

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

Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
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The chemicals listed in the table below appear to have been identified or labeled to communicate a risk of reproductive harm, in accordance with formal requirements of the U.S. Food and Drug Administration. They appear to meet the requirements for listing outlined in Title 22, California Code of Regulations, Section 12902 for the listing of a chemical which a state or federal agency has formally required to be labeled or identified as causing 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.”

Chemical	CAS No.	Toxicological Endpoints	References
Amoxapine	14028-44-5	developmental toxicity	FDA (1988a)
Beclomethasone dipropionate	5534-09-8	developmental toxicity	FDA (1988b)
Clobetasol propionate	25122-46-7	developmental toxicity female reproductive toxicity	FDA (1995a)
Codeine phosphate	52-28-8	developmental toxicity	FDA (1989)
Flunisolide	3385-03-3	developmental toxicity female reproductive toxicity	FDA (1984)

Chemical	CAS No.	Toxicological Endpoints	References
Fluticasone propionate	80474-14-2	developmental toxicity	FDA (1995b)
Histrelin acetate	---	developmental toxicity female reproductive toxicity male reproductive toxicity	FDA (1991)
Levonorgestrel implants	797-63-7	female reproductive toxicity	FDA (1995c)
Pravastatin sodium	81131-70-6	developmental toxicity	FDA (1996)

Language taken directly from the FDA-approved product labels which appears to meet the requirements outlined in Title 22 CCR Section 12902 is quoted below for each of these substances.

DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS

Amoxapine (under PRECAUTIONS)

Pregnancy: Pregnancy Category C

“Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3 to 10 times the human dose. Decreased postnatal survival (between days 0 to 4) was demonstrated in the offspring of rats at 5 to 10 times the human dose. There are no adequate and well-controlled studies in pregnant women. *ASENDIN amoxapine* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”

Beclomethasone dipropionate (under PRECAUTIONS)

“Pregnancy: Teratogenic Effects: Glucocorticoids are known teratogens in rodent species and beclomethasone dipropionate is no exception. Teratology studies were done in rats, mice, and rabbits treated with subcutaneous beclomethasone dipropionate. Beclomethasone dipropionate was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and partial agenesis of the thymus.”

“The use of beclomethasone dipropionate in pregnant women, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother, embryo, or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.”

Clobetasol propionate (under PRECAUTIONS)

Carcinogenesis, Mutagenesis, Impairment of Fertility: “Studies in the rat following oral administration at dosage levels up to 50 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.”

Pregnancy: Teratogenic Effects: Pregnancy Category C: “Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.”

“There are no adequate and well-controlled studies of the teratogenic effects of clobetasol propionate in pregnant women. Temovate Cream and Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”

Codeine phosphate (under PRECAUTIONS)

Pregnancy: Pregnancy Category C.

“Nonteratogenic effects: Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. Signs usually appear during the first few days of life. Premethazine taken within two weeks of delivery may inhibit platelet aggregation in the newborn.”

“Labor and delivery: Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required.”

Flunisolide (under PRECAUTIONS)

“Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.”

Pregnancy: Pregnancy Category C. “As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”

“Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.”

Fluticasone propionate (under PRECAUTIONS)

Pregnancy: Teratogenic Effects: Pregnancy Category C: “Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Teratology studies in the mouse demonstrated fluticasone propionate to be teratogenic (cleft palate) when administered subcutaneously in doses of 45 µg/kg per day and 150 µg/kg per day. This dose is approximately 140 and 450 times, respectively, the human topical dose of fluticasone propionate cream, 0.005%. There are no adequate and well-controlled studies in pregnant women. Cultivate Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”

Histrelin acetate (under CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and PRECAUTIONS)

Under CLINICAL PHARMACOLOGY: “Although animal studies have shown that acute administration of SUPPRELIN™ (histrelin acetate) Injection results in stimulation of the reproductive system, chronic SUPPRELIN™ Injection administration in the rat delays sexual development, inhibits estrous cyclicity and pregnancy, reduces reproductive organ weight and inhibits ovarian and testicular steroidogenesis in a reversible fashion. In the rabbit, chronic administration of SUPPRELIN™ Injection resulted in decreased reproductive organ weights.”

Under CONTRAINDICATIONS: “SUPPRELIN™ Injection is contraindicated in women who are or may become pregnant while receiving the drug and in nursing mothers. There was increased fetal size and mortality in rats and increased fetal mortality in rabbits but not in mice after SUPPRELIN™ Injection administration. Other responses to SUPPRELIN™ Injection included dystocia, a greater incidence of unilateral hydroureter, and incomplete ossification in rat fetuses in all treated groups. When administered to rabbits on days 6-18 of pregnancy at doses of 20 to 80 mcg/kg/day (2 to 8 times the human dose), SUPPRELIN™ Injection produced early termination of pregnancy and increased fetal death. In rats administered SUPPRELIN™ Injection on days 7-20 of pregnancy at doses of 1 to 15 mcg/kg/day (0.1 to 1.5 times the human dose) there was an increase in fetal resorptions. In mice treated on days 6-15 of pregnancy at 10 to 100 times the human dose, SUPPRELIN™ Injection had no adverse effects. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is inadvertently used during pregnancy or in the rare event that a patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.”

Under PRECAUTIONS: Pregnancy, Teratogenic effects: Pregnancy Category X.

Levonorgestrel implants (under RISKS OF USING THE NORPLANT SYSTEM and SIDE EFFECTS OF THE NORPLANT SYSTEM)

Under RISKS OF USING THE NORPLANT SYSTEM: “A. *Risks Based on Experience with NORPLANT SYSTEM* 1. *Irregular menstrual bleeding* (also see “SIDE EFFECTS OF THE NORPLANT SYSTEM”) Most women experience some change in their usual monthly pattern . . . If increased frequency of bleeding occurs . . . there have been a few cases that required treatment.” 2. *Delayed Disappearance of Ovarian Follicles/Ovarian Cysts* “. . . disintegration or disappearance of the follicles is sometimes delayed, and the follicles may continue to grow beyond the size they would normally reach. . . . Rarely, they may twist or rupture so that surgery is required.”

Under SIDE EFFECTS OF THE NORPLANT SYSTEM: The information provided under the risk section is repeated, and some additional effects discussed: “If you are pregnant, the NORPLANT SYSTEM must be removed.”

Pravastatin 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. **Pravastatin 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.

“Pravachol (pravastatin 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 the woman becomes pregnant while taking Pravachol (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.”

“Nursing mothers: A small amount of pravastatin is excreted in human milk. Because of the potential for serious adverse effects in nursing infants, women taking Pravachol (pravastatin sodium) should not nurse.”

References

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

Food and Drug Administration (FDA, 1988b). Final printed labeling for the drug beclomethasone dipropionate. FDA approved 1988.

Food and Drug Administration (FDA, 1995a). Final printed labeling for the drug clobetasol propionate. FDA approved 1995.

Food and Drug Administration (FDA, 1989). Final printed labeling for the drug codeine phosphate. FDA approved 1989.

Food and Drug Administration (FDA, 1984). Final printed labeling for the drug flunisolide. FDA approved 1984.

Food and Drug Administration (FDA, 1995b). Final printed labeling for the drug fluticasone propionate. FDA approved 1995.

Food and Drug Administration (FDA, 1991). Final printed labeling for the drug histrelin acetate. FDA approved 1991.

Food and Drug Administration (FDA, 1995c). Final printed labeling for the drug levonorgestrel implants. FDA approved 1995.

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

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