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

The tables below provide the stakeholder 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)*. Stakeholders provided comments on each drug screened and evaluated by NIOSH, as described in the Federal Register notice published in NIOSH Docket 233-B.

The stakeholders' comments are compiled as received and without edit, except as noted, in the tables below, and the tables 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 stakeholders for a criterion, only the criterion is listed. NIOSH reviewed the stakeholders' 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*.**

Generic Drug Name	Proprietary Name	Stakeholder Reviewer Comments
bevacizumab	Avastin	Carcinogenicity • No data • Material Safety Data Sheet (MSDS): Carcinogenicity: not listed by National Toxicology Program (NTP), International Agency for Research on Cancer (IARC) or Occupational Safety and Health Administration (OSHA) • No studies • No carcinogenicity or mutagenicity studies of bevacizumab have been conducted. • N • No carcinogenicity or mutagenicity studies of bevacizumab have been conducted. • N
		Genotoxicity • No studies • No carcinogenicity or mutagenicity studies of evacizumab have been conducted. • N • No data available (mAb [monoclonal antibiody]) • N
		Organ toxicity at low doses • Risk of hemorrhage, slowed wound healing, hypersensitivity • MSDS (Material Safety Data Sheet): This material is not likely to be significantly absorbed via occupational routes of entry due to its chemical structure and large molecular weight. IOEL (Internal Occupational Exposure Limit): 0.05 mg/m3.

		• No but impaired wound healing in rabbits at standard doses. • Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in 743 reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure. o TD effects: ----------**WARNINGS AND PRECAUTIONS**---------- • Perforation or Fistula: Discontinue Avastin if perforation or fistula occurs. (5.1, 5.2) • Arterial Thromboembolic Events (ATE) (e.g., myocardial infarction, cerebral infarction): Discontinue Avastin for severe ATE. (5.5) • Venous Thromboembolic Events: Discontinue Avastin for life-threatening VTE (5.6) • Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend Avastin if not medically controlled. Discontinue Avastin for hypertensive crisis or hypertensive encephalopathy. (5.7) • Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue Avastin. (5.8) • Proteinuria: Monitor urine protein. Discontinue Avastin for nephrotic syndrome. Temporarily suspend Avastin for moderate proteinuria. (5.9) • Infusion Reactions: Stop Avastin for severe infusion reactions. (5.10) • Embryo-fetal Toxicity: Advise females of potential risk to a fetus and the need for use of effective contraception. (5.11, 8.1, 8.3) • Ovarian Failure: Advise females of the potential risk. (5.12, 8.3) Most common adverse reactions incidence (10% and at least twice the control arm rate) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis • N • Most common adverse reactions incidence (> 10% and at least twice the control arm rate) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. Side effect(s) during therapy: tendency to bleeding, thrombophlebitis, proteinuria - NOEL (no observable effect level) 50 mg/kg (i.v. [intravenous], cynomolgus monkey) • Chronic toxicity - LOAEL (lowest-observed-adverse-effect level) 2 mg/kg/w (i.v., cynomolgus monkey; 26 weeks).

		• Y
		Reproductive toxicity • Animal models link drug activity to angiogenesis, VEGF, and VEGFR2 aspects of embryo-fetal and post-natal development. Risk of ovarian failure and impaired fertility. • Ovarian failure • *Contraception* Females Avastin may cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use effective contraception during treatment with Avastin and for 6 months following the last dose of Avastin. [*See Use in Specific Populations (8.1).*] *Infertility* Females Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown. In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. Bevacizumab may impair fertility. Female cynomolgus monkeys streated 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. • N • Reproductive toxicity - teratogenic and embryotoxic (i.v. [intravenous], rabbit) - should be administered during pregnancy only if the Potential benefit justifies the potential risk to the fetus. • Infertility: Females • Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. • Long term effects of Avastin exposure on fertility are unknown.

		• In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. • Y
		Teratogenicity or other developmental toxicity • Fetal malformations in animals studies • Recent warnings re: embryo-fetal toxicity added to DailyMed 05/2015; Unable to determine if already assessed. • Embryo-fetal toxicity in rabbits • Avastin may cause fetal harm based on findings from animal studies and the drug's mechanism of action. [See Clinical Pharmacology (12.1).] Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug associated risks. 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 [*see Data*]. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Animal Data 615 Pregnant rabbits dosed with 10 to 100 mg/kg bevacizumab (approximately 1 to 10 times the 616 clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6-18) 617 exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. 618 There were dose-related increases in the number of litters containing fetuses with any type of 619 malformation (42.1% for the 0 mg/kg dose, 76.5% for the 30 mg/kg dose, and 95% for the 100 620 mg/kg dose) or fetal alterations (9.1% for the 0 mg/kg dose, 14.8% for the 30 mg/kg dose, and 621 61.2% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some 622 abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects 623 included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; 624 fontanel, rib and hind limb deformities; corneal opacity; and absent hind limb phalanges.

		• N • 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 [see Data]. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. • Animal Data • Pregnant rabbits dosed with 10 to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6–18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42.1% for the 0 mg/kg dose, 76.5% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9.1% for the 0 mg/kg dose, 14.8% for the 30 mg/kg dose, and 61.2% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hind limb deformities; corneal opacity; and absent hind limb phalanges. • Y
		Rationale for Proposing Placement 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	Stakeholder Reviewer Comments
blinatumomab	Blincyto	• Carcinogenicity • No data • No carcinogenicity or genotoxicity studies have been conducted with blinatumomab. • Not studied • No carcinogenicity or genotoxicity studies have been conducted with blinatumomab. • N

		• No carcinogenicity or genotoxicity studies have been conducted with blinatumomab. • N
		• Genotoxicity • No data • Not studied • N • No carcinogenicity or genotoxicity studies have been conducted with blinatumomab. • N
		• Organ toxicity at low doses • CRS [cytokine release syndrome] and neurotoxicity risk • When practicable, handle material in enclosed processes or in processes with effective local exhaust ventilation or within a chemical hood. Blinatumomab has been classified per Amgen's Hazard Classification System as an Occupational Exposure Band 5 compound (0.1 µg/m3 – 5 µg/m3)[note: highly potent]. • Yes – neurotoxicity at standard doses (9 – 28mcg/day) • Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred • Neurological toxicities have occurred in approximately 50% of patients. The median time to onset of any neurological toxicity was 7 days. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 15% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. • Infections - - serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections were observed in approximately 25% of patients, some of which were life-threatening or fatal. • Neutropenia and febrile neutropenia, including life-threatening cases transient elevations in liver enzymes. • The most common adverse reactions (≥ 20%) were pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation. • N • The most common adverse reactions (≥ 20%) were pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation. Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. • N
		• Reproductive toxicity

		• No human data • No studies in humans or animals. PI [package insert]: 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. • Not conducted; surrogate molecule had not toxicity in mice. • 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. • N • 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. • N
		Teratogenicity or other developmental toxicity • May cause fetal toxicity including B-cell lymphocytopenia. Animal studies not conducted. • Based on its mechanism of action, BLINCYTO may cause fetal toxicity including B-cell lymphocytopenia when administered to a pregnant woman. BLINCYTO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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. o MSDS [material safety data sheet]: Blinatumomab was tested in an embryo-fetal study where mouse surrogates were dosed intravenously (0, 1, and 5 mg/kg/day) on post-coitum days 6-15. No adverse effects were observed on maternal clinical condition, pregnancy, or embryo-fetal development. • Depletion of B-cells and T-cells in pregnant mice. • Animal reproduction studies have not been conducted with blinatumomab. 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. • N

		• Animal reproduction studies have not been conducted with blinatumomab. 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 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. • N
		Rationale for Proposing Placement on the List
		Organ toxicity at low doses: neurotoxicity at low doses in patients in clinical studies

Generic Drug Name	**Proprietary Name**	**Stakeholder Reviewer Comments**
botulinumtoxin	Dysport, Botox	Carcinogenicity
		Genotoxicity
		Organ toxicity at low doses
		Reproductive toxicity
		Teratogenicity or other developmental toxicity
		Rationale for Proposing Placement 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**	**Stakeholder Reviewer Comments**
ceritinib	Zykadia	Carcinogenicity • No data • Carcinogenicity studies have not been performed with ceritinib. • Not studied • Carcinogenicity studies have not been performed with ceritinib. • Y induced numerical aberrations (aneugenic) in the in vitro cytogenetic assay using human lymphocytes, and micronuclei in the in vitro micronucleus test using TK6 cells. • Carcinogenicity studies have not been performed with ceritinib. • Carcinogenicity studies have not been performed with ceritinib.

		• N
		Genotoxicity • 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 micronucle. • No • 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. • N • 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. • Ceritinib was not mutagenic in the Ames assay, but induced numerical aberrations (aneugenic) in the *in vitro* cytogenetic assay with human lymphocytes, and micronuclei in the *in vitro* micronucleus test using TK6 cells. Ceritinib was not clastogenic in the *in vivo* rat micronucleus assay. • Y
		Organ toxicity at low doses • Hepatic impairment, necrosis and hemorrhage of the duodenum • Target organs in non-clinical 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 (area under the curve) 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 • No • Severe or Persistent Gastrointestinal Toxicity, Heptatoxicity, Interstitial Lung Disease (ILD)/Pneumonitis, QT Interval Prolongation, Hyperglycemia, Brady cardia, 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. • Ceritinib crossed the blood brain barrier in rats with a brain-to-blood exposure (AUCinf) ratio of approximately 15%. • N • Severe or Persistent Gastrointestinal Toxicity: Hepatotoxicity: ZYKADIA can cause hepatotoxicity. Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 4% of patients. QT Interval Prolongation: Hyperglycemia: ZYKADIA can cause hyperglycemia. Bradycardia: ZYKADIA can cause bradycardia. Pancreatitis: Elevations of lipase and/or amylase and pancreatitis can occur. Embryofetal Toxicity: ZYKADIA may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. The most common adverse reactions (incidence of at least 25%) are diarrhea, nausea, elevated transaminases, vomiting, abdominal pain, fatigue, decreased appetite, and constipation. • 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. • Target organs in 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. • Y
		Reproductive toxicity • No data on human fertility • 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. • No in monkeys and rats • 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. • N • 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. • 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. • N
		Teratogenicity or other developmental toxicity

		• Caused fetal harm in animal testing below the human dose. • PI: In animal studies, administration of ceritinib to rats (less than ½ Maximum Recommended Human Dose (MRHD)) and rabbits (0.13% to 1.3% MRHD) during organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. • Fetal deformities at subclinical dosing in rats/rabbits. • Embryofetal toxicity; 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. • N • 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. • Based on its mechanism of action, ZYKADIA may cause fetal harm when administered to a pregnant woman. In a rat embryo-fetal development study 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 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 mal-positioned gallbladder and retro-esophageal 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. • Y
		Rationale for Proposing Placement on the List
		Teratogenicity or other developmental toxicity: embryo-fetal toxicity at low doses in rats and rabbits

Generic Drug Name	**Proprietary Name**	**Stakeholder Reviewer Comments**
clobazam	Onfi	Carcinogenicity • Increased incidence of thyroid follicular cell adenomas in males at high dose. • Not classified as a carcinogen by IARC, AGGIH, NTP, or OSHA. • Yes – rats • 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. • N (effects in one animal/thyrid adenomas), no other effects. • 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.

		• 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. • N
		Genotoxicity • In Vitro tests and mouse studies negative. • No • 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. • N • 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. • 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. • N
		Organ toxicity at low doses • Renal and hepatic impairment • No • Somnolence or sedation – increased response with alcohol consumption. Potentiation of sedation from concomitant use with central nervous system depressants • Withdrawal symptoms • Serious dermatological reactions • Physical and psychological dependence • Suicidal behavior and ideation • N • Adverse reactions that occurred at least 10% more frequently than placebo in any ONFI dose included constipation, somnolence or sedation, pyrexia, lethargy, and drooling. • N
		Reproductive toxicity • Developmental toxicity in animal studies including fetal malformations. • MSDS: Reproductive toxicity - - Laboratory experiments have shown teratogenic effects. • Reproductive toxicity – Rat – Oral - Paternal Effects: Testes, epididymis, sperm duct. Effects on Newborn: Stillbirth.

		• Overexposure may cause reproductive disorder(s) based on tests with laboratory animals. • Developmental Toxicity – Rat – Oral – specific Developmental Abnormalities: Musculoskeletal system. • Yes – rats at supratherapeutic doses • 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. • Y • 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. • N
		Teratogenicity or other developmental toxicity • Inconclusive data for benzodiazepines. • 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 embryo-fetal 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 embryo-fetal 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. • Yes in rabbits/rats. • In animal studies, administration of clobazam during pregnancy resulted in developmental toxicity, including increased incidences of fetal malformations, at plasma exposures for clobazam and its major active metabolite, Ndesmethylclobazam, below those expected at therapeutic doses in patients. 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. • N • 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. • Based on animal data, may cause fetal harm. 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. • Y
		Rationale for Proposing Placement 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**	**Stakeholder Reviewer Comments**
cobimetinib	Cotellic	Carcinogenicity • Reports of cutaneous malignancies

		• No carcinogenicity data; however, new cutaneous malignancies may occur in patients. • Yes – secondary malignancies in humans • Carcinogenicity studies with cobimetinib have not been conducted. • N Not according to PI section 13 but in offspring of pregnant animals! • Carcinogenicity studies with cobimetinib have not been conducted • New primary malignancies, cutaneous and non-cutaneous, can occur. No non-clinical studies identified. Pharmacological inhibitors of MEK as a class are associated with increased cutaneous malignancy. • N
		Genotoxicity • Cobimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in bone marrow of rats. • No • Cobimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in bone marrow of rats. • N • Cobimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in bone marrow of rats. • Cobimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in bone marrow of rats. • N
		Organ toxicity at low doses • Hemorrhage, cardiomyopathy, hepatotoxicity • No information available • No • New primary malignancies, cutaneous and non-cutaneous: Monitor patients for new malignancies prior to initiation of therapy, while on therapy, and for up to 6 months following the last dose of COTELLIC. o (5.1) Hemorrhage: Major hemorrhagic events can occur with COTELLIC. Monitor for signs and symptoms of bleeding. (5.2, 2.4) o Cardiomyopathy: The risk of cardiomyopathy is increased in patients receiving COTELLIC with vemurafenib compared with vemurafenib as a single agent. The safety of COTELLIC has not been established in patients with decreased left ventricular ejection fraction (LVEF). Evaluate LVEF before treatment, after one month of treatment,

		then every 3 months thereafter during treatment with COTELLIC. (5.3, 2.4). o Severe dermatologic reactions: Monitor for severe skin rashes. Interrupt, reduce, or discontinue COTELLIC. (5.4, 2.4) o Serous retinopathy and retinal vein occlusion: perform an ophthalmological evaluation at regular intervals and for any visual disturbances. Permanently discontinue COTELLIC for retinal vein occlusion (RVO). (5.5, 2.4) o Hepatotoxicity: monitor liver laboratory tests during treatment and as clinically indicated. (5.6, 2.4) o Rhabdomyolysis: monitor creatinine phosphokinase periodically and as clinically indicated for signs and symptoms of rhabdomyolysis. (5.7, 2.4) o Embryo-Fetal Toxicity: can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.9, 2.4) • N • New Primary Cutaneous Malignancies o Hemorrhage o Cardiomyopathy Serious Dermatologic Reactions o Serous Retinopathy and Retinal Vein Occlusion o Hepatotoxicity o Rhabdomyolysis o Severe Photosensitivity • Reproductive tissues adversely affected (see above). • Y
		Reproductive toxicity • May reduce fertility • Based on findings in animals, COTELLIC may reduce fertility in females and males of reproductive potential. Administration of cobimetinib to pregnant rats during the period of organogenesis resulted in increased 250 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. • Potential based on animal studies • 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. • Yes, impaired fertility at doses twice the human recommended dose (PI Section 13).

		• Based on findings in animals, COTELLIC may reduce fertility in females and males of reproductive potential o 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. • 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. • Y
		Teratogenicity or other developmental toxicity • Animal studies organogenesis, teratogenic and emryotoxic with AUC up to 1.4X dose. • 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. Post-implantation loss was primarily due to early resorptions. Fetal malformations of the great vessels and skull (eye sockets) occurred at the same exposures. • Yes – in rats • In animal reproduction studies, oral administration of 151 cobimetinib in pregnant rats during the period of organogenesis was teratogenic and embryotoxic at doses 152 resulting in exposures [area under the curves (AUCs)] that were 0.9 to 1.4-times those observed in humans at the recommended human 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. • N Not according to section 13 but in offspring! • 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. • Based on its mechanism of action and findings from animal reproduction studies, COTELLIC can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of cobimetinib in pregnant rats during the period of organogenesis was teratogenic and embryotoxic at doses resulting in exposures [area under the curves (AUCs)] that were 0.9 to 1.4-times those observed in humans at the recommended human dose of 60 mg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with COTELLIC, and for 2 weeks following the final dose of COTELLIC. • Y
		Rationale for Proposing Placement 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**	**Stakeholder Reviewer Comments**
Darbepoetin alfa	Aranesp	Carcinogenicity • Not evaluated in humans. No incidence in animal studies. • No • 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. • N • 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. • No studies identified. • N

		Genotoxicity • Not mutagenic in animal studies. • MSDS: Not genotoxic based on a battery of in vitro and in vivo studies. • No • 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 cells), and in the *in vivo* mouse erythrocyte micronucleus assay • N • 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 cells), and in the in vivo mouse erythrocyte micronucleus assay. • Negative in the in vitro bacterial reverse mutation assay, the in vitro mammalian cell gene mutation assay (using CHO cells), and in the in vivo mouse erythrocyte micronucleus assay. • N
		Organ toxicity at low doses • No • Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism *[see Warnings and Precautions (5.1)]* • Increased Mortality and/or Increased Risk of Tumor Progression or • Recurrence in Patients with Cancer • *[see Warnings and Precautions (5.3)]* • Hypertension *[see Warnings and Precautions (5.4)]* • Seizures *[see Warnings and Precautions (5.5)]* • PRCA *[see Warnings and Precautions (5.7)]* • Serious allergic reactions • N • Aranesp single dose safety pharmacology studies were conducted that evaluated the potential effects on the cardiovascular, respiratory, and central nervous system function in dogs (100 µg/kg), guinea pigs (45 µg/kg), and mice (45 µg/kg), respectively. The observed effects (increased in hematocrit, hemoglobin, red blood cells, and reticulocytes), were seen at all doses and are due to the known pharmacological effect of AranespÒ. In addition, Aranesp was well-tolerated following single IV doses up to 200 µg/kg in rats and 150 µg/kg in dogs. • The expected pharmacologic effects (increases in hematocrit, hemoglobin, red blood cells, and reticulocytes) were seen at all doses tested in these studies (as low as 1.5 µg/kg administered once weekly for 6-months). All toxicities observed in these species were related to exaggerated

		pharmacology and extremely high hematocrit. Aranesp is generally well-tolerated in humans. The most common adverse events in healthy volunteers were headache, abdominal pain and dizziness. In patients administered Aranesp, rare but serious adverse events (e.g., hypertension, cardiovascular events (heart attack, stroke), seizure, and pure red blood cell aplasia) including death have been observed. • Patients with CKD: Adverse reactions in ≥ 10% of Aranesp-treated patients in clinical studies were hypertension, dyspnea, peripheral edema, cough, and procedural hypotension. • Patients with Cancer Receiving Chemotherapy: Adverse reactions in ≥ 1% of Aranesp-treated patients in clinical studies were abdominal pain, edema, and thrombovascular events. • N
		Reproductive toxicity • Increased post-implantation losses in animal testing at 10X dose. • No • 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. • N • 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. • 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. • Y
		Teratogenicity or other developmental toxicity • No evidence of embryo-fetal toxicity in animal studies at 20X higher dose. • When Aranesp was administered intravenously to rats during pregnancy and lactation, fetal effects occurred. Aranesp has also increased the incidence of post-implantation losses in rats. • Yes – post implantation loss in animals; decreased fetal body weights at supra-therapeutic doses. • In animal reproduction and developmental toxicity studies, Aranesp increased early post-implantation loss. o When Aranesp was administered intravenously to healthy pregnant rats and rabbits, there was no evidence of embryofetal toxicity or other adverse outcomes at the intravenous 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. Slightly reduced fetal weights were observed when healthy rat and rabbit mothers received doses of 1 mcg/kg or more. This dose of 1 mcg/kg is near the clinical recommended starting dose. While no adverse effects on uterine implantation occurred in animals, there was an increase in early post-implantation loss

		in animal fertility studies. It is not clear whether the increased post-implantation loss reflects a drug effect on the uterine environment or on the conceptus. No significant placental transfer of Aranesp was detected. o In a peri/postnatal development study, pregnant female rats received Aranesp intravenously every other day from implantation throughout pregnancy and lactation. The lowest dose tested, 0.5 mcg/kg, did not cause fetal toxicity; this dose is approximately equivalent to the clinical recommended starting dose. At maternal doses of 2.5 mcg/kg and higher, pups had decreased fetal body weights, which correlated with a slight increase in the incidence of fetal deaths, as well as delayed eye opening and delayed preputial separation *[see Nonclinical Toxicology (13.3)]*. • N • When Aranesp was administered intravenously to rats during pregancy and lactation, fetal effects occurred. Aranesp has also increased the incidence of post-implantation losses 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). • In animal reproduction and developmental toxicity studies, Aranesp increased early post-implantation loss. When

		Aranesp was administered intravenously to healthy pregnant rats and rabbits, there was no evidence of embryofetal toxicity or other adverse outcomes at the intravenous 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. Slightly reduced fetal weights were observed when healthy rat and rabbit mothers received doses of 1 mcg/kg or more. This dose of 1 mcg/kg is near the clinical recommended starting dose. While no adverse effects on uterine implantation occurred in animals, there was an increase in early post-implantation loss in animal fertility studies. It is not clear whether the increased post-implantation loss reflects a drug effect on the uterine environment or on the conceptus. No significant placental transfer of Aranesp was detected. • 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). • N
		Rationale for Proposing Placement 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**	**Stakeholder Reviewer Comments**
dihydroergotamine	Migranal	Carcinogenicity • No data • No information • Studies ongoing • 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.Tests ongoing – no study reports identified.

		• N
		Genotoxicity • Dihyddroergotamine mesylate 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 of absence of metabolic activation in two gene mutation assays (The Ames and the in vitro mammalian Chinest hamster V79/HGPRT assay for DNA damage (the rat hepatocyte unscheduled DNA synthesis test). Dihydroergotamine was not clastogenic in the in vivo mouse and hamster micronucleus tests. • Clastogenic in chromosomal aberration assays; not with other testing. • 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. • Y • Assessment of the carcinogenic potential of dihydroergotamine mesylate in mice and rats is ongoing. • 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. • N
		Organ toxicity at low doses • Peripheral ischemia with concomitant CYP 3A4 inhibitors. Coronary artery vasospasm. • No data available. • No

		• Contra-indicated – hypertension; other 5HT1 agonists; vascular disease/surgery; Nicotine not to be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hyper-cholesterolemia, smoker, obesity, diabetes, strong family history of CAD, females who are surgically or physiologically post-menopausal, or males who are over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. • In laboratory animals, significant lethality occurs when dihydroergotamine is given at I.V. doses of 44 mg/kg in mice, 130 mg/kg in rats, and 37 mg/kg in rabbits. • N • Serious cardiac events, including some that have been fatal, have occurred following use of the parenteral form of dihydroergotamine mesylate (D.H.E. 45® Injection), but are extremely rare. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. • N
		Reproductive toxicity • No data. Developmental toxicity in animal models. • No human data. 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). • No • 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] approximately 9 to 11 times those in humans receiving the MRDD of 4 mg). • Y • Migranal® (dihydroergotamine mesylate, USP) Nasal Spray may cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties and, therefore, should not be administered during pregnancy. • Impairment of fertility not evaluated for 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] approximately 9 to 11 times those in humans receiving the MRDD of 4 mg). • Y
		Teratogenicity or other developmental toxicity • Yes – oxytocic properties; toxicity in rabbits • In embryo-fetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposures [AUC] approximately 0.4-1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryo-fetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times human exposures at the MRDD) during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. 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.oxytocic properties. • ? • Are no adequate studies of dihydroergotamine in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. In embryofetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposures [AUC] approximately 0.4 -1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryo-fetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times human exposures at the MRDD)

		during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. 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. • May cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties and, therefore, should not be administered during pregnancy. Developmental toxicity has been demonstrated in experimental animals. In embryo-fetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposures [AUC] approximately 0.4-1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryo-fetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times human exposures at the MRDD) during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. 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 utero-=placental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone. • Y
		Rationale for Proposing Placement on the List

		Reproductive toxicity: oxytocic properties at low doses in humans

Generic Drug Name	Proprietary Name	Stakeholder Reviewer Comments
exenatide	Bydureon	Carcinogenicity • Risk of thyroid C-cell tumors in animal studies higher than human dosing. • 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% o 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 was observed at any dose. The human relevance of these findings is currently unknown. o A 104-week carcinogenicity study was conducted with exenatide, the active ingredient of 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-cell adenomas were observed in female rats at all exenatide doses. The incidences of female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups. o 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. • Yes – thyroid tumors • In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. 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% (non-statistically 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. • Y • 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). 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. • 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). 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, 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 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. • N
		Genotoxicity • No data • 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. • No • 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. • N

		• 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. • Exenatide was 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. • N
		Organ toxicity at low doses • No data • Pancreatitis, renal dysfunction • Contra-indicated in individuals with medullary thyroid carcinoma, acute pancreatitis, hypoglycemia is increased when exenatide is used in combination with insulin secretagogues. • N • Most common (≥5%) and occurring more frequently than comparator in clinical trials: nausea, diarrhea, headache, vomiting, constipation, injection-site pruritus, injection-site nodule, and dyspepsia. • N
		Reproductive toxicity • No human data. Animal data showed skeletal ossification. • 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. • No • 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. • Y • 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 mouse fertility studies with exenatide, 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. • N
		Teratogenicity or other developmental toxicity • No teratogenic findings in animal studies • 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 area under the time-concentration curve (AUC). • Birth defects in rats. • Exenatide extended-release administered during the major period of organogenesis reduced fetal growth and produced skeletal ossification deficits in association with maternal effects; exenatide extended-release was not teratogenic in rats. In animal developmental studies, exenatide, the active ingredient of BYDUREON, caused cleft palate, irregular skeletal ossification, and an increased number of neonatal deaths. o 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 an dproduced 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 area under the time-concentration curve (AUC). • Y • Pregnancy Category C o There are no adequate and well-controlled studies of BYDUREON use in pregnant women. In rats, exenatide extended-release administered during the major period of organogenesis reduced fetal growth and produced skeletal ossification deficits in association with maternal effects; exenatide extended-release was not teratogenic in rats. In animal developmental studies, exenatide, the active ingredient of BYDUREON, caused cleft palate, irregular skeletal ossification, and an increased number of neonatal deaths. BYDUREON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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 area under the time-concentration curve (AUC) [see Nonclinical Toxicology (13.3)]. Female mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7 had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see Nonclinical Toxicology (13.3)]. In developmental toxicity studies, pregnant animals received exenatide, the active ingredient of BYDUREON, subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given subcutaneous doses of exenatide at 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 4 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. Fetuses from pregnant mice given subcutaneous doses of exenatide at 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate, and skeletal effects at systemic exposure that is equivalent to the human exposure

		resulting from the recommended dose of 2 mg/week, based on AUC [see Nonclinical Toxicology (13.3)]. o Lactating mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2 to 4 in dams given 6 mcg/kg/day, a systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. • 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 area under the time-concentration curve (AUC). o Female mice given subcutaneous doses of exenatide, at 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7 had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. In developmental toxicity studies, pregnant animals received exenatide subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given subcutaneous doses of exenatide at 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 4 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. Fetuses from pregnant mice given subcutaneous doses of exenatide at 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate, and skeletal effects at systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. • N
		Rationale for Proposing Placement on the List
		Carcinogenicity and Teratogenicity or other developmental toxicity: thyroid C-cell tumors in rat studies; adverse fetal effects in rats and mice

Generic Drug Name	Proprietary Name	Stakeholder Reviewer Comments
interferon beta-1b	Betaseron, Extavia	Carcinogenicity • No data • No information • Not studied • BETASERON has not been tested for its carcinogenic potential in animals. • N • BETASERON has not been tested for its carcinogenic potential in animals. • Not evaluated – no structural or mechanism of action-based rationale to suspect carc. potential. • N
		Genotoxicity • Interferon beta-1b was not genotoxic in the in vitro Ames bacterial test or the in vitro chromosomal aberration assay in human peripheral blood lymphocytes. Interferon beta-1b treatment of mouse BALBc-3T3 cells did not result in increased transformation frequency in an in vitro model of tumor transformation. • No • 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. • N • 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. • 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. No structural or mechanism of action-based rationale to suspect mutagenic potential. • N
		Organ toxicity at low doses • Hepatic injury, depression, CHF, leukopenia. • Lupus at therapeutic doses (0.25mg every other day). • Flu-like sympotoms o Hepatotoxicity o Suicide

		○ Leukopenia ○ Thrombotic Micro-angiopathy ○ Seizure • In controlled clinical trials, the most common adverse reactions (at least 5% more frequent on BETASERON than on placebo) were: injection site reaction, lymphopenia, flu-like symptoms, myalgia, leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia. Adverse Reactions: Hepatic Injury Anaphylaxis and Other Allergic Reactions Depression and Suicide Congestive Heart Failure Injection Site Necrosis and Reactions Leukopenia Thrombotic Microangiopathy Flu-like Symptom Complex Seizures Postmarketing Adverse Effects: Blood and lymphatic system disorders: Anemia, Thrombocytopenia Endocrine disorders: Hypothyroidism, Hyperthyroidism, Thyroid dysfunction. Metabolism and nutrition disorders: Triglyceride increased, Anorexia, Weight decrease, Weight increase Psychiatric disorders: Anxiety, Confusion, Emotional lability Nervous system disorders: Convulsion, Dizziness, Psychotic symptoms: Cardiac disorders: Cardiomyopathy, Palpitations, Tachycardia; Vascular disorders: Vasodilatation Respiratory, thoracic and mediastinal disorders: Bronchospasm Gastrointestinal disorders: Diarrhea, Nausea, Pancreatitis, Vomiting Hepatobiliary disorders: Hepatitis, Gamma GT increased Skin and subcutaneous tissue disorders: Alopecia, Pruritus, Skin discoloration, Urticaria Musculoskeletal and connective tissue disorders: Arthralgia Reproductive system and breast disorder: Menorrhagia • N
		Reproductive toxicity • Increased risk of abortion in higher doses in animal studies. • Administration of interferon beta-1b (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/m2) basis. The potential for other effects on fertility or reproductive performance was not evaluated. • No • 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/m2) basis. The potential for other effects on fertility or reproductive performance was not evaluated. • Y • 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/m2) 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/m2) basis. The potential for other effects on fertility or reproductive performance was not evaluated. • N
		Teratogenicity or other developmental toxicity • No data • When interferon beta-1b (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/m2) basis. A no-effect dose for embryo-fetal developmental toxicity in rhesus monkeys was not established. • Abortifacient activity at supra-therapeutic doses.

		• 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/m2) basis. A no-effect dose for embryo-fetal developmental toxicity in rhesus monkeys was not established. • N • 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/m2) basis. A no-effect dose for embryo-fetal developmental toxicity in rhesus monkeys was not established. • 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/m2) basis. A no-effect dose for embryo-fetal developmental toxicity in rhesus monkeys was not established. • N
		Rationale for Proposing Placement on the List
		Reproductive toxicity: spontaneous abortions in human clinical trials

Generic Drug Name	**Proprietary Name**	**Stakeholder Reviewer Comments**
isotretinoin	Accutane	Carcinogenicity • Pheochromocytoma in rats. • In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain
		Genotoxicity

		• Weakly positive Ames in one of two tests; other was negative. • The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6 x background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose-response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D7 assay, in vitro clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.
		Organ toxicity at low doses • No • Many Adverse Reactions; Contraindications at Therapeutic Dose.
		Reproductive toxicity • In dogs at supratherapeutic doses • In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area). • In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving Accutane (isotretinoin) therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.
		Teratogenicity or other developmental toxicity • Multiple birth defects • Accutane must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking Accutane in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be

		affected. There are no accurate means of determining whether an exposed fetus has been affected. o 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. o 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 Placement on the List
		Teratogenicity or other developmental toxicity: severe fetal malformations at any dose in humans

Generic Drug Name	**Proprietary Name**	**Stakeholder Reviewer Comments**
ivabradine	Corlaner	Carcinogenicity • Not carcinogenic in 2-year rat and mouse studies. (MSDS). • 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. • No • Not carcinogenic in 2-year rat and mouse studies. SDS; 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. • N • 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. • 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. • N
		Genotoxicity • Not genotoxic based on a battery of in vitro and in vivo studies (MSDS). • 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 • No • 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. • N • 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. • 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. • N
		Organ toxicity at low doses • Risk of atrial fib, bradycardia and conduction disorders. • No • Acute decompensated heart failure • Blood pressure less than 90/50 mm-Hg. • Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present. • Resting heart rate less than 60/bpm prior to treatment. • Severe hepatic impairment. • Pacemaker dependence (heart rate maintained exclusively by the pacemaker). • Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors. -Fetal Toxicity -Atrial Fibrillation -Bradycardia and Conduction Disturbances • 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 effect of ivabradine related to its interaction with hyperpolarization-activated Ih currents in the retina, which share homology with the cardiac pacemaker If current. • N • Most common adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes). • Fetal Toxicity, Atrial Fibrillation, Bradycardia and Conduction Disturbances • Corlanor increases the risk of atrial fibrillation. In SHIFT, the rate of atrial fibrillation was 5.0% per patient-year in patients treated with Corlanor and 3.9% per patient-year in patients treated with placebo. • Bradycardia, sinus arrest, and heart block have occurred with Corlanor. The rate of bradycardia was 6.0% per patient-year in patients treated with Corlanor (2.7% symptomatic; 3.4% asymptomatic) and 1.3% per patient-year in patients treated with placebo.

		• 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. • 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. • N
		Reproductive toxicity • May cause fetal harm in animal studies 1-3X 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. • No • 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. • Y • 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. • 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. • N
		Teratogenicity or other developmental toxicity • Based on findings in animals, Corlanor may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Corlanor in pregnant women to inform any drug-associated risks. In animal reproduction studies, oral administration of ivabradine to pregnant rats during organogenesis at a dosage providing 1 to 3 times the human exposure (AUC0-24hr) at the MRHD resulted in embryo-fetal toxicity and teratogenicity manifested as abnormal shape of the heart, interventricular septal defect, and complex anomalies of primary arteries. Increased postnatal mortality was associated with these teratogenic effects in rats. In pregnant rabbits, increased post-implantation loss was noted at an exposure (AUC0-24hr) 5 times the human exposure at the MRHD. Lower doses were not tested in rabbits. The background risk of major birth defects for the indicated population is unknown.

		• 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 invabradine during the period of organogenesis (gestation day 618) at doses of 7, 14, or 28 mg/kg/day resulted in fetal toxicity and teratogenicity. Treatment with all doses $\underline{\geq}$ 7 mg/kg/day (equivalent to 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). • Fetal toxicity at clinical doses • 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) at the maximum recommended human dose (MRHD). In pregnant rabbits, increased post-implantation loss was noted at an exposure (AUC0-24hr) 5 times the human exposure at the MRHD (LOAEL). • 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 618) 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). • Y • In animal reproduction studies, oral administration of ivabradine to pregnant rats during organogenesis at a dosage providing 1 to 3 times the human exposure (AUC0-24hr) at the MRHD resulted in embryo-fetal toxicity and teratogenicity manifested as abnormal shape of the heart, interventricular septal defect, and complex anomalies of primary arteries. Increased postnatal mortality was associated with these teratogenic effects in rats. In pregnant rabbits, increased post-implantation loss was noted at an exposure (AUC0-24hr) 5 times the human exposure at the MRHD. Lower doses were not tested in rabbits. The background risk of major birth defects for the indicated population is unknown. The estimated background risk of major birth defects in the U.S. general population is 2 to 4%, however, and the estimated risk of miscarriage is 15 to 20% in clinically recognized pregnancies. Advise a pregnant woman of the potential risk to the fetus. • 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 618) 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. • 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 618) 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). • Y
		Rationale for Proposing Placement on the List
		Teratogenicity or other developmental toxicity: embryo-fetal toxicity and teratogenicity at low doses in rats

Generic Drug Name	**Proprietary Name**	**Stakeholder Reviewer Comments**

lenvatinib	Lenvima	Carcinogenicity • No data • No data available • No • Not tested • N • Carcinogenicity studies have not been conducted with lenvatinib. • Carcinogenicity studies have not been conducted with lenvatinib. • N
		Genotoxicity • No data • 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. • No • 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. • Y • 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. • 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. • N
		Organ toxicity at low doses • Cardiac, hepatic and renal toxicity • No • Hypertension • Cardiac Dysfunction • Arterial Thromboembolic Events • Hepatotoxicity • Proteinuria • Renal Failure and Impairment • Gastro-intestinal Perforation and Fistula Formation • QT Interval Prolongation • Hypocalcemia • Reversible Posterior Leukoencephalopathy Syndrome • Hemorrhagic Events • Impairment of Thyroid Stimulating Hormone Suppression. • N

		• The most common adverse reactions (incidence greater than or equal to 30%) for LENVIMA are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting. • Hypertension • Cardiac Dysfunction • Arterial Thromboembolic Events • Hepatotoxicity • Proteinuria • Renal Failure and Impairment • Gastrointestinal Perforation and Fistula Formation • QT Interval Prolongation • Hypocalcemia Reversible Posterior Leukoencephalopathy Syndrome • Hemorrhagic Events • Impairment of Thyroid Stimulating Hormone Suppression • Y
		Reproductive toxicity • Embryotoxicity, fetotoxicity • 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. • Potential for reduced fertility in males and females • 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. • Y • 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. 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. • 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. • Y
		Teratogenicity or other developmental toxicity • Embryotoxicity, fetotoxicity, and teratogenicity in animal studies below human doses • 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% post-implantation 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). • Present in animal models • 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). • Y • 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). • 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). • Y
		Rationale for Proposing Placement 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**	**Stakeholder Reviewer Comments**
miltefosine	Impavido	Carcinogenicity • 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. • No studied • 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). • ? • 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. • 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. • N
		Genotoxicity • No data • 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. • No • Miltefosine tested negative in the AMES-Salmonella test, DNAamplification 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. • N • Miltefosine tested negative in the AMES-Salmonella test, DNAamplification 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. • 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. • N
		Organ toxicity at low doses • Elevated serum creatinine and liver transaminases noted in clinical trials. • 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: o 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). • No • 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). • Adverse reactions occurring in ≥2% of patients include nausea, vomiting, diarrhea, headache, decreased appetite,

		dizziness, abdominal pain, pruritus, somnolence, elevated transaminases, and elevated creatinine. • Renal Effects. • Hepatic Effects. • Gastrointestinal Effects. Thrombocytopenia. • 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). • N
		Reproductive toxicity • Embryo-fetal toxicity. Testicular atrophy and impaired fertility in male rats. • 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. o 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. • In rats and dogs. • Miltefosine caused impaired fertility in rats and caused reversible follicular atresia and diestrus in dogs at doses approximately 1.0 and 0.2 times respectively the MRHD. 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. 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. • Y (embryofetal toxicity including death and teratogenicity, was observed in embryo-fetal studies in rats and rabbits administered oral miltefosine during organogenesis at doses that were respectively 0.06 and 0.2 times the maximum recommended human dose (MRHD), based on body surface area (BSA) comparison. Numerous visceral and skeletal fetal malformations were observed in a fertility study in female rats administered miltefosine prior to mating through day 7 of pregnancy at doses 0.3 times the MRHD.). • Reproductive effects. Miltefosine caused testicular atrophy and impaired fertility in male rats and impaired fertility in female rats. Advise patients of reproductive toxicities in animal studies and that the potential effects on human fertility have not been adequately evaluated. 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. Effects on human female fertility have not been formally studied. 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. Scrotal pain and decreased or absent ejaculation during therapy have been reported during IMPAVIDO therapy. The effects of IMPAVIDO on human male fertility have not been adequately studied. 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. • 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. • Y
		Teratogenicity or other developmental toxicity • 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. [see Contraindications (4.1), Nonclinical Toxicology (13.1)]. • Fetal death in animals at less than human doses • Human pregnancy data not available, however, embryo-fetal toxicity including death and teratogenicity, was observed in embryo-fetal studies in rats and rabbits administered oral miltefosine during organogenesis at doses that were respectively 0.06 and 0.2 times the maximum recommended human dose (MRHD), based on body surface area (BSA) comparison. Numerous visceral and skeletal fetal malformations were observed in a fertility study in female rats administered miltefosine prior to mating through day 7 of pregnancy at doses 0.3 times the MRHD. Miltefosine administration in 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 mal-positioned 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. • Y

		• 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. • 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 mal-positioned 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. • Y

		Rationale for Proposing Placement on the List
		Teratogenicity or other developmental toxicity: fetal death and teratogenicity at low doses in rats and rabbits

Generic Drug Name	**Proprietary Name**	**Stakeholder Reviewer Comments**
olaparib	Lynparza	Carcinogenicity • Not classified as a human carcinogen by IARC, ACGIH, NTP, and OSHA. • Yes – AML/MDS • Not assessed • Likely • Carcinogenicity studies have not been conducted with olaparib. • Carcinogenicity studies have not been conducted with olaparib. • N
		Genotoxicity • 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. • Clastogenic • 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. • Y • 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. • 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.

		• Y
		Organ toxicity at low doses • MDS and AML in exposed patients, pneumonitis • No • Lymphatic disorders o Anemia 34 18 o Gastro-intestinal disorders o Abdominal paid/discomfort 43 8 o Decrease appetite 22 1 o Nausea 64 3 o Vomiting 43 4 o Diarrhea 31 1 o Dyspepsia 25 0 o General disorders o Fatigue/asthenia 66 8 o Infections and infestations • Nasopharyngitis/URI 26 0 • **Musculoskeletal and Connective Tissue disorders** • Arthralgia/musculoskeletal pain 21 0 • Myalgia 22 • Decrease in hemoglobin (anemia) 90 15 • Decrease in absolute neutrophil count (neutropenia) 25 7 • Decrease in platelets (thrombocytopenia) 30 3 • Decrease in lymphocytes (lymphopenia) 56 17 • Mean corpuscular volume elevation 57 - • Increase in creatinine* • Most common adverse reactions (≥20%) in clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/pharyngitis/URI, cough, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash and abdominal pain/discomfort. o Most common laboratory abnormalities (≥25%) were increase in creatinine, mean corpuscular volume elevation, decrease in hemoglobin, decrease in lymphocytes, decrease in absolute neutrophil count, and decrease in platelets. • N
		Reproductive toxicity • Embryo-Fetal toxicity • 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). o 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). • No • 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 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). • Y • 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 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 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). • N
		Teratogenicity or other developmental toxicity • Teratogenic and embryo-fetal toxicity below human dose. • Can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Olaparib was teratogenic and caused embryo-fetal toxicity in rats at exposures below those in patients receiving the recommended human dose of 400 mg twice daily. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for loss of the pregnancy. 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. • Embryo-fetal toxicity • Lynparza can cause fetal harm • Y (Olaparib was teratogenic and caused embryo-fetal toxicity in rats at exposures below those in patients receiving the recommended human dose of 400 mg twice daily.) • 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 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. • Y
		Rationale for Proposing Placement 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**	**Stakeholder Reviewer Comments**
osimertinib	Tagrisso	Carcinogenicity • (Carcinogenicity studies have not been performed with osimertinib. • No studied • Not assessed • N • Carcinogenicity studies have not been performed with osimertinib.

		• Carcinogenicity studies have not been performed with osimertinib. • N
		Genotoxicity • Suspected of causing genetic defects (MSDS). • Osimertinib did not cause genetic damage in in vitro and in vivo assays. • No • Osimertinib did not cause genetic damage in in vitro and in vivo assays. • N • Osimertinib did not cause genetic damage in in vitro and in vivo assays. • Osimertinib did not cause genetic damage in in vitro and in vivo assays. • N
		Organ toxicity at low doses • No data • No data available • No • Most common adverse reactions (≥25%) were diarrhea, rash, dry skin, and nail toxicity. o Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 3.3% of patients. o QTc Interval Prolongation. o Cardiomyopathy: Occurred in 1.4% of patients. • Y
		Reproductive toxicity • May impair fertility in females and males (PI). • 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. • Potential for infertility • 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. • Based on studies in animals, male fertility may be impaired by treatment with TAGRISSO. Degenerative changes were present in the tests 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. • Nonclinical female fertility studies have not been conducted. 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. • Y also male fertility impairment • 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. • Nonclinical female fertility studies have not been conducted. 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. • 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. • Nonclinical female fertility studies have not been conducted. 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. • Y
		Teratogenicity or other developmental toxicity • Embryonic death in animals at 1.5X human dose. • 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. • Embryo-fetal toxicity at 1.5 times human doses • 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 recommended human dose.

		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. • N • 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. • 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. • Y
		Rationale for Proposing Placement 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**	**Stakeholder Reviewer Comments**
sonidegib	Odomzo	Carcinogenicity • Carcinogenicity studies with sonidegib have not been performed. • No studied • Not performed • N • Carcinogenicity studies with sonidegib have not been performed. • Carcinogenicity studies with sonidegib have not been performed. • N
		Genotoxicity • Suspected of causing genetic damage (MSDS). • Sonidegib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and was not clastogenic or aneugenic in the in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus assay. • No • Sonidegib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and was not clastogenic or aneugenic in the in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus assay. • N • Sonidegib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and was not clastogenic or aneugenic in the in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus assay. • Sonidegib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and was not clastogenic or aneugenic in the in vitro human chromosome aberration assay or in vivo rat bone marrow micronucleus assay. • N
		Organ toxicity at low doses

		• Respiratory system toxicity with single exposure (MSDS). • No • Musculoskeletal Adverse Reactions • Usual chemotherapy AEs. • The most common adverse reactions occurring in ≥10% of patients are muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus. • Musculoskeletal Adverse Reactions. 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). • N
		Reproductive toxicity • Suspected of damaging fertility or the unborn child (MSDS); No data available. • 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. • Yes – female rats • Amenorrhea lasting for at least 18 months occurred in two of 14 pre-menopausal women treated with ODOMZO 200 mg or 800 mg once daily. 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. • Y (In animal reproduction studies, oral administration of sonidegib during organogenesis at doses below the recommended human dose of 200 mg resulted in embryotoxicity, fetotoxicity, and teratogenicity in rabbits *[see Data]*. Teratogenic effects observed included severe midline defects, missing digits, and other irreversible malformations). • 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. • Y
		• Teratogenicity or other developmental toxicity • Embryo-fetal death or severe birth defects when administered to a pregnant woman and is embryo-toxic, feto-toxic and teratogenic in animals (PI). • Can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. In animal reproduction studies, sonidegib was embryotoxic, fetotoxic, and

		teratogenic at maternal exposures below the recommended human dose of 200 mg. • Based on its mechanism of action and data from animal reproduction studies, ODOMZO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available data on the use of ODOMZO in pregnant women. In animal reproduction studies, oral administration of sonidegib during organogenesis at doses below the recommended human dose of 200 mg resulted in embryotoxicity, fetotoxicity, and teratogenicity in rabbits [see Data]. Teratogenic effects observed included severe midline defects, missing digits, and other irreversible malformations. Advise pregnant women of the potential risk to a fetus. • 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. • As above • 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. • N • Based on its mechanism of action and data from animal reproduction studies, ODOMZO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available data on the use of ODOMZO in pregnant women. In animal reproduction studies, oral administration of sonidegib during organogenesis at doses below the recommended human dose of 200 mg resulted in embryotoxicity, fetotoxicity, and teratogenicity in rabbits [see Data]. Teratogenic effects observed included severe midline defects, missing digits, and other irreversible malformations. • 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. • 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. • Y
		Rationale for Proposing Placement on the List
		Reproductive toxicity and Teratogenicity or other developmental toxicity: embryo-fetal toxicity, teratogenesis, and spontaneous abortions at low doses in rabbits

Generic Drug Name	**Proprietary Name**	**Stakeholder Reviewer Comments**
trastuzumab	Herceptin	Carcinogenicity • Formulation not listed by NTP, IARC or OSHA. • Herceptin has not been tested for carcinogenic potential • Not studied • Not tested • N • Herceptin has not been tested for carcinogenic potential. • N
		Genotoxicity • 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. • No • 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 Herceptin. • N

		• 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 Herceptin. • N
		Organ toxicity at low doses • Renal and cardiac risks during treatment • No • Cardiomyopathy o Pulmonary toxicity o Usual chemotherapy AEs • Adjuvant Breast Cancer • Most common adverse reactions (≥5%) are headache, diarrhea, nausea, and chills. Metastatic Breast Cancer • Most common adverse reactions (≥ 10%) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. Metastatic Gastric Cancer • Most common adverse reactions (≥10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions in patients receiving Herceptin in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [see Boxed Warning: Cardiomyopathy]. Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF). There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions The following adverse reactions are discussed in greater detail in other sections of the label:

		Cardiomyopathy Infusion reactions Embryo-fetal Toxicity Pulmonary toxicity Exacerbation of chemotherapy-induced neutropenia • Y
		Reproductive toxicity • Parenteral administration to pregnant women can cause fetal harm. • A fertility study was conducted in female Cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg of trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels. • No • 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. • Y (oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.) • 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. • N
		Teratogenicity or other developmental toxicity • Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as 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. • Oligohydraminios, pulmonary hypoplasia, neonatal death in humans. • In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. • No teratogenic effects were observed in offspring from pregnant cynomolgus monkeys administered trastuzumab during the period of organogenesis at doses up to 25 times the 546 recommended weekly human dose of 2 mg/kg. Trastuzumab administration to cynomolgus monkeys during early gestation (Days 20 to 50) or late gestation (Days 120 to 150) resulted in 548 offspring with trastuzumab plasma levels of 15 to 28% of maternal plasma levels. 549 In mutant mice lacking HER2, embryos died in early gestation. • Y • Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. • N
		Rationale for Proposing Placement 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**	**Stakeholder Reviewer Comments**
triazolam	Halcion	Carcinogenicity • No evidence of carcinogenic potential in 24-month study. • No • No – Safety Data Sheet (SDS) • N

		• No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4,000 times the human dose. • No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4,000 times the human dose. • N
		Genotoxicity • No information • Not stated • No – SDS • N • No data available • N
		Organ toxicity at low doses • Animal studies indicate that this material may cause adverse effects on the heart, liver, lungs, and central nervous system. • Not stated • Yes - potent drug • Some side effects reported in association with the use of HALCION appear to be dose related. These include drowsiness, dizziness, light-headedness, and amnesia. • Symptoms of overdose include drowsiness, slurred speech, o motor incoordination, coma, and respiratory depression. o Animal studies indicate that this material may cause adverse o effects on the heart, liver, lungs, central nervous system. o Known Clinical Effects: Adverse effects most commonly • reported in clinical use include fatigue, clumsy motion of • limbs/trunk (ataxia), state of intense good feeling (euphoria), • incoordination. Other less common effects include • hallucinations, delirium, amnesia, addiction, impairment of • motor and cognitive skills. The effects are reversible in • nature. All observed adverse effects were consistent with • the Sedative action of this compound. • N
		Reproductive toxicity • No information • Not stated • Y 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.

		• No data available • N
		Teratogenicity or other developmental toxicity • Suspected of damaging the unborn child. May cause harm to breastfed babies. • Congenital malformations • Yes • Y • Benzodiazepines may cause fetal damage when administered during pregnancy. 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. Transplacental distribution has resulted in neonatal CNS depression following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy. • Pharmacological / structural class related concern. • Y
		Rationale for Proposing Placement 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 placenta in patients

Generic Drug Name	**Proprietary Name**	**Stakeholder Reviewer Comments**
urofollitropin	Bravelle	Carcinogenicity • No studies performed • Ovarian neoplasms • Long-term toxicity studies in animals and in vitro mutagenicity tests have not been performed • ? • 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. • N
		Genotoxicity • No studies • Long-term toxicity studies in animals and in vitro mutagenicity tests have not been performed. • ?

		• 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. • N
		Organ toxicity at low doses • Renal and Hepatic Insufficiency: Safety, efficacy, and pharmacokinetics of BRAVELLE® in women with renal or hepatic insufficiency have not been established. (8.6) Excreted via liver and kidneys. Pulmonary and vascular complications reported. Transient liver function test abnormalities suggestive of hepatic dysfunction • Not studied • Abnormal Ovarian Enlargement (5.2) Ovarian Hyper-stimulation Syndrome (5.3) Pulmonary and Vascular Complications (5.4) Ovarian Torsion (5.5) Multi-fetal Gestation and Birth (5.6) Congenital Malformations (5.7) Ectopic Pregnancy (5.8) Spontaneous Abortion (5.9) Ovarian Neoplasms (5.10) • Ovarian Hyper-stimulation Syndrome (OHSS) Pulmonary and Vascular Complications Ovarian Torsion Multi-fetal gestation and Birth Congenital Malformations Ectopic Pregnancy Spontaneous Abortion Ovarian Neoplasms The most common adverse reactions (≥5% incidence) in ovulation induction include: headache, hot flashes, OHSS, pain, and respiratory disorder. The most common adverse reactions (≥2% incidence) in ART include: abdominal cramps, abdominal fullness/enlargement, headache, nausea, OHSS, pain, pelvic pain, and post retrieval pain. • N
		Reproductive toxicity • Ovarian hyper-stimulation syndrome with accompanying fluid accumulation in the peritoneal cavity, thorax and pericardium seen in treated women. No information regarding those handling the drug. • Not studied • Yes - mechanism of action • Y • Multi-fetal gestation and births have been reported with all gonadotropin therapy including therapy with BRAVELLE®. In a controlled study of 72 patients undergoing induction of

		ovulation, 66.7% of pregnancies of women treated with subcutaneous BRAVELLE® were multiples, while 28.6% of pregnancies in women treated with intramuscular BRAVELLE® were multiples. In a controlled study of 60 patients undergoing IVF, 34.8% of pregnancies of women treated with subcutaneous BRAVELLE® were multiples. Before beginning treatment with BRAVELLE®, advise the woman and her partner of the potential risk of multi-fetal gestation and birth. • N
		Teratogenicity or other developmental toxicity • Teratogenic effects noted in PI • Spontaneous abortion, congenital malformations • No specific info provided • Y (BRAVELLE® may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. BRAVELLE® is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the woman becomes pregnant while taking this drug, the woman should be apprised of the potential hazard to a fetus). • Congenital Malformations: The incidence of congenital malformations after some ART [specifically in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)] may be slightly higher than after spontaneous conception. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g., maternal age, maternal and paternal genetic background, sperm characteristics) and to the higher incidence of multi-fetal gestations after IVF or ICSI. There are no indications that the use of gonadotropins during IVF or ICSI is associated with an increased risk of congenital malformations. • The incidence of congenital malformations after some ART [specifically in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)] may be slightly higher than after spontaneous conception. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g., maternal age, maternal and paternal genetic background, sperm characteristics) and to the higher incidence of multi-fetal gestations after IVF or ICSI. There are no indications that the use of gonadotropins during IVF or ICSI is associated with an increased risk of congenital malformations. • Y
		Rationale for Proposing Placement on the List
		Teratogenicity or other developmental toxicity: drug is known to cause fetal harm in patients