NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings:
Proposed Additions to the NIOSH Hazardous Drug List 2018
Peer Review Comments

The tables below provide the independent peer reviews received regarding NIOSH's proposal to place or not place drugs on the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2018 (List)*. Peer reviewers provided comments on each drug screened and evaluated by NIOSH, as described in the Federal Register notice published in NIOSH Docket 233-B.

The peer reviewers' comments in the tables below are organized by drug. Both generic and proprietary drug names are provided for ease of determining the drug reviewed and criteria. For each drug, the comments received are organized by the categories in the NIOSH Hazardous Drug definition: carcinogenicity, genotoxicity, organ toxicity at low dose, reproductive toxicity, and teratogenicity or other developmental toxicity as defined in the *Policy and Procedures*. If there were no comments provided by the peer reviewers for a criterion, only the criterion is listed. NIOSH reviewed the peer reviewers' comments and the available information for each drug and considered these to establish the **NIOSH Rationale for Proposing to Place or Not Place on the *List*.**

In accordance with NIOSH policy, attribution of specific peer reviewer comments is blinded in this document.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
bevacizumab	Avastin	*Carcinogenicity* - No studies of carcinogenicity or mutagenicity. - No studies conducted. - No carcinogenicity or mutagenicity studies of bevacizumab have been conducted. - No carcinogenicity or mutagenicity studies of bevacizumab have been conducted.
		Genotoxicity - No Studies conducted. - No carcinogenicity or mutagenicity studies of bevacizumab .have been conducted.
		Organ toxicity at low doses - Ovarian failure. - Reproductive and acute toxicity regarding wound healing, bleeding and thrombosis.
		Reproductive Toxicity - Significant Insult to organogenesis in rabbits at HD; PI says scrupulous contraception: significant ovarian failure (34%vs 2%) in treated pts. - Embryo-fetal toxicity. Congenital malformations in rabbits at clinical dose. Advise contraception during treatment and for 6 months after last dose. - Advise female patients of 636 reproductive potential to use effective contraception during treatment with Avastin and for 6 months 637 following the last dose of Avastin. [See Use in Specific Populations (8.1).] 638 Infertility 639 Females 640

		Avastin increases the risk of ovarian failure and may impair fertility. Inform females of 641 reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long 642 term effects of Avastin exposure on fertility are unknown. 643 In a prospectively designed substudy of 179 premenopausal women randomized to receive 644 chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin 645 arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, 646 recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. - Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.
		Teratogenicity or Other Developmental Toxicity - Skeletal malformations at all dose levels. - Dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects [see Data]. - In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development.
		Rationale for Proposing To Place on the List
		Reproductive Toxicity and teratogenicity or other developmental toxicity: ovarian failure in patients in clinical trials, embryo-fetal toxicity in rabbits.

Generic Drug Name	Proprietary Name	Peer Reviewer Comments
blinatumomab	Blincyto	*Carcinogenicity* - No studies conducted. - Not tested. - No information. - No carcinogenicity or genotoxicity studies have been conducted with blinatumomab.
		Genotoxicity - Not tested. - No studies conducted. - No carcinogenicity or genotoxicity studies have been conducted with blinatumomab.
		Organ toxicity at low doses - B and T cell depletion, neurotoxicity.
		Reproductive Toxicity - No reproduction studies conducted. - Limited to mice; no adverse effects were observed. - No studies have been conducted to evaluate the effects of blinatumomab on fertility. A murine surrogate molecule had no adverse effects on male and female reproductive organs in a 13-week repeat-dose toxicity study in mice.
		Teratogenicity or Other Developmental Toxicity - None. - May cause fetal harm. - In embryo-fetal developmental toxicity studies, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause embryo-fetal toxicity or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice, but hematological effects were not assessed in fetuses.
		Rationale for Proposing To Place on the List
		Organ toxicity at low doses: neurotoxicity at low doses in patients in clinical studies.

Generic Drug Name	Proprietary Name	Peer Reviewer Comments
botulinumtoxins	Botox, Dysport	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity

		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing To Place on the List
		Organ toxicity at low doses and Teratogenicity or Other Developmental Toxicity: spread of toxin effects; reductions in fetal body weight and decreased fetal skeletal ossification at human dose.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
ceritinib	Zykadia	*Carcinogenicity* - Studies not conducted. - Not performed. - Carcinogenicity studies have not been performed with ceritinib.
		Genotoxicity - CA (chromosomal aberration) in *in vitro* cytogenetic assay using human lymphocytes and micronuclei. - Ceritinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay but induced numerical aberrations (aneugenic) in the *in vitro* cytogenetic assay using human lymphocytes, and micronuclei in the *in vitro* micronucleus test using TK6 cells. Ceritinib was not clastogenic in the *in vivo* rat micronucleus assay.
		Organ toxicity at low doses - Hepatotoxicity; pancreatitis. - Target organs in nonclinical animal models included, but were not limited to, the pancreas, biliopancreatic/bile ducts, gastrointestinal tract, and liver. Pancreatic focal acinar cell atrophy was observed in rats at 1.5-fold the human exposure by AUC at the recommended dose. Biliopancreatic duct and bile duct necrosis was observed in rats at exposures equal to or greater than 5% of the human exposure by AUC at the recommended dose. Bile duct inflammation and vacuolation were also noted in monkeys at exposures equal to or greater than 0.5-fold the human exposure by AUC at the recommended dose. Frequent minimal necrosis and hemorrhage of the duodenum was exhibited in monkeys at 0.5-fold the human exposure by AUC, and in rats at an exposure similar to that observed clinically.
		Reproductive Toxicity - Embryofetal toxicity; maternal toxicity and abortion in rabbits; embryolethality in rabbits. - Embryolethal at doses less than 0.5 the human dose - No human data; There were no adverse effects on male or female reproductive organs in general toxicology studies conducted in monkeys and rats at exposures equal to or greater than 0.5- and 1.5-fold, respectively, of the human exposure by AUC at the recommended dose of 750 mg.

		- There are no data on the effect of ceritinib on human fertility. Fertility/early embryonic development studies were not conducted with ceritinib. There were no adverse effects on male or female reproductive organs in general toxicology studies conducted in monkeys and rats at exposures equal to or greater than 0.5- and 1.5-fold, respectively, of the human exposure by AUC at the recommended dose of 750 mg.
		Teratogenicity or Other Developmental Toxicity - Significant insult to organogenesis in rabbits at HD (human dose); Package Insert says scrupulous contraception: significant ovarian failure (34%vs 2%) in treated patients. - Increased skeletal anomalies in rats and rabbits a doses below the recommended human dose; visceral anomalies including absent or malpositioned gallbladder. - Potential risk to fetus; In animal studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits. - In an embryo-fetal development study in which pregnant rats were administered daily doses of ceritinib during organogenesis, dose-related skeletal anomalies were observed at doses as low as 50 mg/kg (less than 0.5-fold the human exposure by AUC at the recommended dose). Findings included delayed ossifications and skeletal variations. - In pregnant rabbits administered ceritinib daily during organogenesis, dose-related skeletal anomalies, including incomplete ossification, were observed at doses equal to or greater than 2 mg/kg/day (approximately 0.015-fold the human exposure by AUC at the recommended dose). A low incidence of visceral anomalies, including absent or malpositioned gallbladder and retroesophageal subclavian cardiac artery, was observed at doses equal to or greater than 10 mg/kg/day (approximately 0.13-fold the human exposure by AUC at the recommended dose). Maternal toxicity and abortion occurred in rabbits at doses of 35 mg/kg or greater. In addition, embryolethality was observed in rabbits at a dose of 50 mg/kg.
		Rationale for Proposing To Place on the List
		Teratogenicity or Other Developmental Toxicity; embryo-fetal toxicity at low doses in rats and rabbits

Generic Drug Name	Proprietary Name	Peer Reviewer Comments
clobazam	Onfi	*Carcinogenicity* - Not adequately assessed. In rats: increased incidence of thyroid follicular cell adenomas (high dose). - The carcinogenic potential of clobazam has not been adequately assessed. In a limited study in rats, oral administration of clobazam (4, 20, and 100 mg/kg/day) for 2 years resulted in an increased incidence of thyroid follicular cell adenomas in males at the high dose. Mutagenesis Clobazam and the major active metabolite, N-desmeth. - The carcinogenic potential of clobazam has not been adequately assessed. - In a limited study in rats, oral administration of clobazam (4, 20, and 100 mg/kg/day) for 2 years resulted in an increased incidence of thyroid follicular cell adenomas in males at the high dose.
		Genotoxicity - Negative *in vitro* and *in vivo.* - Clobazam and the major active metabolite, N-desmethylclobazam, were negative for genotoxicity, based on data from a battery of *in vitro* (bacteria reverse mutation, mammalian clastogenicity) and *in vivo* (mouse micronucleus) assays.
		Organ toxicity at low doses - None
		Reproductive Toxicity - Impaired at doses above maximum recommended human dose of 40 mg/day. - Embryolethality at high doses in rats and rabbits, rabbits greater than rats by dose. - In a study in which clobazam (50, 350, or 750 mg/kg/day) was orally administered to male and female rats prior to and during mating and continuing in females to gestation day 6, increases in abnormal sperm and pre-implantation loss were observed at the highest dose tested. The no effect level for fertility and early embryonic development in rats was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, less than those in humans at the maximum recommended human dose of 40 mg/day. - In a study in which clobazam (50, 350, or 750 mg/kg/day) was orally administered to male and female rats prior to and during mating and continuing in females to gestation day 6, increases in abnormal sperm and pre-implantation loss were observed at the highest dose tested. The no effect level for fertility and early embryonic development in rats was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, less than

		those in humans at the maximum recommended human dose of 40 mg/day.
		Teratogenicity or Other Developmental Toxicity - Animals: fetal malformations at doses below therapeutic range. Rats: Embryofetal mortality and fetal skeletal variations at all doses. In rabbits: decreased fetal body weight, increased fetal malformations. Low effect dose for developmental toxicity below MRHD (maximum recommended human dose). - In animals at <human dose, neurobehavior and immune abnormalities in pre-natal animal exposure. - Available human data on the risk of teratogenicity associated with benzodiazepines are inconclusive. There is insufficient evidence in humans to assess the effect of benzodiazepine exposure during pregnancy on neurodevelopment. Administration of benzodiazepines immediately prior to or during childbirth can result in a syndrome of hypothermia, hypotonia, respiratory depression, and difficulty feeding. In addition, infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period. Data for other benzodiazepines suggest the possibility of adverse developmental effects (including long-term effects on neurobehavioral and immunological function) in animals following prenatal exposure to benzodiazepines at clinically relevant doses. - In a study in which clobazam (150, 450, or 750 mg/kg/day) was orally administered to pregnant rats throughout the period of organogenesis, embryofetal mortality and incidences of fetal skeletal variations were increased at all doses. The low effect dose for embryofetal developmental toxicity in rats (150 mg/kg/day) was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, lower than those in humans at the maximum recommended human dose (MRHD) of 40 mg/day. - Oral administration of clobazam (10, 30, or 75 mg/kg/day) to pregnant rabbits throughout the period of organogenesis resulted in decreased fetal body weights, and increased incidences of fetal malformations (visceral and skeletal) at the mid and high doses, and an increase in embryofetal mortality at the high dose. Incidences of fetal variations were increased at all doses. The highest dose tested was associated with maternal toxicity (ataxia and decreased activity). The low effect dose for embryofetal developmental toxicity in rabbits (10 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam lower than those in humans at the MRHD.

		- Oral administration of clobazam (50, 350, or 750 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased embryofetal mortality at the high dose, decreased pup survival at the mid and high doses and alterations in offspring behavior (locomotor activity) at all doses. The low effect dose for adverse effects on pre- and postnatal development in rats (50 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam lower than those in humans at the MRHD (maximum recommended human dose).
		Rationale for Proposing To Place on the List
		Reproductive Toxicity and teratogenicity or other developmental toxicity: embryo-fetal mortality and other harm at low doses in rats and rabbits, present in human breast milk.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
cobimetinib	Cotellic	*Carcinogenicity* - Second malignancies; cutaneous and non-cutaneous. - No studies conducted, secondary cutaneous and non-cutaneous malignancies in treated patients. - *Carcinogenicity* studies with cobimetinib have not been conducted. - Carcinogenicity studies with cobimetinib have not been conducted.
		Genotoxicity - Not genotoxic. - Cobimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in bone marrow of rats.
		Organ toxicity at low doses - Cardiomyopathy; ocular toxicity; hepatotoxicity. - Retinopathy, rhabdomyolysis, liver toxicity.
		Reproductive Toxicity - Based on animal findings, may reduce fertility in females and males. - Yes. - Based on findings in animals, COTELLIC may reduce fertility in females and males of reproductive potential. - No dedicated fertility studies have been performed with cobimetinib in animals; however, effects on reproductive tissues observed in general toxicology studies conducted in animals suggest that there is potential for cobimetinib to impair fertility. In female rats, degenerative changes included increased apoptosis/necrosis of corpora lutea and vaginal epithelial cells at cobimetinib doses approximately twice those in humans at the clinically recommended dose of 60 mg based on body surface area. In male dogs, testicular degeneration occurred at exposures as low as

		approximately 0.1 times the exposure in humans at the clinically recommended dose of 60 mg.
		Teratogenicity or Other Developmental Toxicity - Teratogenic and embryotoxic in animals at 0.9-1.4 times the recommended human dose. Fetal malformation of great vessels and the skull. - In animal reproduction studies, oral administration of cobimetinib in pregnant rats during organogenesis was teratogenic and embryotoxic at exposures (AUC) that were 0.9 to 1.4-times those observed in humans at the recommended human dose of 60 mg [see Data]. - Administration of cobimetinib to pregnant rats during the period of organogenesis resulted in increased post-implantation loss, including total litter loss, at exposures (AUC) of 0.9–1.4 times those in humans at the recommended dose of 60 mg. Post-implantation loss was primarily due to early resorptions. Fetal malformations of the great vessels and skull (eye sockets) occurred at the same exposures.
		Rationale for Proposing To Place on the List
		Reproductive Toxicity and teratogenicity or other developmental toxicity: increased post-implantation loss, including total litter loss in rats at low doses; post-implantation loss and fetal malformations in humans.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
darbepoetin alfa	Aranesp	*Carcinogenicity* - Not evaluated in long-term studies. - The carcinogenic potential of Aranesp has not been evaluated in long-term animal studies. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. - The carcinogenic potential of Aranesp has not been evaluated in long-term animal studies. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type.
		Genotoxicity - Negative mutatogen or clastogen. - None. - Aranesp was not mutagenic or clastogenic under the conditions tested. Aranesp was negative in the *in vitro* bacterial reverse mutation assay, the *in vitro* mammalian cell gene mutation assay (using CHO [Chinese hamster ovary] cells), and in the *in vivo* mouse erythrocyte micronucleus assay.

		Organ toxicity at low doses - None.
		Reproductive Toxicity - Slightly reduced fetal weight. Increased post-implantation loss in rats. - Increased post-implantation loss in rats. - When Aranesp was administered intravenously during organogenesis to pregnant rats (gestational days 6 to 15) and rabbits (gestational days 6 to 18), no evidence of direct embryotoxic, fetotoxic, or teratogenic outcomes were observed at the doses tested, up to 20 mcg/kg/day. This animal dose level of 20 mcg/kg/day is approximately 20-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication. The only adverse effect observed was a slight reduction in fetal weight, which occurred only at doses causing exaggerated pharmacological effects in both the rat and rabbit dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. - Aranesp increased the incidence of post-implantation losses in rats. Male and female rats received intravenous doses prior to and during mating; then females were treated 3 times weekly during the first trimester of gestation (gestation days 1, 3, 5, and 7). No effect on reproductive performance, fertility, or sperm assessment parameters were detected at any of the doses evaluated (up to 10 mcg/kg, administered 3 times weekly). The dose of 10 mcg/kg is more than 10-fold higher than the clinical recommended starting dose. An increase in post-implantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg, administered 3 times weekly. The dose of 0.5 mcg/kg is approximately equivalent to the clinical recommended starting dose. Signs of exaggerated pharmacology were not observed in the mother receiving 0.5 mcg/kg or less, but were observed at 2.5 mcg/kg and higher.
		Teratogenicity or Other Developmental Toxicity - None. - Slightly lower birth weights in rats. - When Aranesp was administered intravenously during organogenesis to pregnant rats (gestational days 6 to 15) and rabbits (gestational days 6 to 18), no evidence of direct embryotoxic, fetotoxic, or teratogenic outcomes were observed at the doses tested, up to 20 mcg/kg/day. This animal dose level of 20 mcg/kg/day is approximately 20-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication. The only adverse effect observed was a slight reduction in fetal weight, which occurred only at doses causing exaggerated pharmacological effects in both the rat and rabbit dams

		(1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. - No significant placental transfer of Aranesp was observed in rats; placental transfer was not evaluated in rabbits. - In a peri/postnatal development study, pregnant female rats were treated intravenously with Aranesp day 6 of gestation through day 23 of lactation at 2.5 mcg/kg and higher every other day. Pups of treated mothers had decreased fetal body weights, which correlated with slight increases in the incidences of fetal death, as well as delayed eye opening and delayed preputial separation. The offspring (F1 generation) of the treated rats were observed postnatally; rats from the F1 generation reached maturity and were mated; no Aranesp-related effects were apparent for their offspring (F2 generation fetuses).
		Rationale for Proposing To Place on the List
		Carcinogenicity: progression or recurrence of several cancers in studies of patients with cancer; reduced body weight in offspring at low doses in rats and rabbits.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
dihydroergotamine	Migranal	*Carcinogenicity* - No information. - Tests on-going. - Assessment of the carcinogenic potential of dihydroergotamine mesylate in mice and rats is ongoing. - Assessment of the carcinogenic potential of dihydroergotamine mesylate in mice and rats is ongoing.
		Genotoxicity - Clastogenic *in vitro* CA (chromosomal aberration) assays, but not *in vivo* tests. - Pos. clastogen in 2 *in vitro* CA; negative Ames. Negative *in vivo* mouse MN (micronucleus test). - Dihydroergotamine mesylate was clastogenic in two *in vitro* chromosomal aberration assays, the V79 Chinese hamster cell assay with metabolic activation and the cultured human peripheral blood lymphocyte assay. There was no evidence of mutagenic potential when dihydroergotamine mesylate was tested in the presence or absence of metabolic activation in two gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster V79/HGPRT assay) and in an assay for DNA damage (the rat hepatocyte unscheduled DNA synthesis test). Dihydroergotamine was not clastogenic in the *in vivo* mouse and hamster micronucleus tests.

		Organ toxicity at low doses - No. - Rare fibrotic complications (pleural and retroperitoneal) but at high doses.
		Reproductive Toxicity - Oxytocic properties; contraindicated during pregnancy. - Impairment of fertility was not evaluated for D.H.E. 45® (dihydroergotamine mesylate) Injection, USP. There was no evidence of impairment of fertility in rats given intranasal doses of Migranal® Nasal Spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposures [AUC (area under the curve)] approximately 9 to 11 times those in humans receiving the MRDD of 4 mg). - There was no evidence of impairment of fertility in rats given intranasal doses of Migranal Nasal Spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposures [AUC] approximately 9 to 11 times those in humans receiving the MRDD of 4 mg).
		Teratogenicity or Other Developmental Toxicity - Rats: decreased fetal weight; skeletal ossification at 0.4-1.2 times human exposure doses. No effect dose not established. Similar effects in rabbits at 2.5 times human exposure doses - Yes, no NOEL (No Observed Effect Level) observed. - Developmental toxicity has been demonstrated in experimental animals. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.
		Rationale for Proposing To Place on the List
		Reproductive Toxicity: oxytocic properties at low doses in humans

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
exenatide	Bydureon	*Carcinogenicity* - Risk of thyroid C-cell tumors (adenomas and carcinomas) at clinically relevant doses in rats. - A 104-week carcinogenicity study was conducted with exenatide extended-release in male and female rats at doses of 0.3, 1.0, and 3.0 mg/kg (2-, 9-, and 26-times human systemic exposure based on AUC, respectively) administered by subcutaneous injection every other week. A statistically significant increase in thyroid C-cell tumor incidence was observed in both males and females. The incidence of C-cell adenomas was statistically significantly increased at all doses

		(27%-31%) in females and at 1.0 and 3.0 mg/kg (46% and 47%, respectively) in males compared with the control group (13% for males and 7% for females). A statistically significantly higher incidence of C-cell carcinomas occurred in the high-dose group females (6%), while numerically higher incidences of 3%, 7%, and 4% (nonstatistically significant versus controls) were noted in the low-, mid-, and high-dose group males compared with the control group (0% for both males and females). - 104-week carcinogenicity study was conducted with exenatide extended-release in male and female rats at doses of 0.3, 1.0, and 3.0 mg/kg (2-, 9-, and 26-times human systemic exposure based on AUC, respectively) administered by subcutaneous injection every other week. A statistically significant increase in thyroid C-cell tumor incidence was observed in both males and females. The incidence of C-cell adenomas was statistically significantly increased at all doses (27%-31%) in females and at 1.0 and 3.0 mg/kg (46% and 47%, respectively) in males compared with the control group (13% for males and 7% for females). A statistically significantly higher incidence of C-cell carcinomas occurred in the high-dose group females (6%), while numerically higher incidences of 3%, 7%, and 4% (nonstatistically significant versus controls) were noted in the low-, mid-, and high-dose group males compared with the control group (0% for both males and females). An increase in benign fibromas was seen in the skin subcutis at injection sites of males given 3 mg/kg. No treatment-related injection-site fibrosarcomas were observed at any dose. The human relevance of these findings is currently unknown. - A 104-week carcinogenicity study was conducted with exenatide, the active ingredient in BYDUREON, in male and female rats at doses of 18, 70, or 250 mcg/kg/day (3-, 6-, and 27-times human systemic exposure based on AUC, respectively) administered by once-daily bolus subcutaneous injection. Benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups. - In a 104-week carcinogenicity study with exenatide, the active ingredient in BYDUREON, in male and female mice at doses of 18, 70, or 250 mcg/kg/day administered by once-daily bolus subcutaneous injection, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 16 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. The carcinogenicity of exenatide extended-release has not been evaluated in mice.

		Genotoxicity - Negative Ames, chromosomal aberration (CA) in Chinese hamster Ovary, *in vivo* mouse micronucleus assay. - Not mutagenic or clastogenic (Ames, CA [chromosomal aberration] or micronucleus assays). - BYDUREON and exenatide, the active ingredient in BYDUREON, were not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells. Exenatide was negative in the *in vivo* mouse micronucleus assay.
		Organ toxicity at low doses - Pancreatitis. - Fatal and non-fatal pancreatitis and renal impairment.
		Reproductive Toxicity - Reduced fetal growth. - Decreased fetal growth at all doses in rat. - In mouse fertility studies with exenatide, the active ingredient in BYDUREON, at twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day, males were treated for 4 weeks prior to and throughout mating, and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 760 mcg/kg/day, a systemic exposure 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. - In female mice given twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, beginning 2 weeks prior to and throughout mating until gestation day 7, there were no adverse fetal effects at doses up to 760 mcg/kg/day, systemic exposures up to 148 times the human exposure resulting from the maximum recommended dose of 2 mg/week, based on AUC.
		Teratogenicity or Other Developmental Toxicity - Reduced fetal growth and skeletal ossification in rats. Cleft palate and irregular fetal skeletal ossificationin mice at exposure equal to humans. Irregular fetal skeletal ossification in rabbits at 4 times the human exposure - Increased cleft palates and reduced skeletal ossification at human dose. - In animal developmental studies, exenatide, the active ingredient of BYDUREON, caused cleft palate, irregular skeletal ossification, and an increased number of neonatal deaths. - Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1, or 3 mg/kg on gestation days 6, 9, 12, and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain).

		There was no evidence of malformations. Doses of 0.3, 1, and 3 mg/kg correspond to systemic exposures of 3, 7, and 17 times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on AUC (area under the curve). - In pregnant mice given twice-daily subcutaneous doses of 6, 68, 460, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through 15 (organogenesis), cleft palate (some with holes), and irregular fetal skeletal ossification of rib and skull bones were observed at 6 mcg/kg/day, a systemic exposure equal to the human exposure resulting from the maximum recommended dose of 2 mg/week, based on AUC (area under the curve). - In pregnant rabbits given twice-daily subcutaneous doses of 0.2, 2, 22, 156, or 260 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through 18 (organogenesis), irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a systemic exposure 4 times the human exposure resulting from the maximum recommended dose of 2 mg/week, based on AUC. - In pregnant mice given twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through lactation day 20 (weaning), an increased number of neonatal deaths was observed on postpartum days 2 to 4 in dams given 6 mcg/kg/day, a systemic exposure equal to the human exposure resulting from the maximum recommended dose of 2 mg/week, based on AUC (area under the curve).
		Rationale for Proposing To Place on the List
		Carcinogenicity and teratogenicity or other developmental toxicity: thyroid C-cell tumors in rat studies; adverse fetal effects in rats and rabbits.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
interferon beta-1b	Betaseron, Extavia	*Carcinogenicity* - Not tested. - BETASERON has not been tested for its carcinogenic potential in animals. - BETASERON has not been tested for its carcinogenic potential in animals.
		Genotoxicity - Ames negative; *in vitro* CA (chromosomal aberration) negative. - Not genotoxic. - Betaseron was not genotoxic in the *in vitro* Ames bacterial test or the *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes. Betaseron treatment of

		mouse BALBc- 3T3 cells did not result in increased transformation frequency in an *in vitro* model of tumor transformation.
		Organ toxicity at low doses - Hepatic failure
		Reproductive Toxicity - Spontaneous abortions in humans and rhesus monkeys. No fertility impairment. - No reproductive toxicity. - Administration of BETASERON (doses of up to 0.33 mg/kg/day) to normally cycling female rhesus monkeys had no apparent adverse effects on either menstrual cycle duration or associated hormonal profiles (progesterone and estradiol) when administered over three consecutive menstrual cycles. The highest dose tested is approximately 30 times the recommended human dose of 0.25 mg on a body surface area (mg/m^2) basis. The potential for other effects on fertility or reproductive performance was not evaluated. - Administration of BETASERON (doses of up to 0.33 mg/kg/day) to normally cycling female rhesus monkeys had no apparent adverse effects on either menstrual cycle duration or associated hormonal profiles (progesterone and estradiol) when administered over three consecutive menstrual cycles. The highest dose tested is approximately 30 times the recommended human dose of 0.25 mg on a body surface area (mg/m^2) basis. The potential for other effects on fertility or reproductive performance was not evaluated.
		Teratogenicity or Other Developmental Toxicity - No. - Dose related abortifacient in monkeys at 3 times human dose. - When Betaseron (doses ranging from 0.028 to 0.42 mg/kg/day) was administered to pregnant rhesus monkeys throughout the period of organogenesis (gestation days 20 to 70), a dose-related abortifacient effect was observed. The low-effect dose is approximately 3 times the recommended human dose of 0.25 mg on a body surface area (mg/m^2) basis. A no-effect dose for embryo-fetal developmental toxicity in rhesus monkeys was not established.
		Rationale for Proposing To Place on the List
		Reproductive Toxicity: spontaneous abortions in human clinical trials.

Generic Drug Name	Proprietary Name	Peer Reviewer Comments
isotretinoin	Accutane	*Carcinogenicity* - Increased incidence of pheochromocytoma in rats.
		Genotoxicity - Weak positive Ames test.
		Organ toxicity at low doses - Acute pancreatitis and hepatitis.
		Reproductive Toxicity Testicular atrophy in dogs at high doses over 30 weeks.
		Teratogenicity or Other Developmental Toxicity - Multiple abnormalities in humans. - Birth defects which have been documented following Accutane exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported. Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.
		Rationale for Proposing To Place on the List
		Teratogenicity or Other Developmental Toxicity: severe fetal malformations in humans at any dose.

Generic Drug Name	Proprietary Name	Peer Reviewer Comments
ivabradine	Corlaner	*Carcinogenicity* - None in rats and mice up to 104 weeks. - There was no evidence of carcinogenicity when mice and rats received ivabradine up to 104 weeks by dietary administration. High doses in these studies were associated with mean ivabradine exposures of at least 37 times higher than the human exposure (AUC0-24hr [area under the curve from 0-24 hours]) at the MRHD (maximum recommended human dose). - There was no evidence of carcinogenicity when mice and rats received ivabradine up to 104 weeks by dietary administration. High doses in these studies were associated

		with mean ivabradine exposures of at least 37 times higher than the human exposure (AUC0-24hr) at the MRHD.
		Genotoxicity - Negative Ames, micronucleus and CA (chromosomal aberration) assays. Positive at 1500 times the MRHD (Maximum Recommended Human Dose). - Positive in mouse lymphoma, UDS (unscheduled DNA synthesis assay) in rat hepatocytes at high doses. - Ivabradine tested negative in the following assays: bacterial reverse mutation (Ames) assay, *in vivo* bone marrow micronucleus assay in both mouse and rat, *in vivo* chromosomal aberration assay in rats, and *in vivo* unscheduled DNA synthesis assay in rats. Results of the *in vitro* chromosomal aberration assay were equivocal at concentrations approximately 1,500 times the human Cmax at the MRHD. Ivabradine tested positive in the mouse lymphoma assays and *in vitro* unscheduled DNA synthesis assay in rat hepatocytes at concentrations greater than 1,500 times the human Cmax at the MRHD.
		Organ toxicity at low doses - Ocular toxicity. - Retinal toxicity in dogs at 2 times the human dos Reversible changes in retinal function were observed in dogs administered oral ivabradine at total doses of 2, 7, or 24 mg/kg/day (approximately 0.6 to 50 times the human exposure at the MRHD based on AUC0-24hr) for 52 weeks. Retinal function assessed by electroretinography demonstrated reductions in cone system responses, which reversed within a week post-dosing, and were not associated with damage to ocular structures as evaluated by light microscopy. These data are consistent with the pharmacological Reference ID: 3732763 effect of ivabradine related to its interaction with hyperpolarization-activated Ih currents in the retina, which share homology with the cardiac pacemaker If current. - Reversible changes in retinal function were observed in dogs administered oral ivabradine at total doses of 2, 7, or 24 mg/kg/day (approximately 0.6 to 50 times the human exposure at the MRHD based on AUC0-24hr) for 52 weeks. Retinal function assessed by electroretinography demonstrated reductions in cone system responses, which reversed within a week post-dosing, and were not associated with damage to ocular structures as evaluated by light microscopy. These data are consistent with the pharmacological Reference ID: 3732763 effect of ivabradine related to its interaction with hyperpolarization-activated Ih currents in the retina, which share homology with the cardiac pacemaker If current.

		Reproductive Toxicity - Fetal toxicity based on animal studies, post implantation loss in rabbits at 5 time the maximum recommended human dose. No effects on fertility. - Embryo-fetal toxicity in pregnant rats at 1-3 time the human dose; post-implantation loss in rabbits at 5 times HD (human dose). - Reproduction toxicity studies in animals demonstrated that ivabradine did not affect fertility in male or female rats at exposures 46 to 133 times the human exposure (AUC0-24hr [area under the curve from 0-24 hours]) at the MRHD (maximum recommended human dose). - Reproduction toxicity studies in animals demonstrated that ivabradine did not affect fertility in male or female rats at exposures 46 to 133 times the human exposure (AUC0-24hr) at the MRHD.
		Teratogenicity or Other Developmental Toxicity - Also cardiac abnormality in pregnant rats. - Cardiac teratogenic effects in rats at 1-3 time human exposure. - Corlanor may cause fetal toxicity when administered to a pregnant woman based on findings in animal studies. Embryo-fetal toxicity and cardiac teratogenic effects were observed in fetuses of pregnant rats treated during organogenesis at exposures 1 to 3 times the human exposures (AUC0-24hr [area under the curve from 0-24 hours]) at the maximum recommended human dose (MRHD) - In pregnant rats, oral administration of ivabradine during the period of organogenesis (gestation day 6-15) at doses of 2.3, 4.6, 9.3, or 19 mg/kg/day resulted in fetal toxicity and teratogenic effects. Increased intrauterine and post-natal mortality and cardiac malformations were observed at doses ≥ 2.3 mg/kg/day (equivalent to the human exposure at the MRHD based on AUC0-24hr). Teratogenic effects including interventricular septal defect and complex anomalies of major arteries were observed at doses ≥ 4.6 mg/kg/day (approximately 3 times the human exposure at the MRHD based on AUC0-24hr). - In pregnant rabbits, oral administration of ivabradine during the period of organogenesis (gestation day 6-18) at doses of 7, 14, or 28 mg/kg/day resulted in fetal toxicity and teratogenicity. Treatment with all doses ≥ 7 mg/kg/day (equivalent to the human exposure at the MRHD based on AUC0-24hr) caused an increase in post-implantation loss. At the high dose of 28 mg/kg/day (approximately 15 times the human exposure at the MRHD based on AUC0-24hr), reduced fetal and placental weights were observed, and evidence of teratogenicity (ectrodactylia observed in 2 of 148 fetuses from 2 of 18 litters) was demonstrated.

		- In the pre- and postnatal study, pregnant rats received oral administration of ivabradine at doses of 2.5, 7, or 20 mg/kg/day from gestation day 6 to lactation day 20. Increased postnatal mortality associated with cardiac teratogenic findings was observed in the F1 pups delivered by dams treated at the high dose (approximately 15 times the human exposure at the MRHD based on AUC0-24hr).
		Rationale for Proposing To Place on the List
		Teratogenicity or Other Developmental Toxicity embryo-fetal toxicity and teratogenicity at low doses in rats.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
lenvatinib	Lenvima	*Carcinogenicity* - No studies. - *Carcinogenicity* studies have not been conducted with lenvatinib. - *Carcinogenicity* studies have not been conducted with lenvatinib.
		Genotoxicity - Not mutagenic or clastogenic. - Lenvatinib mesylate was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay. Lenvatinib was not clastogenic in the *in vitro* mouse lymphoma thymidine kinase assay or the *in vivo* rat micronucleus assay.
		Organ toxicity at low doses - Arterial throboembolic events in 5%; HTN (hypertension) in 67%; proteinuria in 36%. - Hepatotoxicity.
		Reproductive Toxicity - 80% postimplantation loss in rats & 1/3 of rabbits at 0.5 times human dose. Based on animal studies, may reduce fertility in males and females. - Embro, feto and teratogenic in rats and rabbits at less than the HD (human dose). - LENVIMA may result in reduced fertility in females of reproductive potential LENVIMA may result in damage to male reproductive tissues leading to reduced fertility of unknown duration. results from general toxicology studies in rats, monkeys, and dogs suggest there is a potential for lenvatinib to impair fertility. Male dogs exhibited testicular hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides at lenvatinib exposures approximately 0.02 to 0.09 times the clinical exposure by AUC at the recommended human dose. Follicular atresia of the ovaries was observed in monkeys and rats at exposures 0.2 to 0.8 times and 10 to 44 times the clinical exposure by AUC at the 24 mg clinical dose, respectively. In addition, in monkeys, a

		decreased incidence of menstruation was reported at lenvatinib exposures lower than those in humans at the 24 mg clinical dose. - No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility; however, results from general toxicology studies in rats, monkeys, and dogs suggest there is a potential for lenvatinib to impair fertility. Male dogs exhibited testicular hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides at lenvatinib exposures approximately 0.02 to 0.09 times the clinical exposure by AUC at the recommended human dose. Follicular atresia of the ovaries was observed in monkeys and rats at exposures 0.2 to 0.8 times and 10 to 44 times the clinical exposure by AUC at the 24 mg clinical dose, respectively. In addition, in monkeys, a decreased incidence of menstruation was reported at lenvatinib exposures lower than those in humans at the 24 mg clinical dose.
		Teratogenicity or Other Developmental Toxicity - Embryotoxicity, fetotoxicity and teratogenicity in rats and rabbits. - Embryofetal toxicity and teratogenicity in rat and rabbits at less than the human dose. - In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses greater than or equal to 0.3 mg/kg [approximately 0.14 times the recommended human dose based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral, and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.5 times the recommended human dose based on BSA). - Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroesophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the human dose of 24 mg based on body surface area). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).
		Rationale for Proposing To Place on the List
		Teratogenicity or Other Developmental Toxicity: embryo-fetal toxicity at low doses in rats and rabbits; abortifacient in rabbits at low doses.

Generic Drug Name	Proprietary Name	Peer Reviewer Comments
miltefosine	Impavido	*Carcinogenicity* - Not done, but 3 of 30 rats with Leydig adenomas in 52 week study. - No studies. - Studies not performed. - *Carcinogenicity* studies were not performed. In a 52-week oral rat toxicity study, testicular Leydig cell adenoma was observed in 3 of 30 male rats with daily administration of 21.5 mg/kg/day miltefosine (1.0 times the MRHD based on BSA comparison). The carcinogenic potential of miltefosine in humans is unknown.
		Genotoxicity - Mostly negative. - Negative Ames test, CA (chromosomal aberration assay) - Miltefosine tested negative in the AMES-Salmonella test, DNA-amplification test, chromosomal aberration test *in vitro*, UDS-test *in vivo*/*in vitro*, and oral mouse micronucleus test *in vivo*. The V 79 mammalian cell HPRT gene mutation test showed an increase in mutant frequency without dose dependency. In view of all mutagenicity test results, the single positive finding in the V 79 HPRT test is considered to be not of toxicological relevance with respect to a mutagenic risk to humans.
		Organ toxicity at low doses - The oral administration of miltefosine in rats was associated with lesions affecting the eyes (retinal degeneration). Retinal degeneration was observed after 8- weeks treatment at doses of 10 mg/kg/day (0.5 times the MRHD based on BSA comparison). Juvenile rats were more sensitive to the miltefosine-induced effects, especially on eyes and Reference ID: 3473184 Page 15 of 18 kidneys, than adult rats with retinal degeneration occurring at doses ≥ 2.15 mg/kg/day (0.1 times the MRHD based on BSA comparison), and reversible damage to proximal tubule epithelium occurring at doses ≥ 4.64 mg/kg/day (0.2 times the MRHD based on BSA comparison). - Toxicological studies with miltefosine have been performed in mice, rats, dogs, and rabbits. Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: - Acute and chronic toxicity: The oral administration of miltefosine in rats was associated with lesions affecting the eyes (retinal degeneration). Retinal degeneration was observed after 8-weeks treatment at doses of 10 mg/kg/day (0.5 times the MRHD based on BSA comparison). Juvenile

		rats were more sensitive to the miltefosine-induced effects, especially on eyes and kidneys, than adult rats with retinal degeneration occurring at doses ≥ 2.15 mg/kg/day (0.1 times the MRHD based on BSA comparison), and reversible damage to proximal tubule epithelium occurring at doses ≥ 4.64 mg/kg/day (0.2 times the MRHD based on BSA comparison).
		Reproductive Toxicity - Impaired fertility in male and female rats at low doses. Package Insert recommends contraception for 5 months after therapy. - Male reproductive effects at less than the human dose. - Miltefosine caused impaired fertility in rats and reversible follicular atresia and diestrus in dogs at doses approximately 1.0 and 0.2 times respectively the MRHD based on body surface area comparisons. Miltefosine caused reduced viable sperm counts and impaired fertility in rats at doses approximately 0.4 times the MRHD. A higher dose in rats, approximately 1.0 times the MRHD, caused testicular atrophy and impaired fertility that did not fully reverse 10 weeks after drug administration ended. - In a Segment I fertility study in male rats, testicular atrophy, reduced numbers of viable sperm, and impaired fertility were observed in rats following daily oral doses of ≥ 8.25 mg/kg (0.4 times the MRHD based on BSA comparison). These findings were reversible within a recovery period of 10 weeks except at the highest dose tested, 21.5 mg/kg/day (1.0 times the MRHD based on BSA comparison), where effects were not fully reversible. - In a female fertility study in rats, estrus cycle arrest in the metestrus or diestrus phases occurred with the high-dose of 21.5 mg/kg (1.0 times the MRHD based on BSA comparison). At doses of 6.81 and 21.5 mg/kg (0.3 and 1.0 times the MRHD respectively based on BSA comparison) increased numbers of embryonic and fetal resorptions and dead fetuses were observed. In a 52-week toxicology study in dogs, increased numbers of atretic follicles in the ovaries, and cycle arrest in the uterus, vagina, and mammary gland with morphology consistent with anestrus or diestrus was observed at doses ≥ 1 mg/kg/day (0.2 times the MRHD based on BSA comparison). The effects in dogs were fully reversible after a recovery period of 6 weeks.
		Teratogenicity or Other Developmental Toxicity - Numerous visceral and skeletal malformations in rats and rabbits at doses 0.06 and 0.2 times maximum recommended human dose, no viable litters at 0.3 or 0.6 times maximum recommended human dose. - IMPAVIDO may cause fetal harm. Fetal teratogenicity, occurred in animals administered miltefosine at doses lower than the recommended human dose.

		- Miltefosine administration in rat embryo-fetal toxicity studies during early embryonic development (Day 6 to Day 15 of gestation) caused embryo-fetal toxicity including death and teratogenicity at dosages of ≥ 1.2 mg/kg/day (0.06 times the MRHD based on BSA comparison). Teratogenic effects included undeveloped cerebrum, hemorrhagic fluid filling the lumina of the skull, cleft palate and generalized edema. Embryo-fetal toxicity was also observed in rabbits after oral administration of miltefosine during organogenesis (Day 6 to Day 18 of gestation) at doses ≥ 2.4 mg/kg/day (0.2 times the MRHD based on BSA comparison). In both rats and rabbits, there were no viable litters at miltefosine doses ≥ 6.0 mg/kg/day (0.3 or 0.6 times the MRHD based on BSA comparisons for rats and rabbits respectively). - In a separate female fertility study in rats, miltefosine doses ≥ 6.81 mg/kg/day (0.3 times the MRHD based on BSA comparison) administered for four weeks before mating and up to Day 7 of pregnancy produced numerous visceral (misshapen cerebral structures, dilated ventricles filled with brown masses, misshapen spinal cord, misshapen and malpositioned eyes, hypophysis, and absent inner ear) and skeletal (cleft palate, dumbbell-shaped ossification of thoracic vertebral centers, markedly enlarged skull bones, and markedly dilated suturae) fetal malformations.
		Rationale for Proposing To Place on the List
		Teratogenicity or Other Developmental Toxicity: fetal death and teratogenicity in rats and rabbits at low doses.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
olaparib	Lynparza	*Carcinogenicity* - Studies not conducted. MDS (Myelodysplastic Syndrome)/ AML (Acute Myeloid Leukemia) occurred in treated patients. - Fatal MDS/AML. - *Carcinogenicity* studies have not been conducted with olaparib.
		Genotoxicity - Clastogenic *in vitro* (CA [chromosomal aberration assay) and *in vivo* (micronucleus) assays. - Clastogenic –CA in CHO (Chinese hamster ovary) and MN in rat BM (bone marrow), genomic instability. - Olaparib was clastogenic in an *in vitro* chromosomal aberration assay in mammalian CHO cells and in an *in vivo* rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of olaparib and indicates potential for genotoxicity in humans. - Olaparib was clastogenic in an *in vitro* chromosomal aberration assay in mammalian CHO cells and in an *in vivo*

		rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of olaparib and indicates potential for genotoxicity in humans. Olaparib was not mutagenic in a bacterial reverse mutation (Ames) test.
		Organ toxicity at low doses - Pneumonitis. - Pneumonitis in treated patients.
		Reproductive Toxicity - Post implantation loss at low doses. - Fetotoxicity in rats at less than the human dose. - In a fertility study, female rats received oral olaparib at doses of 0.05, 0.5, and 15 mg/kg/day for at least 14 days before mating through the first week of pregnancy. There were no adverse effects on mating and fertility rates at doses up to 15 mg/kg/day (maternal systemic exposures approximately 11% of the human exposure (AUC0-24h) at the recommended dose). In a male fertility study, olaparib had no effect on mating and fertility in rats at oral doses up to 40 mg/kg/day following at least 70 days of olaparib treatment (with systemic exposures of approximately 7% of the human exposure (AUC0-24h) at the recommended dose). - In a fertility study, female rats received oral olaparib at doses of 0.05, 0.5, and 15 mg/kg/day for at least 14 days before mating through the first week of pregnancy. There were no adverse effects on mating and fertility rates at doses up to 15 mg/kg/day (maternal systemic exposures approximately 11% of the human exposure (AUC0-24h) at the recommended dose). - In a male fertility study, olaparib had no effect on mating and fertility in rats at oral doses up to 40 mg/kg/day following at least 70 days of olaparib treatment (with systemic exposures of approximately 7% of the human exposure (AUC0-24h) at the recommended dose).
		Teratogenicity or Other Developmental Toxicity - Major malformations of eyes, vertebrae/ribs, skull, and diaphragm in rats at 0.3% of maximum recommended human dose. - In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.3% of human exposure (AUC0-24h) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital) and diaphragm (hernia). Additional abnormalities or variants included incomplete or

		absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter and umbilical artery. Some findings noted above in the eyes, ribs and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence. - In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 11% of the human exposure (AUC0-24h) at the recommended dose). - In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.3% of human exposure (AUC0-24h) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital) and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter and umbilical artery. Some findings noted above in the eyes, ribs and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.
		Rationale for Proposing To Place on the List
		Carcinogenicity and Teratogenicity or Other Developmental Toxicity: myelodysplastic syndrome/acute myeloid leukemia in patients in clinical studies; embryo-fetal toxicity, post-implantation loss, malformations at low doses in rats.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
osimertinib	Tagrisso	*Carcinogenicity* - Not studied. - No studies. - *Carcinogenicity* studies have not been performed with osimertinib. - *Carcinogenicity* studies have not been performed with osimertinib. - Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays.

		Genotoxicity - No. - Negative. - Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays.
		Organ toxicity at low doses - Interstitial lung disease.
		Reproductive Toxicity - In rats: embryolethality, reduced fetal growth and postnatal death at 1.5 times MRHD (maximum recommended human dose). Impaired male fertility in rats and dogs; impaired female fertility in rats. - Male and female mediated reproductive toxicity at less than human dose. - Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. - Based on studies in animals, male fertility may be impaired by treatment with TAGRISSO. Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for 1 month or more with evidence of reversibility in the rat. Following administration of osimertinib to rats for approximately 10 weeks at a dose of 40 mg/kg, at exposures 0.5-times the AUC observed in patients at the recommended dose of 80 mg, there was a reduction in male fertility, demonstrated by increased pre-implantation loss in untreated females mated to treated males. - Based on studies in animals, female fertility may be impaired by treatment with TAGRISSO. In repeat dose toxicity studies, histological evidence of anestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to osimertinib for 1 month or more at exposures 0.3-times the AUC observed in patients at the recommended dose of 80 mg. Findings in the ovaries seen following 1 month of dosing exhibited evidence of reversibility. In a female fertility study in rats, administration of osimertinib from 2 weeks prior to mating through Day 8 of gestation at a dose of 20 mg/kg/day (approximately 1.5-times the human Cmax at the recommended dose of 80 mg/day) had no effects on oestrus cycling or the number of females becoming pregnant, but caused early embryonic deaths. These findings showed evidence of reversibility when females were mated 1 month after treatment discontinuation.
		Teratogenicity or Other Developmental Toxicity - Greater than 3% of patients with ILD (interstitial lung disease). - Malformations and variations in fetal rats. - Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies,

		osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the 4 Reference ID: 3846512 recommended human dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5-times those observed in patients at the 80 mg dose level. - When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1-times the AUC observed in patients at the recommended dose of 80 mg), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.
		Rationale for Proposing To Place on the List
		Teratogenicity or Other Developmental Toxicity: embryo-fetal toxicity and lethality and reduced growth in offspring in rats.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
sonidegib	Odomzo	*Carcinogenicity* - Not tested. - No studies. - *Carcinogenicity* studies with sonidegib have not been performed. - *Carcinogenicity* studies with sonidegib have not been performed.
		Genotoxicity - Not mutagenic or clastogenic. - Negative Ames and clastogen.
		Organ toxicity at low doses - Body tremors along with significant increases in creatine kinase were observed in rats administered oral sonidegib for 13 weeks or longer at ≥10 mg/kg/day (approximately ≥2 times the recommended human dose based on AUC).

		- Body tremors along with significant increases in creatine kinase were observed in rats administered oral sonidegib for 13 weeks or longer at ≥10 mg/kg/day (approximately ≥2 times the recommended human dose based on AUC).
		Reproductive Toxicity - Embryotoxic, fetotoxic in rabbits at does below maximum recommended human dose, decreased viable fetuses in rats at 0.12 times maximum recommended human dose, may compromise female fertility. - Referenced decision criteria for reproductive toxicity: Reproductive, developmental, and semen quality effects. - Sonidegib resulted in a lack of fertility when administered to female rats at ≥20 mg/kg/day (approximately 1.3 times the recommended human dose based on body surface area (BSA). A reduction of the number of pregnant females, an increase in the number of early resorptions, and a decrease in the number of viable fetuses was also noted at 2 mg/kg/day (approximately 0.12 times the recommended human dose based on BSA). In addition, in a 6 month repeat-dose toxicology study in rats, effects on female reproductive organs included atrophy of the uterus and ovaries at doses of 10 mg/kg (approximately ≥2 times the exposure in humans at the recommended dose of 200 mg based on AUC). No adverse effects on fertility were noted when male rats were administered sonidegib at doses up to 20 mg/kg/day, the highest dose tested. - Sonidegib resulted in a lack of fertility when administered to female rats at ≥20 mg/kg/day (approximately 1.3 times the recommended human dose based on body surface area (BSA). A reduction of the number of pregnant females, an increase in the number of early resorptions, and a decrease in the number of viable fetuses was also noted at 2 mg/kg/day (approximately 0.12 times the recommended human dose based on BSA). In addition, in a 6 month repeat-dose toxicology study in rats, effects on female reproductive organs included atrophy of the uterus and ovaries at doses of 10 mg/kg (approximately ≥2 times the exposure in humans at the recommended dose of 200 mg based on AUC). No adverse effects on fertility were noted when male rats were administered sonidegib at doses up to 20 mg/kg/day, the highest dose tested.
		Teratogenicity or Other Developmental Toxicity - In animals: severe midline defects, missing digits and craniofacial malformations. - ODOMZO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and is embryotoxic, fetotoxic, and teratogenic in animals. - Daily oral administration of sonidegib to pregnant rabbits resulted in abortion, complete resorption of fetuses, or severe malformations at ≥ 5 mg/kg/day (approximately 0.05

		times the recommended human dose based on AUC). Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations, and other severe midline defects. Skeletal variations were observed when maternal exposure to sonidegib was below the limit of detection.
		Rationale for Proposing To Place on the List
		Reproductive Toxicity and Teratogenicity or Other Developmental Toxicity: embryo-fetal toxicity, teratogenicity, and spontaneous abortions in rabbits.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
trastuzumab	Herceptin	*Carcinogenicity* - Not tested. - No studies. - Herceptin has not been test for carcinogenic potential.
		Genotoxicity - Not mutagenic, no evidence of chromosomal damage. - Negative. - No evidence of mutagenic activity was observed when trastuzumab was tested in the standard Ames bacterial and human peripheral blood lymphocyte mutagenicity assays, at concentrations of up to 5000 mcg/mL. In an *in vivo* micronucleus assay, no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg of trastuzumab.
		Organ toxicity at low doses - Neutropenia of threated patients. - Pulmonary toxicity, cardiomyopathy.
		Reproductive Toxicity - No evidence of female infertility; fertility in males not tested. - A fertility study conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels. Studies to evaluate the effects of trastuzumab on male fertility have not been conducted. - A fertility study conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.

		Teratogenicity or Other Developmental Toxicity - Oligohydramnios, pulmonary hypoplasia, skeletal abnormalities and neonatal death. - Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death. - In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities and neonatal death. These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy resumed after amniotic index improved, and oligohydramnios recurred. - In studies where trastuzumab was administered to pregnant Cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), trastuzumab crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.
		Rationale for Proposing To Place on the List
		Organ toxicity at low doses and Teratogenicity or Other Developmental Toxicity: cardiac and pulmonary toxicity in patients; malformations and neonatal death in patients.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
triazolam	Halcion	*Carcinogenicity* - None.
		Genotoxicity
		Organ toxicity at low doses - During placebo-controlled clinical studies in which 1,003 patients received triazolam tablets, the most troublesome side effects were extensions of the pharmacologic activity of triazolam, e.g., drowsiness, dizziness, or light-headedness.
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity - Congenital malformations when used during 1st trimester of pregnancy. No dosing information.

		- An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies.
		Rationale for Proposing To Place on the List
		Mimics existing drugs determined hazardous by exhibiting teratogenicity or other developmental toxicity: drug is a benzodiazepine, a class known to cause congenital malformations and cross the placenta in patients.

Generic Drug Name	**Proprietary Name**	**Peer Reviewer Comments**
urofollitropin	Bravelle	*Carcinogenicity* - Not tested. - Studies not done. - There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have had multiple drug therapy for controlled ovarian stimulation; however, a causal relationship has not been established. Long-term toxicity studies in animals and *in vitro* mutagenicity tests have not been performed to evaluate the carcinogenic potential of urofollitropin for injection, purified. - Long-term toxicity studies in animals and *in vitro* mutagenicity tests have not been performed to evaluate the carcinogenic potential of urofollitropin for injection, purified.
		Genotoxicity - Not tested. - Studies not done. - Long-term toxicity studies in animals and *in vitro* mutagenicity tests have not been performed to evaluate the carcinogenic potential of urofollitropin for injection, purified.
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity May cause fetal harm when administered to pregnant woman. Yes. There are no indications that the use of gonadotropins during IVF or ICSI is associated with an increased risk of congenital malformations.
		Rationale for Proposing To Place on the List
		Teratogenicity or Other Developmental Toxicity: drug is known to cause fetal harm in patients.

Generic Drug Name	Proprietary Name	Peer Review Comments
alglucosidase	Lumizyme	*Carcinogenicity* - No data
		Genotoxicity
		Organ toxicity at low doses - Anaphylaxis in patients.
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
aaectinib	Alcensa	*Carcinogenicity*
		Genotoxicity - Micronucleus assay positive aneuploidy; Ames test negative.
		Organ toxicity at low doses
		Reproductive - Toxicity - Fetal toxicity at 2.7 times human dose.
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
alendronate	Fosamax	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
alogliptin	Nesina	*Carcinogenicity* - Negative at high fold doses greater than human dose.
		Genotoxicity

		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
apremilast	Otezla	*Carcinogenicity* - No evidence of tumors in mice at doses up to 8.8 times maximum recommended human dose or in rats at doses up to 0.08 and 1.1 times maximum recommended human dose - No evidence of tumors in "rats at oral doses up to approximately 0.08- and 1.1-times the MRHD (Maximum Recommended Human Dose), (20 mg/kg/day in males and 3 mg/kg/day in females, respectively)." - No evidence of apremilast-induced tumors was observed in mice at oral doses up to 8.8-times the MRHD on an AUC (Area Under the Curve) basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively). - Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors were observed in mice at oral doses up to 8.8-times the Maximum Recommended Human Dose (MRHD) on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively).
		Genotoxicity - Negative in Ames assay, *in vitro* chromosome aberration assay and *in vivo* mouse micronucleus assay - No - Apremilast tested negative in the Ames assay, *in vitro* chromosome aberration assay of human peripheral blood lymphocytes, and the *in vivo* mouse micronucleus assay.
		Organ toxicity at low doses - Respiratory sensitization - Depression, suicidal ideation
		Reproductive Toxicity - No effects on male fertility in mice. Prolonged estrous cycles in female mice. Increased early post-implantation losses in mice at greater than or equal to 20mg/kg/day - Malformations in monkeys at 2 times the Human Dose - In a fertility study of male mice, apremilast at oral doses up to approximately 3-times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered

		at oral doses of 10, 20, 40 or 80 mg/kg/day. At doses ≥1.8 times the MRHD (≥20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early postimplantation losses. .There was no effect of apremilast approximately 1.0-times the MRHD (10 mg/kg/day). - In a fertility study of male mice, apremilast at oral doses up to approximately 3-times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral doses of 10, 20, 40 or 80 mg/kg/day. At doses ≥1.8 times the MRHD (≥20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early postimplantation losses. There was no effect of apremilast approximately 1.0-times the MRHD (10 mg/kg/day).
		Teratogenicity or Other Developmental Toxicity - None - In animal embryo-fetal development studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure 1.4-times the MRHD. In mice, there were no apremilast induced malformations up to exposures 4.0-times the MRHD.
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
calcipotriene	Dovonex	*Carcinogenicity* - When calcipotriene was applied topically to mice for up to 24 months at doses of 3, 10 and 30 µg/kg/day (corresponding to 9, 30 and 90 µg/m2/day), no significant changes in tumor incidence were observed compared to the controls.
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.

cetuximab	Erbitux	*Carcinogenicity* - Long-term animal studies have been performed to test cetuximab for carcinogenic potential, and no mutagenic or clastogenic potential of cetuximab was observed in the SalmonellaEscherichia coli (Ames) assay or in the *in vivo* rat micronucleus test.
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
clarithromycin	Biaxin	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
diazoxide	Proglycem	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
flotuzumab	Empliciti	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity

		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
finafloxacin	Xtoro	*Carcinogenicity* - No studies - Animal studies have not been conducted to determine the carcinogenic potential of finafloxacin. - Animal studies have not been conducted to determine the carcinogenic potential of finafloxacin.
		Genotoxicity - Genotoxic and clastogenic *in vitro* and *in vivo.* - Yes and clastogenic, with and without metabolic activation (S9). Many test systems - Finoflaxacin was shown to be genotoxic and clastogenic *in vitro*, with and without metabolic activation, and *in vivo*. In a bacterial reverse mutation assay, finafloxacin was positive in only one stain (TA102). Finafloxacin was positive in mammalian cell culture assays: mouse lymphoma cell forward mutation assay, a mutagenicity assay in V79 Chinese hamster lung cells, and a micronucleus test in V79 cells. Finafloxacin was clastogenic in mouse micronucleus studies.
		Organ toxicity at low doses - No
		Reproductive Toxicity - Impaired fertility at high doses. Toxic to sperm at high doses. - Male and female infertility. At very hi doses in rats; sperm toxicity - An oral rat fertility study detected a No Observed Adverse Effect Level (NOAEL) for male and female fertility of 100 mg/kg/day (estimated 60,000 times the maximum human systemic exposure following topical otic administration with 0.3% finafloxacin). At 500 mg/kg/day, males were completely infertile, presumably due to low sperm count and sperm immobility. General toxicity studies in rats have confirmed sperm toxicity following oral and intravenous dosing. Following intravenous dosing, the NOAEL for sperm toxicity was 30 mg/kg/day (150,000 times the maximum human exposure following topical otic administration with 0.3% finafloxacin). - An oral rat fertility study detected a NOAEL for male and female fertility of 100 mg/kg/day (estimated 60,000 times the maximum human systemic exposure following topical otic administration with 0.3% finafloxacin). At 500 mg/kg/day, males were completely infertile, presumably due to low sperm count and sperm immobility. General

		toxicity studies in rats have confirmed sperm toxicity following oral and intravenous dosing. Following intravenous dosing, the NOAEL for sperm toxicity was 30 mg/kg/day (150,000 times the maximum human exposure following topical otic administration with 0.3% finafloxacin).
		Teratogenicity or Other Developmental Toxicity - Teratogenic in rabbits and rats at 1300 times the maximum human exposure following topical administration. Neural tube defects and skeletal anomalies - Yes in rabbits and rats at 1300 times the human dose by oral administration
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
golimumab	Simponi	*Carcinogenicity* - Malignancies: Incidence of lymphoma was greater than in the general U.S. population. Cases of other malignancies have been observed among patients receiving tumor necrosis factor (TNF) blockers.
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
idelalisib	Zydelig	*Carcinogenicity* -No studies have been conducted.
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity - The low dose in males resulted in an exposure (area under the curve, AUC) that is approximately 50% of the exposure in patients at the recommended dose of 150mg twice daily.
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
isavuconazonium	Cresemba	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses

		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
itraconazole	Sporanox	*Carcinogenicity* - Negative in rats except not statistically significant increase in sarcomas and squamous cell carcinoma of the lung. - Increased incidence of squamous cell carcinoma in lung at 6.25 times maximum recommended human dose - Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10x the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1x MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25x MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant. - Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10x the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1x MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25x MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.
		Genotoxicity - Negative in large battery of *in vitro* and *in vivo* testing - No mutagenic changes using multiple tests. - Itraconazole produced no mutagenic effects when assayed in DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with Salmonella typhimurium (6 strains) and Escherichia coli, in the mouse lymphoma

		gene mutation tests, in a sex-linked recessive lethal mutation (Drosophila melanogaster) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus in mice and rats.
		Organ toxicity at low doses - Liver failure
		Reproductive Toxicity - Dose related increase in embryotoxicity and teratogenicity in rats at ~5-20 times the maximum recommended human dose and in mice at ~10 times the maximum recommended human dose - No effects on fertility at 5 times maximum recommended human dose - Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels up to 40 mg/kg/day (5x MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20x MRHD). - Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels up to 40 mg/kg/day (5x MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20x MRHD).
		Teratogenicity or Other Developmental Toxicity - Dose related increase in embryotoxicity and teratogenicity in rats at ~5-20 times the maximum recommended human dose and in mice at ~10 times the maximum recommended human dose - Major skeletal defects in rats at 5-20 times maximum recommended human dose; encephaloceles and macroglossia in mice at 10 times maximum recommended human dose. Cases of congenital abnormalities in post-marketing experience - Rodent malformations at less than human dose. - Itraconazole was found to cause a dose-related increase in maternal toxicity, embrotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5-20x MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10x MRHD). Itraconazole has been shown to cross the placenta in a rat model. In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia. - Itraconazole was found to cause a dose-related increase in maternal toxicity, embrotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5-20x MRHD), and in mice at dosage levels of approximately 80

		mg/kg/day (10x MRHD). Itraconazole has been shown to cross the placenta in a rat model. In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
lamotrigine	Lamictal	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity - The no-effect doses for embryo-fetal developmental toxicity in mice, rats, and rabbits (75, 6.25, and 30 mg/kg, respectively) are similar to (for mice and rabbits) and less than (for rats) the human dose of 400 mg/day on a body surface area (mg/m2) basis.
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
lanreotide	Somatuline	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
metreleptin	Myalept	*Carcinogenicity* - No - Lymphoma - Two-year carcinogenicity studies in rodents have not been conducted with metreleptin. No proliferative or preneoplastic lesions were observed in mice or dogs following treatment up to six months. However, leptin is reported in the literature to promote cell proliferation *in vitro* and tumor progression in some mouse models of cancer. Risk of lymphoma. - Two-year carcinogenicity studies in rodents have not been conducted with metreleptin. No proliferative or preneoplastic lesions were observed in mice or dogs following treatment up to six months. However, leptin is

		reported in the literature to promote cell proliferation in vitro and tumor progression in some mouse models of cancer.
		Genotoxicity - Not mutagenic in Ames assay or clastogenic in chromosomal aberrations assay or human peripheral blood lymphocytes. - Mostly negative, but tumor progression. Positive is some models - Metreleptin was not mutagenic in the Ames bacterial mutagenicity assay or clastogenic in an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and human peripheral blood lymphocytes. Metreleptin was not mutagenic or clastogenic in an *in vivo* mouse micronucleus assay.
		Organ toxicity at low doses
		Reproductive Toxicity - Prolonged gestation and dystocia in mice at maximum recommended human dose. No adverse effect on fertility - Mice, dystocia at Max of Human Dose - In a fertility study in mice, metreleptin had no adverse effects on mating, fertility, or early embryonic development at doses ranging between 7 and 15 times the maximum recommended clinical dose based on body surface area of a 20- and 60-kg patient, respectively.
		Teratogenicity or Other Developmental Toxicity - Not teratogenic in mice - No - Metreleptin administered to pregnant mice during the period of organogenesis was not teratogenic at doses ranging between 7- and 15-fold the maximum recommended clinical dose, based on body surface area of a 20- and 60-kg patient, respectively. - Metreleptin administered to pregnant mice during the period of organogenesis was not teratogenic at doses ranging between 7- and 15-fold the maximum recommended clinical dose, based on body surface area of a 20- and 60-kg patient, respectively. - In a pre-and postnatal development study in mice, metreleptin administered at doses of 3, 10, and 30 mg/kg (approximately 1-, 5-, and 15-fold the clinical dose for a 60-kg subject, based on body surface area) from gestation day 6 to lactation day 21 caused prolonged gestation and dystocia at all doses, starting at approximately the maximum recommended clinical dose. Prolonged gestation resulted in the death of some females during parturition and lower survival of offspring within the immediate postnatal period. Consistent with metreleptin pharmacology, decreased maternal body weight was

		observed from gestation throughout lactation at all doses and resulted in reduced weight of offspring at birth, which persisted into adulthood. However, no developmental abnormalities were observed and reproductive performance of the first or second generations was not affected at any dose. - Placental transfer of metreleptin into the fetus was low (approximately 1%) following subcutaneous dosing.
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
milnacipran	Savella	*Carcinogenicity*
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity - Reproduction studies have been performed in rats, rabbits, and mice. Milnacipran was shown to increase embryo-fetal and perinatal lethality in rats and the incidence of a minor skeletal variation in rabbits at doses below (rat) or approximately equal to (rabbit) the maximum recommended human dose (MRHD) of 200 mg/day on a mg/m2 basis.
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
nindetanib	Ofev	*Carcinogenicity* - Negative 2-year carcinogenicity study at up to 4 times human dose.
		Genotoxicity Negative
		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity - In animal reproduction toxicity studies, nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults [on a plasma area under the curve (AUC) basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). The malformations included abnormalities in the vasculature, urogenital and skeletal systems.
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.

peginterferon beta 1-A	Plegridy	*Carcinogenicity* - No studies.
		Genotoxicity - Negative clastogen and Ames.
		Organ toxicity at low doses
		Reproductive Toxicity - Negative; abortifacient after 3-5 doses; in monkeys administered interferon beta by subcutaneous infection over the course of one menstrual cycle, menstrual irregularities, anovulation, and decreased serum progesterone levels in monkeys were observed. These effects were reversible after discontinuation of drug.
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
pirfenidone	Esbriet	*Carcinogenicity* - In a 24-month carcinogenicity study of B6C3F1 mice, pirfenidone caused statistically significant dose-related increase of the combination of hepatocellular adenoma and carcinoma and hepatoblastoma in male mice at doses of 800 mg/kg and above [area under the curve (AUC) exposure approximately 0.4 times adult exposure at the maximum recommended daily dose (MRDD)] statistically significant dose-related increases of the combination of hepatocellular adenoma and carcinoma in female mice at doses of 2000 mg/kg and above (AUC exposure approximately 0.7 times the adult exposure at the MRDD).
		Genotoxicity
		Organ toxicity at low doses
		Reproductive Toxicity - A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone.
		Teratogenicity or Other Developmental Toxicity
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.
tasimelteon	Hetlioz	*Carcinogenicity* - Negative at 5-10 times human dose.
		Genotoxicity

		Organ toxicity at low doses
		Reproductive Toxicity
		Teratogenicity or Other Developmental Toxicity - In animal studies, administration of tasimelteon during pregnancy resulted in development toxicity (embryo-fetal mortality, neurobehavioral impairment, and decreased growth and development in offspring) at doses greater than those used clinically.
		Rationale for Proposing to Not Place on the List
		This drug does not meet the NIOSH definition of a hazardous drug.