CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE "FORMALLY REQUIRED TO BE LABELED OR IDENTIFIED" MECHANISM

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Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
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The chemicals in the table below may meet the requirements outlined in Title 22, California Code of Regulations, Section 12902 for the listing of a chemical that a state or federal agency has formally required to be labeled or identified as causing cancer or reproductive toxicity.

According to Title 22 CCR Section 12902,

- " 'labeled' means that a warning message about the carcinogenicity or reproductive toxicity of a chemical is printed, stamped, written, or in any other manner placed upon the container in which the chemical is present or its outer or inner packaging including any material inserted with, attached to, or otherwise accompanying such a chemical;"

- " 'identified' means that a required message about the carcinogenicity or reproductive toxicity of the chemical is to be disclosed in any manner to a person or legal entity other than the person or legal entity who is required to make such disclosure"; and

- "as causing cancer or reproductive toxicity" means: "For chemicals that cause cancer, the required label or identification uses any words or phrases intended to communicate a risk of cancer or tumors." "For chemicals that cause reproductive toxicity, the required label for identification uses any words or phrases intended to communicate a risk of reproductive harm to men or women or both, or a risk of birth defects or other developmental harm."

The chemicals in the table below appear to have been identified or labeled to communicate a risk of cancer or reproductive or developmental harm, in accordance with formal requirements by the U.S. Food and Drug Administration (FDA). Following the table, language taken directly from the FDA-approved product labels which appears to meet the requirements outlined in Title 22 CCR Section 12902 is quoted for each of the substances listed.

Chemical	CAS No.	Toxicological Endpoints	References
Albuterol	18559-94-9	Developmental toxicity	FDA (1986)
Amantadine hydrochloride	665-66-7	Developmental toxicity	FDA (1993a)
Atorvastatin calcium	134523-03-8	Developmental toxicity	FDA (1998a)
Diazoxide	364-98-7	Developmental toxicity	FDA (1994a)
Dichlorphenamide	120-97-8	Developmental toxicity	FDA (1994b)
Diltiazem hydrochloride	42399-41-7	Developmental toxicity	FDA (1996b)
Famciclovir	104227-87-4	Male reproductive toxicity	FDA (1997a)
Felodipine	72509-76-3	Developmental toxicity Female reproductive toxicity	FDA (1998b)
Filgrastim	121181-53-1	Developmental toxicity	FDA (1992)
Fluvastatin sodium	93957-55-0	Developmental toxicity Male reproductive toxicity	FDA (1999)
Nimodipine	66085-59-4	Developmental toxicity	FDA (1996c)
Ribavirin*	36791-04-5	Male reproductive toxicity	FDA (1993b)
Rifampin	13292-46-1	Developmental toxicity Female reproductive toxicity	FDA (1997b)
Trientine hydrochloride	38260-01-4	Developmental toxicity	FDA (1988)

* Ribavirin was added to the list of chemicals known to cause reproductive toxicity on the basis of a developmental toxicity endpoint on April 1, 1990.

Albuterol (under PRECAUTIONS)
Teratogenic Effects: Pregnancy Category C. "Albuterol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25 and 2.5 mg/kg, corresponding to 1.4, 14 and 140 times the maximum human inhalational dose) showed cleft palate formation in 5 of 111(4.5 percent) fetuses at 0.25 mg/kg and in 10 of 108 (9.3 percent) fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5 percent) fetuses treated with 2.5 mg/kg isoproterenol (positive control)."

Amantadine hydrochloride (under PRECAUTIONS)
Pregnancy Category C: "Symmetrel [amantadine hydrochloride] has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day (estimated human equivalent dose of 7.1 mg/kg/day based on body surface area conversion)… There are no adequate and well-controlled studies in pregnant women. Symmetrel [amantadine hydrochloride] should be used during pregnancy only if the potential benefit justifies potential risk to the embryo or fetus."

Atorvastatin calcium (under CONTRAINDICATIONS and PRECAUTIONS)
Under CONTRAINDICATIONS: Pregnancy and Lactation. " … Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus."

Under PRECAUTIONS: Pregnancy Category X. See CONTRAINDICATIONS. "Safety in pregnant women has not been established…"

"In a study in rats given 20, 100, or 225 mg/kg/day from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day."

"Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital body deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Lipitor should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus."

Diazoxide (Under PRECAUTIONS)

Pregnancy Category C. "Reproduction studies using the oral preparation in rats have revealed increased fetal resorptions and delayed parturition, as well as fetal skeletal anomalies; evidence of skeletal and cardiac teratogenic effects in rabbits has been noted

with intravenous administration. The drug has also been demonstrated to cross the placental barrier in animals and to cause degeneration of the fetal pancreatic beta cells (see ANIMAL PHARMACOLOGY AND/OR TOXICOLOGY). . . . When the use of PROGLYCEM is considered, the indications should be limited to those specified above for adults (See INDICATIONS AND USAGE) and the potential benefits to the mother must be weighed against possible harmful effects to the fetus."

Non-teratogenic effects: "Diazoxide crosses the placental barrier and appears in cord blood. When given to the mother prior to delivery of the infant, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other side effects that have occurred in adults."

*Dichlorphenamide (*Under PRECAUTIONS)
Pregnancy: Pregnancy Category C. "Dichlorphenamide has been shown to be teratogenic in the rat (skeletal anomalies) when given in doses 100 times the human dose. There are no adequate and well-controlled studies in pregnant women. DARANIDE [dichlorphenamide] should not be used in women of childbearing age or in pregnancy, especially during the first trimester, unless the potential benefits outweigh the potential risks."

Diltiazem hydrochloride (under PRECAUTIONS)
Pregnancy: Category C. "Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater."

"There are no well-controlled studies in pregnant women; therefore, use CARDIZEM [diltiazem hydrochloride] in pregnant women only if the potential benefit justifies the potential risk to the fetus."

Famciclovir (under PRECAUTIONS)
Impairment of Fertility: "Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir.... Testicular changes included atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed after 10 weeks of dosing at 500 mg/kg/day (1.9 to 11.4x the human AUC). The no observable effect level for sperm and testicular toxicity in rats following chronic administration (26 weeks) was 50 mg/kg/day (0.2 to 1.2x the human systemic exposure based on AUC comparisons). Testicular toxicity was observed following chronic administration to mice (104 weeks) and dogs (26 weeks) at doses of 600 mg/kg/day (0.4 to 2.4x the human AUC) and 150 mg/kg/day (1.7 to 10.2x the human AUC), respectively."

Felodipine (Under PRECAUTIONS)
Pregnancy Category C. Teratogenic Effects: "Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times the maximum recommended human dose on a mg/m^2 basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow…"

"In a teratology study in cynomolgus monkeys, no reduction in the size of the terminal phalanges was observed, but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses."

Nonteratogenic Effects: "A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times the maximum human dose on a mg/ m^2 basis) and above."

"Significant enlargement of the mammary glands, in excess of the normal enlargement for pregnant rabbits, was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/ m^2 basis)…."

"There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery and on the mammary glands of pregnant females."

Filgrastim (under PRECAUTIONS)
Use in Pregnancy: "NEUPOGEN [filgrastim] has been shown to cause adverse effects in pregnant rabbits when given in doses 2 to 10 times the human dose."

"In rabbits, increased abortion and embryolethality were observed in animals treated with NEUPOGEN at 80 μg/kg/day. NEUPOGEN administered in pregnant rabbits at doses of 100 μg/kg/day during the period of organogenesis was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities and decreased body weight, live births and food consumption…"

"There are no adequate, well controlled studies in pregnant women, therefore, NEUPOGEN is not recommended for use in pregnant women."

Fluvastatin sodium (Under CONTRAINDICATIONS and PRECAUTIONS)
Under CONTRAINDICATIONS: Pregnancy and Lactation. "…Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Fluvastatin sodium should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus."

Under PRECAUTIONS: Pregnancy. Pregnancy Category X. "Fluvastatin sodium produced delays in skeletal development in rats at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced maternal toxicity. These doses resulted in 2 times (rat at 12 mg/kg) or 5 times (rabbit at 10 mg/kg) the 40 mg human exposure based on mg/m^2 surface area. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at 2 mg/kg/day. A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study with neonatal mortality beginning at 6 mg/kg. A modified Segment III study was performed at dose levels of 12 or 24 mg/kg/day with or without the presence of concurrent supplementation with mevalonic acid, a product of HMG-CoA reductase which is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the maternal and neonatal mortality but did not prevent low body weights in pups at 24 mg/kg/ on days 0 and 7 postpartum. Therefore, the maternal and neonatal lethality observed with fluvastatin sodium reflect its exaggerated pharmacologic effect during pregnancy. There are no data with fluvastatin sodium in pregnant women. However, rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. There has been one report of severe congenital body deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. **Lescol (fluvastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If a woman becomes pregnant while taking Lescol (fluvastatin sodium) the drug should be discontinued and the patient advised again as to the potential hazards to the fetus.

Carcinogenesis, Mutagenesis, Impairment of Fertility: "Seminal vesicles were small in hamsters treated for 3 months at 20 mg/kg/day (approximately three times the 40 milligram human dose based on surface area, mg/m^2). There was tubular degeneration and aspermatogenesis in testes as well as vesiculitis of seminal vesicles. Vesiculitis of seminal vesicles and edema of the testes were also seen in rats treated for 2 years at 18 mg/kg/day (approximately 4 times the human C_{max} achieved with a 40 milligram daily dose).

Nimodipine (Under PRECAUTIONS)
Pregnancy. Pregnancy Category C. "Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral doses of 1 and 10 mg/kg/day administered by gavage) from day 6 through day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from day 16 of gestation and continued

until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Ribavirin (under WARNINGS, CONTRAINDICATIONS, and PRECAUTIONS)
Under boxed WARNINGS in bold type: "Physicians and patients should be aware that ribavirin has been shown to produce testicular lesions in rodents ..."

Under PRECAUTIONS: Impairment of Fertility: "The fertility of ribavirin-treated animals (male or female) has not been fully investigated. However, in the mouse, administration of ribavirin at doses between 35-150 mg/kg/day (estimated human equivalent of 2.92-12.5 mg/kg/day, based on body surface area adjustment for the adult) resulted in significant seminiferous tubule atrophy, decreased sperm concentrations, and increased numbers of sperm with abnormal morphology. Partial recovery of sperm production was apparent 3-6 months following dose cessation. In several additional toxicology studies, ribavirin has been shown to cause testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (estimated human equivalent of 2.29 mg/kg/day, based on body surface area adjustment…)."

Rifampin (under PRECAUTIONS)
Pregnancy-Teratogenic Effects. "Category C. Rifampin has been shown to be teratogenic in rodents given oral doses of rifampin 15-25 times the human dose. Neonates of rifampin-treated mothers should be carefully observed for any evidence of adverse effects. Isolated cases of fetal malformation have been reported; however, there are no adequate and well-controlled studies in pregnant women. Rifampin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Rifampin in oral doses of 150 to 250 mg/kg produced teratogenic effects in mice and rats. Malformations were primarily cleft palate in the mouse and spina bifida in the rat. The incidence of these anomalies was dose-dependent. When rifampin was given to pregnant rabbits in doses up to 20 times the usual daily human dose, imperfect osteogenesis and embryotoxicity were reported."

Pregnancy-Non-Teratogenic Effects: "When administered during the last few weeks of pregnancy, rifampin can cause post-natal hemorrhages in the mother and infant for which treatment with Vitamin K may be indicated."

Trientine hydrochloride (Under PRECAUTIONS)
Pregnancy Category C. Trientine hydrochloride was teratogenic in rats at doses similar to the human dose. The frequencies of both resorptions and fetal abnormalities, including hemorrhage and edema, increased while fetal copper levels decreased when trientine hydrochloride was given in maternal diets of rats. There are no adequate and well-controlled studies in pregnant women. Syprine [trientine hydrochloride] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

References

Food and Drug Administration (FDA, 1986). Final printed labeling for the drug albuterol. FDA approved 1986.

Food and Drug Administration (FDA, 1993a). Final printed labeling for the drug amantadine hydrochloride. FDA approved 1993.

Food and Drug Administration (FDA, 1998a). Final printed labeling for the drug atorvastatin calcium. FDA approved 1998.

Food and Drug Administration (FDA, 1994a). Final printed labeling for the drug diazoxide. FDA approved 1994.

Food and Drug Administration (FDA, 1994b). Final printed labeling for the drug dichlorphenamide. FDA approved 1994.

Food and Drug Administration (FDA, 1996b). Final printed labeling for the drug diltiazem hydrochloride. FDA approved 1996.

Food and Drug Administration (FDA, 1997a). Final printed labeling for the drug famciclovir. FDA approved 1997.

Food and Drug Administration (FDA, 1998b). Final printed labeling for the drug felodipine. FDA approved 1998.

Food and Drug Administration (FDA, 1992). Final printed labeling for the drug filgrastim. FDA approved 1992.

Food and Drug Administration (FDA, 1999). Final printed labeling for the drug fluvastatin sodium. FDA approved 1999.

Food and Drug Administration (FDA, 1996c). Final printed labeling for the drug nimodipine. FDA approved 1996.

Food and Drug Administration (FDA, 1993b). Final printed labeling for the drug ribavirin. FDA approved 1993.

Food and Drug Administration (FDA, 1997b). Final printed labeling for the drug rifampin. FDA approved 1997.

Food and Drug Administration (FDA, 1988). Final printed labeling for the drug trientine hydrochloride. FDA approved 1988.