, 2010). A similar study in rats found the minimum lethal dose to be 100 mg/kg for males and >150 mg/kg for females. The maximum tolerated dose was considered to be 50 mg/kg for male rats and 150 mg/kg for female rats (Health Canada, 2010).

Long-term toxicity studies of 2, 4, and 13 weeks were conducted in rats and dogs, and a 26-week study was conducted in rats (Health Canada, 2010). In the 2-week study with rats that received telavancin 25 mg/kg/day, an increased incidence of granular casts and positive urine occult blood tests were noted. Renal tubular vacuolation was also present. In the 2-week toxicity study in dogs, however, no clinical or anatomical pathology findings were seen with the dose of 25 mg/kg/day. After 4 weeks of 50 mg/kg/day in rats, telavancin was associated with increased levels of blood urea nitrogen (BUN) and creatinine. Renal tubular degeneration, renal tubular vacuolation, and urothelial cell vacuolation were also observed. These effects occurred at a drug exposure similar to those measured in the clinical trials. In the 4-week study in dogs using 50 mg/kg/day, hypersensitivity (histamine) reactions during the first week of dosing were seen. Pathologic changes were confined to multifocal bilateral renal (cortical) tubular dilatation. Renal tubular vacuolation and renal tubular degeneration/necrosis were also present, as well as vacuolation of the urothelium of the renal pelvis and urinary bladder.

After 13 weeks of 50 and 100 mg/kg/day in rats, the effects were consistent with the findings of hepatocyte degeneration and proximal tubular degeneration (Health Canada, 2010). The 13-week toxicity study in dogs resulted in histamine reactions during the first 3 weeks of dosing. Increases in aspartate aminotransferase (AST), alanine transaminase (ALT), BUN and creatinine were also noted. Hepatocellular degeneration/necrosis was seen, as well as macrophage vacuolation in a variety of tissues and organs (liver, kidneys, lungs, lymph nodes, spleen, esophagus, heart, and salivary gland), parenchyma kidney lesions (tubular vacuolation, dilatation, necrosis, and eosinophilic cytoplasmic inclusions), urothelial vacuolation in the kidneys, prostatic urethra and urinary bladder, and tubular vacuolation in the epididymides. The 26-week study in rats resulted in lower red blood cell (RBC) counts, hemoglobin, and hematocrit, as well as increased BUN, creatinine, AST, and ALT. Microscopic alterations included vacuolation of diffuse cortical tubular epithelial cells, renal tubular dilation/casts, vacuolation of epididymal epithelial cells, vacuolation of epithelioid venules, and macrophage hypertrophy/hyperplasia.

*Pharmacokinetics*

In healthy young adults, the pharmacokinetics of telavancin administered intravenously were linear following single doses from 5 to 12.5 mg/kg and multiple doses from 7.5 to 15 mg/kg administered once-daily for up to 7 days (Astellas, 2009). Steady-state

concentrations were achieved by the third daily dose. Telavancin binds to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The mean binding is approximately 90% and is not affected by renal or hepatic impairment.

Televancin is not extensively metabolized (Astellas, 2009). In a mass balance study in male subjects using radiolabeled telavancin, 3 hydroxylated metabolites were identified with the predominant metabolite (THRX-651540) accounting for <10% of the radioactivity in urine and <2% of the radioactivity in plasma. The metabolic pathway for telavancin has not been identified. Telavancin is primarily eliminated by the kidney. In a mass balance study, approximately 76% of the administered dose was recovered from urine and <1% of the dose was recovered from feces (collected up to 216 hours) based on total radioactivity.

*Genotoxicity/Carcinogenicity*

Neither mutagenic nor clastogenic potential of telavancin was found in a battery of tests including: assays for mutagenicity (Ames bacterial reversion), an in vitro chromosome aberration assay in human lymphocytes, and an in vivo mouse micronucleus assay (Astellas, 2009).

*Reproductive Toxicity*

Telavancin did not affect the fertility or reproductive performance of adult male rats (exposed to telavancin for at least 4 weeks prior to mating) or female rats (exposed to telavancin for at least 2 weeks prior to mating) (Astellas, 2009).

*Developmental Toxicity*

The current US labeling for televancin states the following (Astellas, 2009):

> "In embryo-fetal development studies in rats, rabbits, and minipigs, telavancin demonstrated the potential to cause limb and skeletal malformations when given intravenously during the period of organogenesis at doses up to 150, 45 or 75 mg/kg/day, respectively. These doses resulted in exposure levels approximately 1- to 2-fold the human exposure (AUC) at the maximum clinical recommended dose. Malformations observed at <1% (but absent or at lower rates in historical or concurrent controls), included brachymelia (rats and rabbits), syndactyly (rats, minipigs), adactyly (rabbits), and polydactyly (minipigs). Additional findings in rabbits included flexed front paw and absent ulna, and in the minipigs included misshapen digits and deformed front leg. Fetal body weights were decreased in rats. In a prenatal/perinatal development study, pregnant rats received intravenous telavancin at up to 150 mg/kg/day (approximately the same AUC as observed at the maximum clinical dose) from the start of organogenesis through lactation. Offspring

> showed decreases in fetal body weight and an increase in the number of stillborn pups. Brachymelia was also observed. Developmental milestones and fertility of the pups were unaffected."

So in summary, the labeling states that at very high doses in animals, a very low percent of limb effects occurred.

Because of these findings, a further evaluation was performed by Dr. Anthony Scialli (a Board-certified obstetrician-gynecologist with subspecialty training in reproductive and developmental toxicology) in order to assess the importance of these findings (Theravance, 2008).

Key findings from his assessment are summarized below (Theravance, 2008).

In rats, decreases in mean maternal body weight, mean maternal body weight gain and food consumption in the mid- and/or high-dose groups (approximately 1.1- and 1.6-fold, respectively, the plasma exposures of patients) indicated that there was maternal toxicity at these doses, consistent with appropriate dose selection. There was a decrease in fetal weight in the mid and high dose groups. This effect was not pronounced and was only detected using the fetus rather than the litter as the experimental unit. Two fetuses with malformations were noted. One fetus in the mid dose group had protruding tongue, "brachymelia" of the left hindlimb, syndactyly of the left hindlimb, and anophthalmia. One fetus in the high dose group had "brachymelia" of the left hindlimb. Although the study author indicated that the "brachymelia" (short limb) noted on external examination in one high-dose and one mid-dose fetus was considered treatment-related, the independent consultant, Dr. Scialli, disagreed with this conclusion because the observation of short limb on external examination is nonspecific and potentially unreliable. In this study, for instance, the mid-dose fetus with "brachymelia" had no long-bone abnormalities on skeletal examination, calling into question whether there was a limb malformation at all and the highdose fetus with "brachymelia" was not evaluated skeletally, because it was selected by coin toss for visceral evaluation. Therefore, the conclusion of the independent review was that no actual limb abnormalities were documented in this study. Dr. Scialli also noted that the report author had chosen to use the term "brachymelia" rather than the more commonly used term, "micromelia." Micromelia is identified in historical data bases, leading to the conclusion that this finding was within the historical control range. Therefore, the independent review concluded that it is not clear that either of the fetuses in this study truly had a treatment-related limb-shortening abnormality.

In the embryofetal toxicity study in rabbits, maternal toxicity characterized by decreases in body weight, body weight gain, and food consumption was also noted at the highest dose tested indicating that the study was designed appropriately. No effects were noted on fetal weight nor were there statistically significant increases in external, visceral, or skeletal malformations. A number of fetal abnormalities were noted, including:

- One fetus in the high-dose group with limb abnormalities consisting of absence of the ulna and absence of one digit. This fetus also had gastroschisis, diaphragmatic hernia, and gallbladder agenesis.
- Another high-dose fetus from a different litter with an umbilical hernia.
- Three additional fetuses from three different high-dose litters with fusion of the sternebrae
- One additional fetus in a separate litter with a bipartite vertebral centrum, fusion of a pair of ribs, and forking of a rib.

Dr. Scialli noted that although the sternebral, vertebral, and rib abnormalities were considered malformations, their clinical significance is doubtful (Theravance, 2008). Fused sternebrae, a malformation that occurs spontaneously in control litters and that has been associated with maternal toxicity in rat and rabbit studies, was isolated to one litter. While the report author considered 75 mg/kg/day an effect level based on the number and severity of fetal malformations seen at this dose level, Dr. Scialli disagreed with this conclusion. The basis for Dr. Scialli's opinion was that clinically significant malformations in this study were limited to one fetus in the control group with cardiomegaly, one fetus in the high-dose group with multiple malformations, and one fetus in a separate litter with umbilical hernia. Given the diverse nature of these malformations, it was not possible to conclude that there was a treatment-related effect.

The findings in the study in minipigs included fetuses with limb abnormalities in one of the control groups, in the low-dose group, and in the mid-dose group, but none in the high-dose group (i.e., it was not dose-response related) (Theravance, 2008). The limb abnormalities were primarily polydactyly, which is known to occur spontaneously in the minipig. Polydactyly was seen in one fetus in the control group, four fetuses in three litters in the low-dose group, and five fetuses in three litters in the middose group. One of the fetuses with polydactyly in the mid-dose group appeared to have a misshapened leg due to absence of the radius. Another mid-dose fetus, in a litter not otherwise affected, had syndactyly. The report author indicated that because these abnormalities occur spontaneously in the minipig and because the high-dose group was not affected, the abnormalities were not treatment related. While Dr. Scialli noted difficulties in interpretation of the minipig study due to poor reproductive performance, he was in agreement with the author that the highest dose tested, 75 mg/kg/day was a no-effect level. Dr. Scialli concluded that the primary evidence of an adverse developmental effect was a reduction in litter weight in a study in rats and that there was no clear evidence of teratogenicity in any of the developmental studies. After evaluating the few observed limb defects, he noted that there was no embryologically coherent mechanism by which a common malformation syndrome could be postulated to have been caused by telavancin.

So in summary, the developmental effects are doubtful, occur rarely and are at high doses. These doses and associated concentrations in air would not be achievable in practice in a health-care setting for handling of this drug product as these doses could not be achieved in reconstitution unless the entire amount was ingested by the health care worker (highly unlikely to occur).

***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). Theravance has used these approaches for determining a preliminary OEL for televancin. 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.

The most appropriate point of departure (i.e., adverse health endpoint) to set an OEL for televancin is the 10 mg/kg/day dose by intravenous administration given to patients. This dose is considered a LOAEL. This point of departure was considered preferable to animal studies given that the effects in animals were at higher doses. In addition, even if a point of departure based on the most sensitive animal toxicity studies was used, the resultant OEL was similar to the OEL estimated herein based on human data (calculations not shown).

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

As televancin is assumed to be well absorbed after inhalation exposure and the doses used are from intravenous dosing (also totally bioavailable), 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 televancin, a safety factor of 10 was used to adjust the LOAEL to a NOAEL, to be protective of potential effects (developmental and nephrotoxicity). A safety factor of 10 is used to accommodate for human-to-human variability in response. Then, by taking the typical breathing rate assumption of 10 $m^3$/8-hour workday for a 70 kg adult, the televancin OEL is:

OEL = (10 mg/kg/day) (70 kg)/[(10)(10)(10 $m^3$/day)] = 0.7 mg/$m^3$.

This value is more than 70 times the criteria described by NIOSH as defining a "hazardous drug" and provides a significant margin of safety from any health effects reported from clinical and non-clinical studies.

## SUMMARY AND RATIONALE FOR NOT LISTING TELEVANCIN ON NIOSH HAZARDOUS DRUG ALERT

Televancin is a pharmacologically active substance used for the treatment of skin infections. It is not a "potent" drug by industry definitions or a "hazardous drug" by NIOSH definitions (NIOSH Alert, 2004). It does not possess significant pharmacological potency to require special handling by health care employees and lacks the cytotoxic and other properties of currently listed products.

Specifically for the endpoint described by NIOSH as nominating it for consideration for listing, developmental toxicity, effects that were considered questionable upon further review were at doses equivalent to the clinical dose of 500-700 mg/day. These doses cannot be achieved occupationally, and consequently televancin is not likely to pose a significant risk of harm to health-care workers. The margin of safety from doses which cause pharmacological, clinical or toxicological effects to the dose or concentration that may cause development effects is high, and adequately protective of worker health.

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