PRODUCT MONOGRAPH

STEMETIL®

Prochlorperazine (as Maleate) - 5 and 10mg Tablets
Prochlorperazine (as Mesylate) Syrup and Injectable
Prochlorperazine Suppositories 10mg

Antipsychotic - Antiemetic

Aventis Pharma Inc
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2000.11.07

Control # 068880

PRODUCT MONOGRAPH

NAME OF DRUG

Prochlorperazine (as maleate) Tablets 5 and 10 mg - Mfr. Std.
Prochlorperazine (as mesylate) Syrup 5 mg/5 mL
Prochlorperazine (as mesylate) Injectable 5 mg/mL - Mfr. Std.
Prochlorperazine Suppositories 10 mg - Mfr. Std.

THERAPEUTIC CLASSIFICATION

Antipsychotic - Antiemetic

ACTION

Stemetil (prochlorperazine) is a piperazine phenothiazine derivative with antipsychotic, antiemetic and weak sedative activity.

Stemetil has actions similar to those of other phenothiazine derivatives but appears to be less sedating and to have a weak propensity for causing hypotension or potentiating the effects of CNS depressants and anesthetics. however, it produces a highincidence of extrapyramidal reactions.

INDICATIONS

Stemetil (prochlorperazine) is indicated in the management of manifestations of psychotic disorders such as agitation. confusion.delusion tension and anxiety.

It is also effective in controlling nausea and vomiting due to stimulation of the chemoreceptor trigger zone.

In selected patients, Stemetil may be of value for the relief of excessive anxiety, accompanied by severe tension and agitation,associated with psychoneurotic or somatic conditions.

CONTRAINDICATIONS

Stemetil (prochlorperazine) should not be administered in the presence of circulatory collapse. altered states of consciousness or comatose states, particularly when these are due to intoxication with central depressant drugs (alcohol. hypnotics, narcotics, etc...). It is contraindicated in severely depressed patients, in the presence of blood dyscrasias, liver disease. renal insufficiency, pheochromocytoma, or in patients with severe cardiovascular disorders or a history of hypersensitivity to phenothiazine derivatives.

As with other phenothiazines, Stemetil is contraindicated in patients with suspected or established subcortical brain damage, with or without hypothalamic damage, since a hyperthermic reaction with temperatures above 40°C may occur, sometimes not until 14 to 16 hours after drug administration.

Phenothiazine compounds should not be used in patients receiving large doses of hypnotics, due to the possibility of potentiation

Stemetil is contraindicated in children undergoing surgery.

WARNINGS

The antiemetic action of Stemetil (prochlorperazine) may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as brain tumor or intestinal obstruction, Therefore the etiology of nausea and vomiting should be established before using the drug.

The use of this drug may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such asdriving a car or operating machinery. Potentiation of the effects of alcohol may also occur.

As with other neuroleptics, very rare cases of QT interval prolongation have been reported with Stemetil.

Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. STEMETIL should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. The lowest effective dose and the shortest duration of treatment should be used, and treatment should be discontinued at the earliest opportunity, or if a satisfactory response cannot be obtained. If the signs and symptoms of tardive dyskinesia appear during treatment, discontinuation of STEMETIL should be considered.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) may occur in patients receiving antipsychotic drugs. NMS is characterized by hyperthermia, muscle rigidity, altered consciousness, and signs of autonomic instability including irregular blood pressure, tachycardia, cardiac arrhythmias and diaphoresis. Additional signs may include elevated serum creatine kinase, myoglobinuria (rhabdomyolysis), acute renal failure and leukocytosis. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Use in pregnancy: Safety for the use of Stemetil (prochlorperazine) during pregnancy has not been established. Therefore, it is recommended that the drug be given to pregnant patients only when, in the judgment of the physician, the potential benefit to the patient outweighs the possible risk to the fetus.

Use in children: The drug should not be used in children under 2 years unless potentially live-saving.

The extrapyramidal symptoms which can occur secondary to Stemetil may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g. Reye's syndrome or other encephalopathy. The use of prochlorperazine should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

PRECAUTIONS

The increased incidence of seizures, which occasionally occur in epileptics started on antipsychotic medication, may be controlled by increasing the dosage of their anticonvulsant. Patients with a familial history of seizures or febrile convulsions are more likely to develop seizures than those who have no such history.

Phenothiazines may increase the effects of general anesthetics. opiates, barbiturates, and other CNS depressants and the doses of these drugs should be reduced if administered concomitantly with Stemetil (prochlorperazine)

On long-term therapy. particularly during the first two or three months, it is advisable to perform periodic liver function tests and blood counts as cholestatic jaundice and blood dyscrasias may occur, necessitating discontinuation of treatment. Renal function should be monitored and, if BUN (blood urea nitrogen) becomes abnormal, treatment should be discontinued.

To lessen the likelihood of adverse reactions related to drug accumulation. patients on long-term therapy, particularly on high doses, should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

Because of its anticholinergic action, Stemetil should be used with great caution in patients with glaucoma or prostatic hypertrophy.

The effects of anticholinergic drugs may be potentiated by prochlorperazine. Paralytic ileus, even resulting in death, may occur, especially in the elderly. Caution should be observed if constipation develops.

Retinal changes, lenticular and corneal deposits and abnormal skin pigmentation have been observed with other phenothiazines and may occur after prolonged therapy. The possibility of persistent tardive dyskinesia should also be borne in mind when patients are under long-term treatment.

Patients receiving prochlorperazine should be cautioned against exposure to extreme heat or organophosphorous insecticides.

Hypotension and electrocardiographic changes, particularly non-specific and usually reversible Q and T wave distortions, have been associated with the administration of phenothiazines. Therefore, prochlorperazine should be used with caution in patients with compensated cardiovascular and cerebrovascular disorders.

Unexpected. sudden deaths have occurred in hospitalized patients treated with phenothiazines. Previous brain damage or seizures may predispose. High doses should be avoided in known seizure patients. Sudden exacerbations of psychotic behavior patterns occurred in several patients shortly before death. Acute fulminating pneumonia or pneumonitis and aspiration of gastric contents also were observed. Therefore, the physician also should keep in mind the possible development of "silent pneumonias".

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea. gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies, nor epidemiologic studies conducted to date. however, have shown an association between chronic administration of these drugs and mammary tumorogenesis; the available evidence is considered too limited to be conclusive at this time.

Withdrawal Emergent Neurological Signs: Abrupt withdrawal after short-term administration of antipsychotic drugs does not generally pose problems. However, transient dyskinetic signs are experienced by some patients on maintenance therapy after abrupt withdrawal. The signs are very similar to those described under Tardive Dyskinesia, except for duration. Although it is not known whether gradual withdrawal of antipsychotic drugs will decrease the incidence of withdrawal emergent neurological signs, gradual withdrawal would appear to be advisable.

Older Patients: The incidence of adverse reactions may be greater in patients over 55 years of age, since the half-lives of antipsychotic drugs are often prolonged. To minimize this possibility, the maintenance dosage should be reduced to the lowest effective level as soon as possible after initial titration and periodically reviewed.

Since psychiatric syndromes in the elderly can be caused by drugs or organic disease, withdrawal of the precipitating drug or treatment of the medical condition should supersede initiation of antipsychotic medication. These agents should not be used for non-psychiatric conditions for which other drugs are available, since the elderly are especially prone to develop adverse effectsfrom antipsychotic drugs.

Children: Children with an acute febrile illness or suffering from dehydration seem to be much more susceptible than adults to neuromuscular reactions, particularly dystonias. In such patients. the drug should be used under close supervision and at low doses.

ADVERSE REACTIONS

Adverse reactions with different phenothiazines vary in type. frequency, and mechanism of occurrence, i.e., some are dose-related, while others involve individual patient sensitivity. Some adverse reactions may be more likely to occur with greater intensity, in patients with special medical problems.

Not all of the following adverse reactions have been observed with every phenothiazine derivative, but they have been reported with one or more and should be borne in mind when drugs of this class are administered:

Neurological: Extrapyramidal reactions including tremor. rigidity, akathisia, dystonia, dyskinesia. oculogyric crises, opisthotonos. hyperreflexia and sialorrhea. EEG changes, disturbed temperature regulation and seizures have also been encountered.

Persistent Tardive Dyskinesia: As with other antipsychotic agents. tardive dyskinesia may occur in patients on long-term therapy or may be observed after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high doses, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes, these may be accompanied by involuntary movements of the extremities.

There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent. or switch to a different antipsychotic agent, the syndrome may be masked, It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop. The physician may be able to reduce the risk of this syndrome by minimizing the unnecessary use of neuroleptic drugs and reducing the dose or discontinuing the drug, if possible, when manifestations of this syndrome are recognized, particularly in patients over the age of 50.

Behavioral: Sleep disturbances, drowsiness, fatigue, insomnia, and depression have been reported and may, in severe cases, necessitate reduction in dosage. As with other phenothiazine derivatives, reactivation or aggravation of psychotic processes may be encountered. Paradoxical effects such as agitation, anxiety, restlessness, excitement and bizarre dreams, have been observed.

Autonomic Nervous System: Dry mouth, nasal congestion, headache, nausea, constipation, tachycardia, hypotension, syncope, dizziness, blurred vision, vomiting, sweating, nasal congestion, and urinary incontinence have been observed.

Patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to hypotensive reactions with phenothiazine compounds, and should therefore be observed closely when the drug is administered. Should hypotension occur in patients receiving Stemetil (prochlorperazine) and a vasopressor agent be required. i.v. norepinephrine or phenylephrine should be used, and not epinephrine, since phenothiazine derivatives can reverse the pressor effect of the latter drug.

Other autonomic reactions which have occurred with phenothiazines are salivation, polyuria, glaucoma, bladder paralysis, adynamic ileus, and fecal compaction.

Metabolic and Endocrine: Anorexia, menstrual irregularities, impotence, and increased thirst, weight changes, increased appetite, peripheral edema, galactorrhea, gynecomastia, false positive pregnancy tests, and changes in libido have also occurred in patients receiving phenothiazine therapy.

Allergic or Toxic: Pruritus, dermatitis, rash, erythema, urticaria, seborrhea, eczema, exfoliative dermatitis, and photosensitivity. The possibility of an anaphylactoid reaction should be borne in mind.

Blood dyscrasias including leukopenia, agranulocytosis, pancytopenia, thrombocytopenic or non-thrombocytopenic purpura, eosinophilia, and anemia, have been associated with phenothiazine therapy. Routine blood counts are therefore advisable during prolonged therapy. If any soreness of the mouth, gums or throat or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Cholestatic jaundice and biliary stasis may be encountered, particularly during the first months of therapy, and require immediate discontinuation of treatment.

Miscellaneous: The following adverse reactions have been reported in patients receiving phenothiazine derivatives: headache, asthma, laryngeal, cerebral and angioneurotic edema, altered cerebrospinal fluid proteins, systemic lupus erythematosus-like syndrome, hyperpyrexia, ECG and WEG changes and hypotension severe enough to cause fatal cardiac arrest. Skin pigmentation, epithelial keratopathy, lenticular and corneal deposits have been associated with long-term administration. Very rare cases of QT interval prolongation have been reported.

Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown flare-ups of psychotic behaviour patterns shortly before deaths, Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions.

Potentiation of CNS depressants (barbiturates, narcotics, analgesics. alcohol, antihistamines), may occur.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Primarily extrapyramidal reactions, CNS depression which may vary from simple lethargy to coma. Agitation and restlessness may also occur Other possible manifestations include convulsions, fever and autonomic reactions such as hypotension, dry mouth and ileus.

Treatment: Essentially symptomatic and supportive. Early gastric lavage may be helpful.

Maintain an open airway. If hypotension occurs, the standard measures for managing circulatory shock should be initiated; if a pressor agent is required give norepinephrine or phenylephrine and not epinephrine as it may further depress the blood pressure. Extrapyramidal reactions should be treated with an antiparkinsonian agent.

Centrally acting emetics will be ineffective because of prochlorperazine's antiemetic action. Limited experience indicates that phenothiazines are not dialyzable.

DOSAGE AND ADMINISTRATION

Begin with the lowest recommended dosage. Adjust to response of the individual.

ADULTS

Oral or rectal route - To control nausea, vomiting or excessive anxiety: usually 5 to 10 mg, 3 or 4 times daily; in mild cases, a single dose of 5 to 10 mg is often adequate. In psychiatry for moderate to severe conditions, the usual starting dosage is 10 mg 3 or 4 times a day; increase dosage gradually by 5 to 10 mg every 2 or 3 days until symptoms are controlled or adverse reactions intervene. Some patients respond satisfactorily on 50 to 75 mg per day. In more severe disturbances
it may reach 100 to 150 mg a day. For maintenance therapy, the dosage should be reduced to the minimum effective dose.

Parenteral route - I.M. Dosage: The drug is given by deep intramuscular injection. Total daily dosage rarely exceeds 40 mg, except in severe psychiatric cases. When control is achieved, the oral route should be substituted. To control nausea, vomiting or excessive anxiety: 5 to 10 mg, 2 or 3 times a day. In psychiatry for the immediate control of severely disturbed patients. 10 to 20 mg initially, repeated every 2 to 4 hours until control is obtained. More than 3 or 4 doses are seldom necessary. The patients should be kept in bed and under medical supervision. In surgery: 5 to 10 mg I.M., 1 to 2 hours before anesthesia. Repeat once during surgery if necessary. Post-operatively, the same dose of 5 to 10 mg I.M. may be given to control acute symptoms and repeated, if necessary, every 3 to 4 hours (maximum, 40 mg daily).

I.V. Infusion: During and after surgery, Stemetil may be given I.V. in the infusion solution at a concentration of 20 mg per litre. Total daily dose rarely exceeds 30 mg.

CHILDREN

Daily dosage, administered in divided doses, should be based on body weight rather than on age, and should not be exceeded. Do not administer to children under 2 years of age or 9 kg of body weight. Occasionally the patient may react to the drug with signs of restlessness and excitement; if this occurs, treatment should be discontinued.

Oral and rectal routes

From 9 to 14 kg: 2.5 mg, 1 or 2 times a day, maximum 7.5 mg per day.

From 14 to 18 kg: 2,5 mg, 2 or 3 times a day, maximum 10 mg per day,

From 18 to 39 kg: 2,5 mg, 3 times a day, or 5 mg 2 times a day, maximum 15 mg per day.

Vomiting usually subsides after a single day of treatment. In psychiatry: On the first day of treatment a dosage of 10 mg. in divided doses, should not be exceeded. The maximum total daily dosage reached by gradual increments should not exceed 20 mg for children of 2 to 5 years. and 25 mg for children of 6 to 12 years.

Parenteral route

For severe nausea and vomiting and in child psychiatry: calculate each dose on the basis of 0.13 mg/kg of body weight and give by deep I.M. injection. Control is usually obtained with one dose. When further therapy is needed, transfer the patient to an oral form at an equal or higher dose.

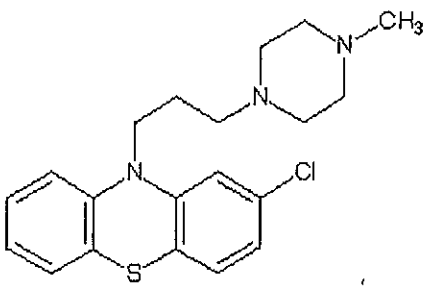
PHARMACEUTICAL INFORMATION

Drug substance

Proper name: Prochlorperazine

Chemical name: 2-chloro-10-[3-(4 methyl-1-piperazinyl)propyl]-10H-phenothiazine

Structural formula:



Molecular formula: $C_{20}H_{24}ClN_3S$

Molecular Weight: 373.94

Physical form: Clear, pale yellow, viscous liquid

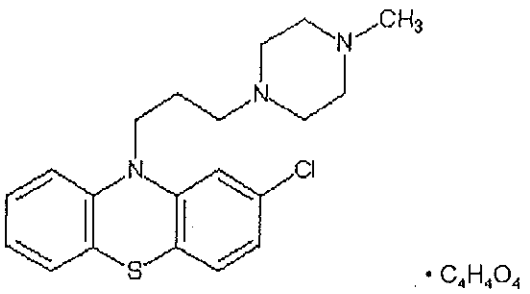
Solubility: Insoluble in water and freely soluble in alcohol, chloroform and ether.

Drug substance

Proper name: Prochlorperazine maleate

Chemical name: 2-chloro-10-[3-(4 methyl-1-piperazinyl)propyl]-10H-phenothiazine maleate

Structural formula:



• $C_4H_4O_4$

Molecular formula: $C_{20}H_{24}ClN_3S \cdot C_4H_4O_4$

Molecular weight: 606.1

Physical form: White or pale yellow crystalline powder

Solubility: Very slightly soluble in water; slightly soluble in methanol, ethanol; practically insoluble in ether, benzene, chloroform.

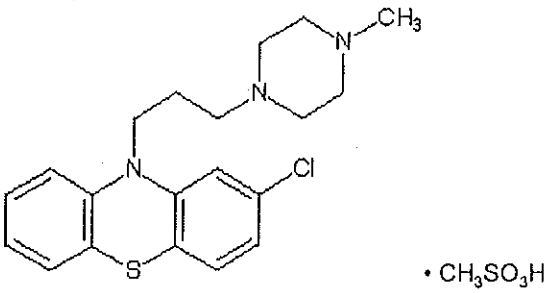
pH: 3.0 to 4.0

Drug substance

Proper name: Prochlorperazine mesylate

Chemical name: 2-chloro-10-[3-(4 methyl-1-piperazinyl)propyl]-10H-phenothiazine mesylate

Structural formula:



• CH_3SO_3H

Molecular formula: $C_{20}H_{24}ClN_3S \cdot CH_3SO_3H$

Molecular weight: 566.2

Physical form: White or almost white powder

Solubility: Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; practically insoluble in ether.

pH: 2.0 to 3.0

Composition

Injectable: Each mL contains: prochlorperazine base 5 mg (as the mesylate). Nonmedicinal ingredients: sodium chloride, sodium citrate, sodium sulphite anhydrous and water for injection.

Syrup: Each 5 mL of red liquid contains: prochlorperazine base 5 mg (as the mesylate). Nonmedicinal ingredients: artificial caramel flavor, artificial chocolate flavor, artificial cognac flavor, poloxamer, purified water, sodium chloride, sodium citrate, strawberry red dye and sucrose.

Suppositories: Each rectal suppository contains: prochlorperazine base 10 mg. Nonmedicinal ingredients: hydrogenated vegetable glycerides.

Tablets: Each peach colored tablet contains: prochlorperazine base 5 or 10 mg (as the bimaleate). Nonmedicinal ingredients: acetic anhydride, carnauba wax, cellulose, colloidal silicon dioxide, D&C Yellow No. 10 (Quinoline Yellow WS) aluminum lake, dicalcium phosphate, diethyl phthalate, FD&C Yellow No. 6 (Sunset Yellow FCF) aluminum lake, magnesium stearate, sodium croscarmellose, sodium oleate, titanium oxide and zein.

Stability and storage recommendation

Stemetil (prochlorperazine) suppositories, Stemetil (prochlorperazine mesylate) syrup, injectable and Stemetil (prochlorperazine maleate) tablets should be stored at 15° to 25°C, protect from light.

AVAILABILITY OF DOSAGE FORMS

Stemetil (prochlorperazine base) 5 mg/mL (as mesylate) injectable is available in amber glass ampoules of 2 mL in boxes of 10 ampoules.

Stemetil (prochlorperazine base) 5 mg/mL (as mesylate) syrup is available in amber glass bottles of 100 mL.

Stemetil (prochlorperazine base) 10 mg suppositories are available in boxes of 10 suppositories.

Stemetil (prochlorperazine base) 5 mg (as maleate) tablets are available in amber plastic bottles of 100 and 500 tablets.

PHARMACOLOGY

The pharmacologic profile of prochlorperazine in experimental animals is similar to that of other phenothiazines. The following findings relate to animal studies in which prochlorperazine and chlorpromazine effects were compared on a drug weight basis. The sedative activity of prochlorperazine, based on the potentiating effects of ether anesthesia and morphine analgesia, is approximately one half that of chlorpromazine. The ability of prochlorperazine to block conditioned avoidance in rats is approximately one and a half times greater than chlorpromazine. The cataleptic effects of prochlorperazine are slightly greater than those of chlorpromazine but both compounds appear to be equi-effective in reducing motor activity.

The antiemetic effect of prochlorperazine, determined by the apomorphine-induced vomiting in dogs, is four to six times greater than that of chlorpromazine. Chlorpromazine exerts more potent adrenergic and serotonin blocking effects and anticholinergic activity than does prochlorperazine.

In rats, prochlorperazine administered intraperitoneally distributes in all body tissues. The liver and spleen appear to store greater concentrations of the drug than other organs. Prochlorperazine enters the entero-hepatic circulation and is excreted chiefly in the feces. Less than 25% of an intraperitoneal dose in rats is excreted in the urine.

TOXICOLOGY

Acute Toxicity:

The following LD50 values have been obtained in mice for prochlorperazine.

- I.V.- 90mg/kg
- S.C.- 400mg/kg
- P.O.- 800mg/kg

Subacute Toxicity:

Administration of prochlorperazine to rats, 50 mg/kg P.O, daily for one month produced no disturbances of liver or kidney functions and no blood or bone-marrow alterations. All the animals survived without loss of weight, and appeared normal. Histological examination of kidney, liver, lung, and spleen did not reveal any toxic lesions.

In the dog, daily doses of 30 mg/kg for one month produced no mortality and all the animals appeared normal throughout treatment. They showed only a slight loss of weight, but no disturbances of liver or kidney functions. Histological examination revealed no abnormalities.

Teratogenicity:

Prochlorperazine administered to pregnant rabbits and rats at dosage levels approximately 80 to 100 times the human therapeutic dose. produced no teratogenic effects.

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