

SEARLE
Cytotec® (misoprostol)

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. Cytotec has been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she were to become pregnant.

The Cytotec package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking Cytotec and each time the prescription is renewed because the leaflet may have been revised.

Keep Cytotec out of the reach of children.

SPECIAL NOTE FOR WOMEN: Because of its abortifacient property, Cytotec is contraindicated for use by pregnant women. Cytotec may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by Cytotec may be incomplete, which could lead to dangerous bleeding, hospitalization, surgery, infertility, or maternal or fetal death.

Cytotec is available only as a unit-of-use package that includes a leaflet containing patient information. See *Patient Information* at the end of this labeling.

Drug interactions: See *Clinical Pharmacology*. Cytotec has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Cytotec does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Cytotec has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

Animal toxicology: A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse. No such increase has been observed in humans administered Cytotec for up to 1 year.

An apparent response of the female mouse to Cytotec in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternbrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with Cytotec.

Carcinogenesis, mutagenesis, impairment of fertility: There was no evidence of an effect of Cytotec on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of Cytotec on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of Cytotec was tested in several *in vitro* assays, all of which were negative.

Misoprostol, when administered to breeding male and female rats at doses 6.25 times to 625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

Pregnancy: Pregnancy Category X. See boxed **CONTRAINDICATIONS AND WARNINGS**. Cases of amniotic fluid embolism, which resulted in maternal and fetal death, have been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Nonteratogenic effects: Cytotec may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. Cytotec produces uterine contractions, uterine bleeding, and expulsion of the products of conception. Miscarriages caused by Cytotec may be incomplete. In studies in women undergoing elective termination of pregnancy during the first trimester, Cytotec caused partial or complete expulsion of the products of conception in 11% of the subjects and increased uterine bleeding in 41%. Anecdotal reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to use of misoprostol as an abortifacient have been received (see boxed **CONTRAINDICATIONS AND WARNINGS**). If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

Teratogenic effects: Cytotec is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.

Labor and Delivery: Cytotec is not approved for the induction of labor and delivery or abortion. Cytotec is a synthetic analog of prostaglandin E₁ and as such can induce or augment uterine contractions. Cytotec has been used, outside of its approved indication, as a cervical ripening agent for the induction of labor or abortion, in spite of specific contraindications to its use during pregnancy.

Serious adverse events reported following off-label use of Cytotec for cervical ripening and/or induction of labor include maternal and fetal death; uterine hyperstimulation, perforation, or rupture requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding; retained placenta; shock; fetal bradycardia; and pelvic pain. There is an increased risk of uterine rupture when Cytotec is used in patients who have had prior Cesarean delivery or major uterine surgery. There may be an increased risk of uterine tachysystole, meconium passage, meconium staining of amniotic fluid, and Cesarean delivery due to uterine hyperstimulation when Cytotec is administered in doses of 50 mcg or more.

Anecdotal reports have been received of congenital anomalies resulting from pregnancies in which Cytotec was unsuccessfully used as an abortifacient. The effects of Cytotec on the later growth, development, and functional maturation of the child when Cytotec is used for cervical ripening or induction of labor have not been established. Information on Cytotec's effect on the possibility that forceps delivery or other intervention will be necessary is unknown.

Nursing mothers: It is unlikely that Cytotec is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, Cytotec should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Pediatric use: Safety and effectiveness of Cytotec in pediatric patients have not been established.

ADVERSE REACTIONS

The following have been reported as adverse events in subjects receiving Cytotec:

Gastrointestinal: In subjects receiving Cytotec 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea at 800 mcg in controlled trials in patients on NSAIDs ranged from 14-40% and in all studies (over 5,000 patients) averaged 13%. Abdominal pain occurred in 13-20% of patients in NSAID trials and about 7% in all studies, but there was no consistent difference from placebo.

Diarrhea was dose related and usually developed early in the course of therapy (after 13 days), usually was self-limiting (often resolving after 8 days), but sometimes required discontinuation of Cytotec (2% of the patients). Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if Cytotec is prescribed. The incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding coadministration of Cytotec with magnesium-containing antacids.

Gynecological: Women who received Cytotec during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to Cytotec administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed **CONTRAINDICATIONS AND WARNINGS**.)

Elderly: There were no significant differences in the safety profile of Cytotec in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

Additional adverse events which were reported are categorized as follows:

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving Cytotec and may be causally related to the drug: nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for Cytotec and placebo.

Causal relationship unknown: The following adverse events were infrequently reported. Causal relationships between Cytotec and these events have not been established but cannot be excluded:

Body as a whole: aches/pains, asthenia, fatigue, fever, rigors, weight changes.

Skin: rash, dermatitis, alopecia, pallor, breast pain.

Special senses: abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.

Respiratory: upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis.

Cardiovascular: chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope.

Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.

Hypersensitivity: anaphylaxis

Metabolic: glycosuria, gout, increased nitrogen, increased alkaline phosphatase.

Genitourinary: polyuria, dysuria, hematuria, urinary tract infection.

Nervous system/Psychiatric: anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.

Musculoskeletal: arthralgia, myalgia, muscle cramps, stiffness, back pain.

Blood/Coagulation: anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

OVERDOSAGE

The toxic dose of Cytotec in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discom-

fort being reported. In animals, the acute toxic effects are diarrhea, gastrointestinal lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy.

It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

DOSAGE AND ADMINISTRATION

The recommended adult oral dose of Cytotec for the prevention of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. (See *Clinical Pharmacology: Clinical studies*.) Cytotec should be taken for the duration of NSAID therapy as prescribed by the physician. Cytotec should be taken with a meal, and the last dose of the day should be at bedtime.

Renal impairment: Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-mcg dose is not tolerated. (See *Clinical Pharmacology*.)

HOW SUPPLIED

Cytotec 100-mcg tablets are white, round, with SEARLE debossed on one side and 1451 on the other side; supplied as:

NDC Number	Size
0025-1451-60	unit-of-use bottle of 60
0025-1451-20	unit-of-use bottle of 120
0025-1451-34	carton of 100 unit dose

Cytotec 200-mcg tablets are white, hexagonal, with SEARLE debossed above and 1461 debossed below the line on one side and a double stomach debossed on the other side; supplied as:

NDC Number	Size
0025-1461-60	unit-of-use bottle of 60
0025-1461-31	unit-of-use bottle of 100
0025-1461-34	carton of 100 unit dose

Store at or below 25°C (77°F), in a dry area.

Rx only

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (misoprostol) and each time your prescription is renewed, because the leaflet may be changed.

Cytotec (misoprostol) is being prescribed by your doctor to decrease the chance of getting stomach ulcers related to the arthritis/pain medication that you take.

Do not take Cytotec® if you are pregnant because it can cause miscarriage at any time during pregnancy. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec may cause the uterus to rupture (tear) in pregnant women if it is used to bring on (induce) labor or to cause an abortion after the first trimester of pregnancy. Miscarriages or rupture of the uterus may result in severe bleeding, hospitalization, surgery, infertility or death.

If you become pregnant during Cytotec therapy, stop taking Cytotec and contact your physician immediately. Remember that even if you are on a means of birth control it is still possible to become pregnant. Should this occur, stop taking Cytotec and contact your physician immediately.

Cytotec may cause diarrhea, abdominal cramping, and/or nausea in some people. In most cases these problems develop during the first few weeks of therapy and stop after about a week. You can minimize possible diarrhea by making sure you take Cytotec with food.

Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take Cytotec. If you have prolonged difficulty (more than 8 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.

Take Cytotec only according to the directions given by your physician.

Do not give Cytotec to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and would be dangerous if the other person were pregnant.

This information sheet does not cover all possible side effects of Cytotec. This patient information leaflet does not address the side effects of your arthritis/pain medication. See your doctor if you have questions.

Keep out of reach of children.

~ 6/29/2000

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