CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-095

Generic Name: Misoprostol Tablets, 0.1mg and 0.2mg

Sponsor: Zenith Goldline Pharmaceuticals, Inc.

Approval Date: July 10, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 76-095

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-095

APPROVAL LETTER

ANDA 76-095

JUL 10 2002

IVAX Pharmaceuticals, Inc.
Attention: Patricia Jaworski
140 Legrand Ave.
Northvale, NJ 07647

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 28, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Misoprostol Tablets, 0.1 mg and 0.2 mg.

Reference is also made to your amendments dated March 29, and November 30, 2001; and January 22, April 23, and May 24, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Misoprostol Tablets, 0.1 mg and 0.2 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cytotec® Tablets, 0.1 mg and 0.2 mg, respectively, of G.D. Searle LLC). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 7/10/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-095

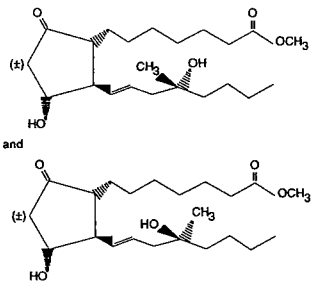
Final Printed Labeling

MISOPROSTOL TABLETS

Rx only

WARNINGS
MISOPROSTOL ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN MISOPROSTOL WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY. (See also **PRECAUTIONS**, and **LABOR AND DELIVERY**). MISOPROSTOL SHOULD NOT BE TAKEN BY PREGNANT WOMEN TO REDUCE THE RISK OF ULCERS INDUCED BY NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) (See **CONTRAINDICTIONS, WARNINGS** and **PRECAUTIONS**).
PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.
Misoprostol should not be used for reducing the risk of NSAID-induced ulcers in women of childbearing potential unless the patient is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, misoprostol may be prescribed if the patient:
- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin misoprostol only on the second or third day of the next normal menstrual period.

DESCRIPTION
Misoprostol oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.
Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



$C_{22}H_{38}O_5$ M. W. 382.5

Misoprostol is a water-soluble, viscous liquid chemically described as (±) methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.
Each misoprostol tablet for oral administration contains either 100 mcg or 200 mcg of misoprostol and has the following inactive ingredients: hydrogenated vegetable oil, hydroxypropyl methylcellulose, microcrystalline cellulose and sodium starch glycolate.

CLINICAL PHARMACOLOGY
Pharmacokinetics
Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs.
In normal volunteers, misoprostol is rapidly absorbed after oral administration with a T_{max} of misoprostol acid of 12 ± 3 minutes and a terminal half-life of 20–40 minutes.
There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200-400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days.
Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid, however, so this effect does not appear to be clinically important.

Mean ± SD	C_{max} (pg/ml)	AUC(0-4) (pg·hr/ml)
Fasting	811 ± 317	417 ± 135
With Antacid	689 ± 315	349 ± 108*
With High Fat Breakfast	303 ± 176*	373 ± 111

*Comparisons with fasting results statistically significant, $p<0.05$

After oral administration of radiolabeled misoprostol, about 80% of detected radioactivity appears in urine. Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $T_{1/2}$, C_{max}, and AUC compared to normals, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.
Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P450) enzyme systems in animals.
Drug interaction studies between misoprostol and several nonsteroidal anti-inflammatory drugs showed no effect on the kinetics of ibuprofen or diclofenac, and a 20% decrease in aspirin AUC, not thought to be clinically significant.
Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.
The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.
Pharmacodynamics
Misoprostol has both antisecretory (inhibiting gastric acid secretion) and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by these agents. Misoprostol can increase bicarbonate and mucus production, but in man this has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to tell whether the ability of misoprostol to prevent gastric ulcer is the result of its antisecretory effect, its mucosal protective effect, or both.
In vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.
Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor on intrinsic factor output.
Effects On Gastric Acid Secretion
Misoprostol, over the range of 50–200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter lived, and only the 200-mcg dose had substantial effects on nocturnal secretion or on histamine and meal-stimulated secretion.
Uterine Effects
Misoprostol has been shown to produce uterine contractions that may endanger pregnancy (see boxed **WARNINGS**).
Other Pharmacologic Effects
Misoprostol does not produce clinically significant effects on serum levels of prolactin, gonadotropins, thyroid-stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones (somatostatin, gastrin, vasoactive intestinal polypeptide, and motilin), creatinine, or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function, or the cardiovascular system are not modified by recommended doses of misoprostol.
Clinical Studies
In a series of small short-term (about 1 week) placebo-controlled studies in healthy human volunteers, doses of misoprostol were evaluated for their ability to prevent NSAID-induced mucosal injury. Studies of 200 mcg q.i.d. of misoprostol with tolmetin and naproxen, and of 100 and 200 mcg q.i.d. with ibuprofen, all showed reduction of the rate of significant endoscopic injury from about 70–75% on placebo to 10–30% on misoprostol. Doses of 25–200 mcg q.i.d. reduced aspirin-induced mucosal injury and bleeding.
Reducing The Risk of Gastric Ulcers Caused By Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
Two 12-week, randomized, double-blind trials in osteoarthritic patients who had gastrointestinal symptoms but no ulcer on endoscopy while taking an NSAID compared the ability of 200 mcg of misoprostol, 100 mcg of misoprostol, and placebo to reduce the risk of gastric ulcer (GU) formation. Patients were approximately equally divided between ibuprofen, piroxicam, and naproxen, and continued this treatment throughout the 12 weeks. The 200-mcg dose caused a marked, statistically significant reduction in gastric ulcers in both studies. The lower dose was somewhat less effective, with a significant result in only one of the studies.

Reduction of Risk of Gastric Ulcers Induced by Ibuprofen, Piroxicam, or Naproxen
[No. of patients with ulcer(s) (%)]

	Therapy Duration		
Therapy	4 weeks	8 weeks	12 weeks
Study No. 1			
Misoprostol 200 mcg q.i.d. (*n*=74)	1 (1.4)	0	0
Misoprostol 100 mcg q.i.d. (*n*=77)	3 (3.9)	1 (1.3)	1 (1.3)
Placebo (*n*=76)	11 (14.5)	4 (5.3)	4 (5.3)
Study No. 2			
Misoprostol 200 mcg q.i.d. (*n*=65)	1 (1.5)	1 (1.5)	0
Misoprostol 100 mcg q.i.d. (*n*=66)	2 (3.0)	2 (3.0)	1 (1.5)
Placebo (*n*=62)	6 (9.7)	2 (3.2)	3 (4.8)
*Studies No. 1 & No. 2***			
Misoprostol 200 mcg q.i.d. (*n*=139)	2 (1.4)	1 (0.7)	0
Misoprostol 100 mcg q.i.d. (*n*=143)	5 (3.5)	3 (2.1)	2 (1.4)
Placebo (*n*=138)	17 (12.3)	6 (4.3)	7 (5.1)

*Statistically significantly different from placebo at the 5% level
**Combined data from Study No. 1 and Study No. 2
In these trials there were no significant differences between misoprostol and placebo in relief of day or night abdominal pain. No effect of misoprostol in reducing the risk of duodenal ulcers was demonstrated, but relatively few duodenal lesions were seen.
In another clinical trial, 239 patients receiving aspirin 650–1300 mg q.i.d. for rheumatoid arthritis who had endoscopic evidence of duodenal and/or gastric inflammation were randomized to misoprostol 200 mcg q.i.d. or placebo for 8 weeks while continuing to receive aspirin. The study evaluated the possible interference of misoprostol on the efficacy of aspirin in these patients with rheumatoid arthritis by analyzing joint tenderness, joint swelling, physician's clinical assessment, patient's assessment, change in ARA classification, change in handgrip strength, change in duration of morning stiffness, patient's assessment of pain at rest, movement, interference with daily activity, and ESR. Misoprostol did not interfere with the efficacy of aspirin in these patients with rheumatoid arthritis.

INDICATIONS AND USAGE
Misoprostol tablets are indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Misoprostol has not been shown to reduce the risk of duodenal ulcers in patients taking NSAIDs. Misoprostol should be taken for the duration of NSAID therapy. Misoprostol has been shown to reduce the risk of gastric ulcers in controlled studies of 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS
See boxed **WARNINGS**. **Misoprostol should not be taken by pregnant women to reduce the risk of ulcers induced by non-steroidal anti-inflammatory drugs (NSAIDs).**
Misoprostol should not be taken by anyone with a history of allergy to prostaglandins.

WARNINGS
See boxed **WARNINGS**.

PRECAUTIONS
Information for Patients
Women of childbearing potential using misoprostol to decrease the risk of NSAID induced ulcers should be told that they must not be pregnant when misoprostol therapy is initiated, and they must use an effective contraception method while taking misoprostol.
See boxed **WARNINGS**.
Misoprostol is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.
Misoprostol should be taken only according to the directions given by a physician.
If the patient has questions about or problems with misoprostol, the physician should be contacted promptly.
THE PATIENT SHOULD NOT GIVE MISOPROSTOL TO ANYONE ELSE. Misoprostol 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 is or were to become pregnant.
The misoprostol package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking misoprostol and each time the prescription is renewed because the leaflet may have been revised.
Keep misoprostol out of the reach of children.
SPECIAL NOTE FOR WOMEN: Misoprostol may cause abortion (sometimes incomplete), premature labor, or birth defects if given to pregnant women.
Misoprostol 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**. Misoprostol has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Misoprostol does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Misoprostol has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

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MISOPROSTOL TA
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PE1283
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ROSTOL TABLETS

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 misoprostol for up to 1 year.
An apparent response of the female mouse to misoprostol in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with misoprostol.
Carcinogenesis, Mutagenesis, Impairment Of Fertility
There was no evidence of an effect of misoprostol 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 misoprostol on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of misoprostol 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
Teratogenic effects: See boxed **WARNINGS**. Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient but the drug's teratogenic mechanism has not been demonstrated. Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects.
Misoprostol is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.
Nonteratogenic effects: See boxed **WARNINGS**. Misoprostol may endanger pregnancy (may cause abortion) and thereby cause harm to the fetus when administered to a pregnant women. Misoprostol may produce uterine contractions, uterine bleeding, and expulsion of the products of conception. Abortions caused by misoprostol may be incomplete. If a woman is or becomes pregnant while taking this drug to reduce the risk of NSAID induced ulcers, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.
Labor and Delivery
Misoprostol can induce or augment uterine contractions. Vaginal administration of misoprostol, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. A major adverse effect of the obstetrical use of misoprostol is hyperstimulation of the uterus which may progress to uterine tetany with marked impairment of uteroplacental blood flow, uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy), or amniotic fluid embolism. Pelvic pain, retained placenta, severe genital bleeding, shock, fetal bradycardia, and fetal and maternal death have been reported.
There may be an increased risk of uterine tachysystole, uterine rupture, meconium passage, meconium staining of amniotic fluid, and Cesarean delivery due to uterine hyperstimulation with the use of higher doses of misoprostol; including the manufactured 100 mcg tablet. The risk of uterine rupture increases with advancing gestational ages and with prior uterine surgery, including Cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.
The effect of misoprostol on the later growth, development, and functional maturation of the child when misoprostol is used for cervical ripening or induction of labor have not been established. Information on misoprostol's effect on the need for forceps delivery or other intervention is unknown.
Nursing Mothers
It is unlikely that misoprostol 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, misoprostol 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 misoprostol in pediatric patients have not been established.
ADVERSE REACTIONS
The following have been reported as adverse events in subjects receiving misoprostol:
Gastrointestinal
In subjects receiving misoprostol 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 misoprostol (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 misoprostol is prescribed. The incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding coadministration of misoprostol with magnesium-containing antacids.
Gynecological
Women who received misoprostol 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 misoprostol administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. (see boxed **WARNINGS**).
Elderly
There were no significant differences in the safety profile of misoprostol 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 misoprostol 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 misoprostol and placebo.
Causal Relationship Unknown
The following adverse events were infrequently reported. Causal relationships between misoprostol 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 misoprostol in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort 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 misoprostol for reducing the risk 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**). Misoprostol should be taken for the duration of NSAID therapy as prescribed by the physician. Misoprostol 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
Misoprostol Tablets are available as white, round, unscored, flat beveled-edged tablets, debossed "Ⅹ" and "100" on one side and "4430" on the reverse side containing 100 mcg misoprostol, packaged in unit-of-use bottles of 120 and unit-dose boxes of 100 tablets.
Misoprostol Tablets are available as white, round, scored, flat beveled-edged tablets, debossed "Ⅹ" and "200" on one side and "4431" on the reverse side containing 200 mcg misoprostol, packaged in unit-of-use bottles of 100 and unit-dose boxes of 100 tablets.
PHARMACIST: Dispense in this unit-of-use, child-resistant container as defined in the USP. Provide Patient Information Leaflet with each dispensing.
Store at controlled room temperature 15°-30°C (59°-86°F) in a dry area (see USP).
NOTE: The Spanish text follows the English text.
El texto español sigue al texto inglés.
Pharmacist - Detach here and give lower portion to patient.

PATIENT INFORMATION

Read this leaflet before taking misoprostol and each time your prescription is renewed, because the leaflet may be changed.
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 misoprostol to reduce the risk of NSAID induced ulcers if you are pregnant (See boxed **WARNINGS**). Misoprostol can cause abortion (sometimes incomplete which could lead to dangerous bleeding and require hospitalization and surgery), premature birth, or birth defects. 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. Misoprostol has been reported to cause the uterus to rupture (tear) when given after the eighth week of pregnancy. Rupture (tearing)of the uterus can result in severe bleeding, hysterectomy, and/or maternal or fetal death.
If you become pregnant during misoprostol therapy, stop taking misoprostol 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 misoprostol and contact your physician immediately.
Misoprostol 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 misoprostol 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 misoprostol. If you have prolonged difficulty (more than 8 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.
Take misoprostol only according to the directions given by your physician.
Do not give misoprostol 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 misoprostol. 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.

MISOPROSTOL TABLETAS
INFORMACION PARA EL PACIENTE

Lea esta hoja informativa antes de tomar misoprostol y cada vez que renueve su receta porque puede haber cambios.
Su médico le ha recetado misoprostol para disminuir la posibilidad de adquirir úlceras estomacales relacionadas con la medicina que usted toma para la artritis/dolor.
Para evitar el riesgo de úlceras inducidas por AINE, no tome Misoprostol durante el período de embarazo (consulte los cuadros de ADVERTENCIAS). Misoprostol puede provocar abortos (algunas veces incompletos, dando lugar a hemorragias peligrosas que pueden requerir hospitalización y cirugía), partos prematuros o malformaciones del feto. Es importante evitar quedarse embarazada durante el tratamiento con este medicamento y durante un mínimo de un mes o un ciclo menstrual después de dejar de tomarlo.
Misoprostol ha sido asociado a desgarros uterinos al tomarlo después de la octava semana de embarazo. El desgarro del útero puede producir graves hemorragias, histerectomía y/o muerte de la madre o del feto.
Si usted queda embarazada durante el tratamiento con misoprostol, deje de tomarlo y avise inmediatamente al médico. Recuerde que si usted emplea algún medio anticonceptivo, existe la posibilidad de que quede embarazada. Si esto ocurriera, deje de tomar misoprostol y avise inmediatamente al médico.
En algunas personas, misoprostol puede causar diarrea, calambres abdominales y/o náuseas. En la mayoría de los casos, estos problemas se presentan durante las primeras semanas del tratamiento y desaparecen después de una semana. Usted puede disminuir al mínimo la posibilidad de diarrea si toma misoprostol con los alimentos.
Como estos efectos secundarios generalmente son de leves a moderados y usualmente desaparecen en unos días, muchos pacientes pueden continuar tomando misoprostol. Si usted sigue teniendo dificultad prolongada (más de 8 días), o si tiene diarrea grave, calambres y/o náuseas, llame al médico.
Tome misoprostol siguiendo las instrucciones de su médico sólamente.
No dé misoprostol a nadie más. Ha sido recetado para su padecimiento específico y puede no ser el tratamiento adecuado para otra persona. También pudiera ser peligroso si la otra persona quedara embarazada.
Esta hoja informativa no cubre todos los posibles efectos secundarios de misoprostol. Esta hoja informativa para el paciente no se refiere a todos los efectos secundarios de su medicina para la artritis/dolor. Si tiene alguna pregunta, llame a su médico.
Manténgase fuera del alcance de los niños.

Manufactured for
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137
By: Norton Waterford
Waterford, Ireland

0172
04/02
B2

Made in Ireland

MISOPROSTOL TABLETS

JUL 10 2002
APPROVED

IVAX
Pharmaceuticals, Inc.

unit dose

IVAX
Pharmaceuticals, Inc.

unit dose

IVAX
Pharmaceuticals, Inc.

JUL 10 2002

APPROVED

IVAX
Pharmaceuticals, Inc.

032

JUL 10 2002

MISOPROSTOL
Tablet
100 mcg
Manufactured for:
Ivax Pharmaceuticals, Inc.
Miami, FL 33137
Lot:
Exp. 1101J

MISOPROSTOL
Tablet
100 mcg
Manufactured for:
Ivax Pharmaceuticals, Inc.
Miami, FL 33137
Lot:
Exp. 1101J

MISOPROSTOL
Tablet
100 mcg
Manufactured for:
Ivax Pharmaceuticals, Inc.
Miami, FL 33137
Lot:
Exp. 1101J

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Ivax Pharmaceuticals, Inc.
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Lot:
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100 mcg
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100 mcg
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Exp. 1101J

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Tablet
100 mcg
Manufactured for:
Ivax Pharmaceuticals, Inc.
Miami, FL 33137
Lot:
Exp. 1101J

MISOPROSTOL
Tablet
100 mcg
Manufactured for:
Ivax Pharmaceuticals, Inc.
Miami, FL 33137
Lot:
Exp. 1101J

MISOPROSTOL
Tablet
100 mcg
Manufactured for:
Ivax Pharmaceuticals, Inc.
Miami, FL 33137
Lot:
Exp. 1101J

NDC 0172-4430-59

MISOPROSTOL
TABLETS

100 mcg

Rx only

100 TABLETS (59)

IVAX Pharmaceuticals, Inc.

[redacted]

Store at controlled room temperature
15° - 30°C (59° - 86°F) in a dry area (See USP).

USUAL ADULT DOSAGE: See Package Insert

PHARMACIST: Dispense in this unit-of-use, child-resistant container as defined in the USP. Provide patient Information Leaflet with each dispensing.

Each Tablet Contains:
Misoprostol 100 mcg

Manufactured for:
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137
by Nelton Waterford
Waterford, Ireland

Made in Ireland

1101A

JUL 10 2002

APPROVED

0172-4430-59 4

LOT:

EXP:

NDC 0172-4430-10

MISOPROSTOL
TABLETS

100 mcg

Rx only

N 3 0172-4430-10 5

100 COUNT
UNIT DOSE TABLETS

IVAX Pharmaceuticals, Inc.

NDC 0172-4430-10

MISOPROSTOL
TABLETS

100 mcg

Rx only

For full prescribing information, see enclosed package insert

100 COUNT
UNIT DOSE TABLETS

IVAX Pharmaceuticals, Inc.

JUL 10

Each Tablet Contains:
Misoprostol 100 mcg

[redacted]

WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
PROTECT FROM MOISTURE
This unit-dose package is not child-resistant.
If dispensed for outpatient use, a child-resistant container should be utilized with a patient leaflet attached.
Store at controlled room temperature
15°-30°C (59°-86°F) in a dry area (See USP).

Manufactured for:
IVAX PHARMACEUTICALS INC.
MIAMI, FL 33137
by Nelton Waterford
Waterford, Ireland

Made in Ireland

APPROVED

1101A

NDC 0172-4431-60

MISOPROSTOL
TABLETS

200 mcg

Rx only

100 TABLETS (White)

IVAX Pharmaceuticals, Inc.

[redacted]

Store at controlled room temperature
15° - 30°C (59° - 86°F) in a dry area (See USP).

USUAL ADULT DOSAGE: 200 mcg four times daily with food. See package insert

PHARMACIST: Dispense in this unit-of-use, child-resistant container as defined in the USP. Provide Patient Information Leaflet with each dispensing.

Each Tablet Contains:
Misoprostol 200 mcg

Manufactured for:
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137
by: Norton (Waterford)
Waterford, Ireland

Made in Ireland

1101A

JUL 10 2002

N 3 0172-4431-60

LOT:

EXP:

APPROVED

NDC 0172-4431-10

MISOPROSTOL
TABLETS

200 mcg

Rx only

N 3 0172-4431-10 2

100 COUNT
UNIT DOSE TABLETS

IVAX Pharmaceuticals, Inc.

NDC 0172-4431-10

MISOPROSTOL
TABLETS

200 mcg

Rx only

For full prescribing information, see enclosed package insert

100 COUNT
UNIT DOSE TABLETS

IVAX Pharmaceuticals, Inc.

JUL 10

Each Tablet Contains:
Misoprostol 200 mcg

[redacted]

WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
PROTECT FROM MOISTURE

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized with a patient leaflet attached.

Store at controlled room temperature
15°-30°C (59°-86°F) in a dry area (See USP).

Manufactured for:
IVAX PHARMACEUTICALS, INC.
MIAMI, FL 33137
by: Norton (Waterford)
Waterford, Ireland
Made in Ireland

APPROVED

1101A

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-095

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 76-095

3. NAME AND ADDRESS OF APPLICANT
Zenith Goldline Pharmaceuticals, Inc.
Attn: Patricia Jaworski
140 Legrand Avenue
Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION
Reference Listed Drug product: Cytotec® Tablets by G.D.Searle & Co. approved in NDA #19-268.

The firm filed a Paragraph II certification indicating that there is 1 expired patent #4,301,146 for this drug which expired July 29, 2000. According to the Orange Book, no exclusivity exists for this drug product.

The proposed drug product contains the same active ingredient and has same strength, dosage form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
Misoprostol Tablets

7. NONPROPRIETARY NAME
NA

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 12-28-00
Accepted for Filing: 1-02-01

10. PHARMACOLOGICAL CATEGORY
Antisecretory and mucosal protector

11. Rx or OTC
Rx

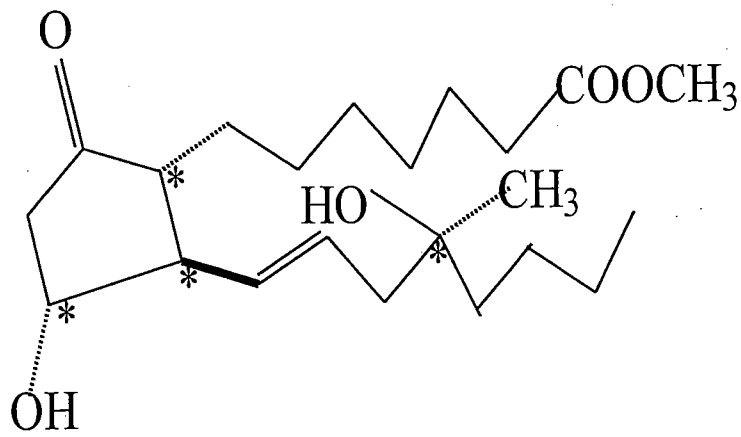
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablet

14. POTENCY
100 mcg and 200 mcg

15. CHEMICAL NAME AND STRUCTURE
methyl(13E)-(±)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate
M.Wt: 382.54 CAS# 59122-46-2 $C_{22}H_{38}O_5$



* Chiral carbons

16. RECORDS AND REPORTS
NA

17. COMMENTS

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS
The application is unapprovable. Minor amendment.

19. REVIEWER: Karen A. Bernard, Ph.D.
DATE COMPLETED: 3-28-01

Redacted 20

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 76-095

3. NAME AND ADDRESS OF APPLICANT
Zenith Goldline Pharmaceuticals, Inc.
Attn: Patricia Jaworski
140 Legrand Avenue
Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION
Reference Listed Drug product: Cytotec® Tablets by G.D.Searle & Co. approved in NDA #19-268.

The firm filed a Paragraph II certification indicating that there is 1 expired patent #4,301,146 for this drug which expired July 29, 2000. According to the Orange Book, no exclusivity exists for this drug product.

The proposed drug product contains the same active ingredient and has same strength, dosage form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
Misoprostol Tablets

7. NONPROPRIETARY NAME
NA

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 12-28-00
Accepted for Filing: 1-02-01
Minor Deficiency letter: 8-20-01
Amendment Response: 9-07-01

10. PHARMACOLOGICAL CATEGORY
Antisecretory and mucosal protector

11. Rx or OTC
Rx

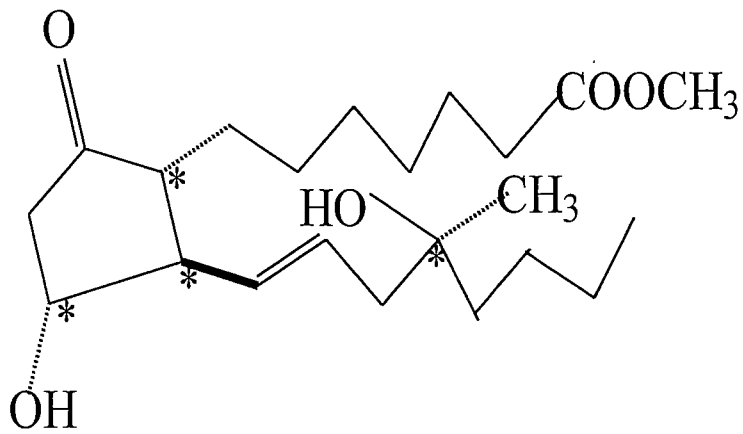
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablet

14. POTENCY
100 mcg and 200 mcg

15. CHEMICAL NAME AND STRUCTURE
methyl(13E)-(±)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate
M.Wt: 382.54 CAS# 59122-46-2 $C_{22}H_{38}O_5$



* Chiral carbons

16. RECORDS AND REPORTS
NA

17. COMMENTS
All chemistry deficiencies have been resolved satisfactorily.
Bioequivalence is acceptable dated 4/20/01.
Labeling is pending.
EER was submitted.
Methods validation is pending. Sent to Phila DO.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: Karen A. Bernard, Ph.D.

DATE COMPLETED: 10-30-01

APPEARS THIS WAY
ON ORIGINAL

Redacted 18

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 76-095

3. NAME AND ADDRESS OF APPLICANT
Ivax Pharmaceuticals, Inc.
Attn: Patricia Jaworski
140 Legrand Avenue
Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION
Reference Listed Drug product: Cytotec® Tablets by G.D.Searle & Co. approved in NDA #19-268.

The firm filed a Paragraph II certification indicating that there is 1 expired patent #4,301,146 for this drug which expired July 29, 2000. According to the Orange Book, no exclusivity exists for this drug product.

The proposed drug product contains the same active ingredient and has same strength, dosage form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
Misoprostol Tablets

7. NONPROPRIETARY NAME
NA

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 12-28-00
Accepted for Filing: 1-02-01
Minor Deficiency letter: 8-20-01
Amendment Response: 9-07-01
*Minor Deficiency: 11-29-01
Amendment Response: 1-22-02

10. PHARMACOLOGICAL CATEGORY
Antisecretory and mucosal protector

11. Rx or OTC
Rx

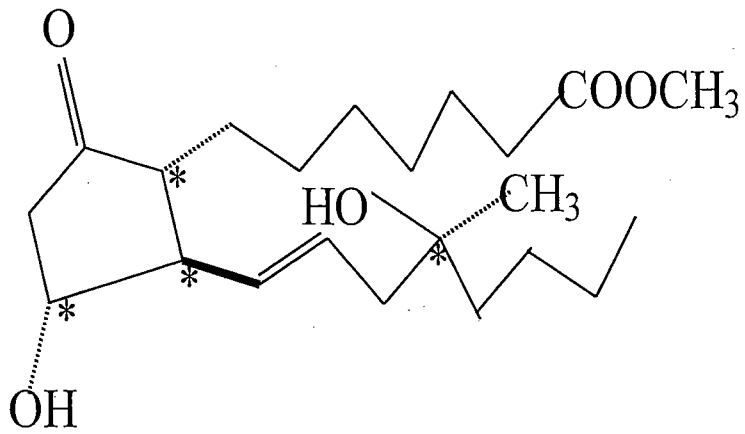
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablet

14. POTENCY
100 mcg and 200 mcg

15. CHEMICAL NAME AND STRUCTURE
methyl(13E)-(±)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate
M.Wt: 382.54 CAS# 59122-46-2 $C_{22}H_{38}O_5$



* Chiral carbons

16. RECORDS AND REPORTS
NA

17. COMMENTS
Chemistry is now acceptable.
Bioequivalence is acceptable dated 4/20/01.
Labeling is acceptable dated 1/15/02.
EER was submitted and found acceptable on 10/22/01.
Methods validation is acceptable, by Phila DO 11/21/01.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is approvable.

19. REVIEWER: Karen A. Bernard, Ph.D.
DATE COMPLETED: 3-15-02

APPEARS THIS WAY
ON ORIGINAL

Redacted 28

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-095

BIOEQUIVALENCE REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-095 APPLICANT: Zenith Goldline Pharmaceuticals
DRUG PRODUCT: Misoprostol Tablets
100 and 200 µg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs.

The dissolution testing should be conducted in [redacted] using USP 24 apparatus II (paddle) at [redacted] The test product should meet the following dissolution specifications:

Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-095 SPONSOR : Zenith Goldline Pharmaceuticals

DRUG AND DOSAGE FORM : Misoprostol Tablets

STRENGTH(S) : 100 and 200 µg

TYPES OF STUDIES : [SD] [SDF] MULT [OTHER]

CLINICAL STUDY SITE(S) : ~~[illegible]~~

ANALYTICAL SITE(S) : ~~[illegible]~~

STUDY SUMMARY : In the single dose fasting and fed bioequivalence studies, Misoprostol tablets, 200 µg were shown to be bioequivalent to Cytotec® tablets, 200 µg.

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: YES / [NO]	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : MSG DATE : 4/13/01

TEAM LEADER : BARBARA M. DAVIT, Ph.D. BRANCH : III

INITIAL : BMD DATE : 4/13/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : [illegible] DATE : 4/20/01

2-1

Misoprostol Tablets
100 and 200 μg
ANDA #76-095
Reviewer: Mamata Gokhale
v:\firmsnz\zenith\76095SDW.D00

Zenith Goldline Pharmaceuticals
140 Legrand Avenue
Northvale New Jersy 07647

Submission Dates: 12/28/00, 3/29/01

Review of Bioequivalence Studies, Waiver Request and Dissolution Data

I. Introduction

Indication: Anti-ulcer agent for prevention of NSAID induced gastric ulcers.
Type of Submission: ANDA for the 100 and 200 μg strengths of Misoprostol Tablets.
Contents of Submission: Single dose fasting and fed bioequivalence studies on the 200 μg strength, dissolution data on both strengths and request for waiver of *in vivo* bioequivalence study requirements for the 100 μg strength.
RLD: Cytotec® Tablets, 100 and 200 mg, manufactured by Searle.
Recommended dose: 200 μg four times a day with food.

Background

Misoprostol is a water soluble synthetic prostaglandin E1 analog comprised of 4 stereoisomers in equal proportions. Following an oral dose, it is undergoes rapid de-esterification to its free acid, which is responsible for its pharmacological activity and, unlike the parent compound, is detectable. In normal volunteers, misoprostol is rapidly absorbed after oral administration. Misoprostol acid has a Tmax of 12 ± 3 minutes and a terminal half life of 20-40 minutes. Plasma levels of misoprostol acid are highly variable between and within studies but mean values after single doses show a linear relationship with dose over the range of 200-400 μg. At present there are no generic misoprostol tablets available on the market.

II. Single-dose Fasting Bioequivalence Study, 200 μg strength

A. Study Information

Study Number BP017
Principal Investigator [redacted]
Clinical Site [redacted]
Study Dates Period I: 9/16/00, Period II: 9/23/00
Analytical Site [redacted]
Analytical Director [redacted]
Analysis Dates 10/24/00-11/27/00
Storage Period 38-65 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Misoprostol	Cytotec®

Manufacturer	Zenith Goldline Pharmaceuticals	Searle
Lot No.	N0071	OC695
Manufacture Date	6/2000	N/A
Expiration Date	N/A	9/2002
Strength	200 µg	200 µg
Dosage Form	Tablets	Tablets
Batch Size	———	N/A
Production Batch Size	———	N/A
Potency	101.2%	100.6%
Content Uniformity (mean, %cv, range, n)	102.9, 1.3, 101.2-105.2,10	99.0, 1.4, 96.9-100.9, 10
Formulation	See Table #1	N/A
Dose Administered	400 µg	400 µg
Route of Administration	Oral	Oral
Length of Fasting	10 hours pre-dosing 4 hours post-dosing	10 hours pre-dosing 4 hours post-dosing

No. of Sequences	2	**Crossover**	Y
No. of Periods	2	**Replicate Design**	N
No. of Treatments	2	**Balanced**	Y
No. of Groups (if appropriate)	0	**Washout Period**	7 days
Randomization Scheme	**AB:** 2, 3, 4, 5, 7, 8, 9, 13, 15, 16, 21, 22, 23, 26, 27, 30, 33, 35 **BA:** 1, 6, 10, 11, 12, 14, 17, 18, 19, 20, 24, 25, 28, 29, 31, 32, 34, 36		
Blood Sampling Times	0 (pre-misoprostol dose), 3, 6, 9, 12, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, 165, 240 minutes		
Blood Volume Collected/Sample	7 mL		
Blood Sample Processing/Storage	Heparinized plasma samples were stored at –20^{0}C		

IRB Approval	Y
Informed Consent	Y
No. Enrolled	36
No. Dosed and completed	36
No. Analyzed	36
No. of Dropouts	0
Restrictions	Along with the standard dietary, activity and drug restrictions, the exclusion criteria included hypersensitivity to prostaglandins.
Length of Confinement	From 10 hours pre-dosing to 4 hours post-dosing.
Safety Monitoring	Vital signs (blood pressure and heart rate) were monitored prior to misoprostol administration and after the last blood draw at 4 hours. Along with the physical examination, hematology and clinical

chemistry measurements were repeated at the completion of the study.

Healthy Subjects Only Y

B. Study Results

1. Clinical

Dropout Information There were no dropouts.

Adverse Events Six drug-related mild or moderate adverse events, three were related with treatment A (test) and three were related with treatment B (reference). For additional information see Appendix III on pages 238-247 of volume 1.2.

Protocol Deviations The 180 minute post-dose sampling point, as stated in the protocol, was replaced by the 165 minute sampling point. There were 89 minor deviations in blood sampling times. Actual sampling times were used for all calculations. See vol. 1.2, pages 10 and 20 for details. The reviewer concludes that these deviations do not compromise the integrity of the study.

Comments: None

2. Analytical

Analytical Method Validation
NOT TO BE RELEASED UNDER FOI

Comments: None

Conclusion: The analytical method is acceptable.

3 Pharmacokinetic/Statistical Analysis

Mean Plasma Concentrations	Table #2, Figure #1	
Mean Pharmacokinetic Parameters	Table #4	
90% Confidence Intervals	lnAUCt: 91.76-105.43 lnAUCi: 91.77-104.29 lnCmax: 80.45-105.39 Details in Table #5	
AUCt/AUCi ratio	Test	Reference
Mean, %CV	0.97, 1.96	0.96, 3.41

Total SD and within-subject error (root MSE): Values are shown below

(for ln-transformed AUCt and Cmax only)

Total standard deviation and root mean square error, ln-transformed PK data		
Drug (parent)	Misoprostol	
PK parameter	lnCmax	lnAUCt
Root MSE, test & ref combined	0.3388	0.1742

Comments: (on pharmacokinetic and statistical analyses)

1) During misoprostol PK analysis, the firm was able to determine the Kel and AUCi values for all the subjects. The reviewer agrees with this decision.

2) In the pharmacokinetic analysis of misoprostol, subjects with

a) measurable drug concentrations at 0 hour: 0
b) first scheduled post-dose sampling time as Tmax: None
c) first measurable concentration as Cmax: None

3) The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.

4) No statistically significant sequence or period effects were seen for parameters lnAUCt, lnAUCi and lnCmax during the pharmacokinetic analysis of misoprostol.

5) The 90% confidence intervals for the log transformed AUCt, AUCi and Cmax are within the acceptable limits of 80.00-125.00%.

Conclusion: The single-dose fasting bioequivalence study on the 200 μg strength of Misoprostol Tablets is acceptable.

III. Single-dose Post-Prandial Bioequivalence Study, 200 μg strength

A. Study Information

Study Number BP019
Principal Investigator [redacted]
Clinical Site [redacted]
Study Dates Period I: 9/23/00, Period II: 9/30/00, Period III: 10/7/00
Analytical Site [redacted]
Analytical Director [redacted]
Analysis Dates 11/14-12/20/00
Storage Period 31-74 days

Treatment ID A B C

Test or Reference	Test	Reference	Test
Product Name	Misoprostol	Cytotec®	Misoprostol
Manufacturer	Zenith Goldline Pharmaceuticals	Searle	Zenith Goldline Pharmaceuticals
Lot No.	please correct		
Dose Administered	400 µg	400 µg	400 µg
Route of Administration	Oral	Oral	Oral
Length of Fasting	9.5 hours pre-dosing, 4 hours post-dosing	9.5 hours pre-dosing, 4 hours post-dosing	10 hours pre-dosing, 4 hours post-dosing
Food/Drug Interval	10 minutes	10 minutes	N/A
Standardized Breakfast	Yes	Yes	No
Breakfast Description	Standard high-fat	Standard high-fat	N/A

No. of Sequences	3	**Crossover**	Y
No. of Periods	3	**Replicate Design**	N
No. of Treatments	3	**Balanced**	Y
No. of Groups (if appropriate)	0	**Washout Period**	7 days

Randomization Scheme	**ABC:** 2, 9, 13, 21, **CBA:** 6, 7, 17, 20, **CAB:** 3, 10, 15, 24, **ACB:** 5, 12, 18, 23, **BCA:** 4, 8, 16, 19, **BAC:** 1, 11, 14, 22
Blood Sampling Times	0 (pre-misoprostol dose), 3, 6, 9, 12, 15, 20, 30, 40, 50, 60, 70, 80, 90, 105, 120, 150, 180, 240, 300 and 360 minutes
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Heparinized plasma samples were stored at -20^0C
IRB Approval	Y
Informed Consent	Y
No. Enrolled	24
No. Dosed and completed	23
No. Analyzed	23
No. of Dropouts	1
Restrictions	Along with the standard dietary, activity and drug restrictions, the exclusion criteria included hypersensitivity to prostaglandins.
Length of Confinement	From 10 hours pre-dosing to 6 hours post-dosing.
Safety Monitoring	Vital signs (blood pressure and heart rate) were monitored prior to misoprostol administration and after the last blood draw at 4 hours. Along with the physical examination, hematology and clinical chemistry measurements were repeated at the completion of the study.
Healthy Subjects Only	Yes

B. Study Results

1. Clinical

Dropout Information

Subject No	5
Reasons	Subject #5 had a positive test for opiate metabolites caused by pain medication taken for a dental abscess.
Period	3
Replacement	None

Adverse Events Eight drug-related mild or moderate events, one was related with treatment A (test) under fed conditions, three were related with treatment B (reference) under fed conditions and four were related with treatment C (test) under fasting conditions. For additional information see Appendix III on pages 263-283 of volume 1.6.

Protocol Deviations There were 70 minor deviations in blood sampling times. Actual sampling times were used for all calculations. See vol. 1.6, pages 11-12 for details. Other minor deviations were with sample storage, blood volume drawn and the safety assessment. See vol. 1.6, page 21 for details. The reviewer concludes that these deviations do not compromise the integrity of the study.

2. Analytical

Conclusion: The analytical method is acceptable.

3. Pharmacokinetic/Statistical Analysis

Mean Plasma Concentrations	Table #3, Figure #2		
Mean Pharmacokinetic Parameters	Table #6		
Geometric Mean Ratio	lnAUCt 1.06 lnAUCi 1.03 lnCmax 1.06 Details in Table #7		
AUCt/AUCi ratio	Test (Fed)	Reference (Fed)	Test (Fasted)
Mean	0.94	0.93	0.97
%CV	3.36	10.42	1.28

Comments: (on pharmacokinetic and statistical analyses)

1) During misoprostol PK analysis, the firm was able to determine the Kel and AUCi values for all subjects. The reviewer agrees with this decision.

2) In the pharmacokinetic analysis of misoprostol, subjects with

a) measurable drug concentrations at 0 hour: 0
b) first scheduled post-dose sampling time as Tmax: None
c) first measurable concentration as Cmax: None

3) The pharmacokinetic parameters calculated by the reviewer agree with the firm's calculations.

4) During the pharmacokinetic analysis of misoprostol, a statistically significant period effect was seen for parameters lnAUCt and lnCmax.

5) The ratios of ln-transformed geometric means (Test fed/Reference fed) AUCt, AUCi, Cmax (calculated by the reviewer and the firm) are within the acceptable limits of 0.8-1.25.

Conclusion: The single-dose post-prandial bioequivalence study on the 200 μg strength of Misoprostol Tablets is acceptable.

IV Waiver Request

The firm is requesting a waiver of in vivo bioequivalence testing for the 100 μg strength under 21 CFR 320.22 (d). Formulation data and comparative dissolution profiles were provided for the 100 μg strength of the test and reference products.

V. Formulation(s)

Table #1 indicates that the formulation of Zenith's 100 μg strength of Misoprostol Tablets is proportional to the 200 μg strength with respect to active and inactive ingredients.

Comments: The formulation of Zenith's Misoprostol Tablets, 100 and 200 μg is acceptable.

VI. Dissolution

A. Dissolution Method

There is no compendial method for the dissolution testing of Misoprostol Tablets. The firm has used the FDA method for in vitro testing of the test and reference products. The firm also used basket apparatus at [redacted] keeping other conditions similar to the FDA method. Data obtained by using the FDA method is included in the review.

FDA Method
Analyte: Misoprostol
Unit: 12 tablets
Dissolution Medium: [redacted]
Temperature: [redacted]
Volume: [redacted]
Apparatus: Paddle (USP Apparatus II) at [redacted]
Sampling Times: 2, 5, 10, 15 and 20 minutes
Assay Method: [redacted]
Dissolution Specifications: NLT [redacted] (Q) in 20 minutes

Results: The dissolution data are presented in Table #11 and Figure 3. For both strengths, more than [redacted] of misoprostol is released within 15 minutes, irrespective of the test or reference formulations. For both strengths, the mean percentage of the labeled amount of misoprostol released exceeded [redacted] by the second sampling time (5 minutes). Therefore f2 analysis was not performed for this drug product.

Comments:

1) For the 200 μg strength of Misoprostol Tablets, Lots #N0071(Test) and OC695 (Reference) used in the dissolution testing were same as those used in the *in vivo* bioequivalence studies.

2) Misoprostol Tablets, 100 and 200 μg meet the FDA dissolution specification of NLT (Q[redacted]% in 20 minutes.

3) Due to the rapid dissolution of Misoprostol Tablets (Table #8), analysis of similarity factor (f2) across different strengths and comparison with the RLD is not relevant for this drug product.

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Recommendations

1) The single-dose fasting bioequivalence study, protocol #BP017 and single-dose post-prandial bioequivalence study, protocol #BP019 conducted by Zenith Goldline Pharmaceuticals on its Misoprostol Tablets 200 μg, Lot #N0071, comparing them to Cytotec® Tablets, 200 μg, Lot #OC695, manufactured by Searle have been found acceptable by the Division of Bioequivalence. These studies demonstrate that Misoprostol Tablets, 200 μg, manufactured by Zenith Goldline Pharmaceuticals are bioequivalent to Cytotec® Tablets, 200 μg, manufactured by Searle.

2) The in vitro dissolution testing conducted by Zenith Goldline Pharmaceuticals using the FDA method on its Misoprostol Tablets, 100 and 200 μg, lots #N0070 and N0071 respectively is acceptable. The firm conducted an acceptable bioequivalence study comparing its 200 μg tablets to the reference product Cytotec® 200 μg tablets. Waiver of in vivo bioequivalence testing requirements for the 100 μg mg strengths of Misoprostol Tablets is granted. The Division of Bioequivalence deems Zenith Goldline's

Misoprostol Tablets, 100 and 200 μg bioequivalent to Cytotec® Tablets, 100 and 200 μg, manufactured by Searle.

3) The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in using USP Apparatus II (paddle) at The test product should meet the following specifications:

> Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

4) The firm has met requirements of in vivo bioequivalence and in vitro dissolution testing. The application is acceptable.

The firm should be informed of the above recommendations.

Mamata S. Gokhale, Ph.D. /S/ 4/13/01
Division of Bioequivalence

BMD 4/12/01

RD INITIALED BDAVIT
FT INITIALED BDAVIT /S/ Date 4/13/01

Concur: /S/ Date 4/20/01
Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-095 (original, duplicate), Davit, HFD-658, Gokhale, HFD-658, Drug File, Division File

List of Tables

1) Formulation of Misoprostol Tablets, 100 and 200 μg.

2) Mean Plasma Concentrations of Misoprostol after an oral dose of 200 μg under fasting conditions.

3) Mean Plasma Concentrations of Misoprostol after an oral dose of 200 μg under fed conditions.

4) Misoprostol Pharmacokinetic Parameters, 200 μg dose, fasting study.

5) Summary Statistics for Misoprostol, 200 μg dose, fasting study.

6) Misoprostol Pharmacokinetic Parameters, 200 μg dose, fed study.

7) Summary Statistics for Misoprostol, 200 μg dose, fed study.

8) Results of In vitro Dissolution Testing of Misoprostol Tablets, 100 and 200 μg.

List of Figures

1) Mean Plasma Concentrations of Misoprostol after an oral dose of 200 μg (Test vs Reference) under fasting conditions.

2) Mean Plasma Concentrations of Misoprostol after an oral dose of 200 μg (Test vs Reference) under fed conditions.

3) Dissolution Profiles of Misoprostol Tablets, 100 and 200 μg (Test vs Reference).

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Table #1
Formulation

Misoprostol Tablets		
Ingredient	**100 μg** **[1]Batch #N0070**	**200 μg** **[2]Batch #N0071**
	mg/tablet	**mg/tablet**
[3,4]Misoprostol [redacted] ([redacted]	[redacted]	[redacted]
[5]Microcrystalline Cellulose [redacted]	[redacted]	[redacted]
[5]Sodium Starch Glycolate, NF [redacted]	[redacted]	[redacted]
[5]Hydrogenated Vegetable Oil, NF [redacted]	[redacted]	[redacted]

[1]To be scaled up to ANDA Batch size of [redacted] tablets and production batch size of [redacted] tablets.
[2]To be scaled up to ANDA Batch size of [redacted] tablets and production batch size of [redacted] tablets.
[3,4]Active ingredient, [redacted] containing Misoprostol [redacted] and [redacted]
[5]Inactive ingredients, all are within approved safety limits (FDA Inactive Ingredient Guide, January, 1996).

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Table #2
Mean Plasma Concentrations of Misoprostol
Following an Oral Dose of 400 μg (Fasting Study)
Treatment A: Misoprostol Tablets, 2 x 200 μg, Lot #N0071A
Treatment B: Cytotec® Tablets, 2 x 200 μg, Lot #OC695

Time (minutes)	Mean (± SD) Plasma Concentrations (ng/mL)				
	Treatment A		Treatment B		Ratio A/B
0	0.00	0.00	0.00	0.00	0.0
3	0.04	0.05	0.03	0.02	1.3
6	0.20	0.21	0.17	0.18	1.2
9	0.36	0.28	0.34	0.25	1.1
12	0.43	0.28	0.44	0.26	1.0
15	0.45	0.23	0.48	0.25	0.9
20	0.42	0.17	0.48	0.22	0.9
30	0.34	0.13	0.36	0.14	0.9
40	0.24	0.10	0.24	0.10	1.0
50	0.17	0.08	0.17	0.08	1.0
60	0.12	0.07	0.12	0.06	1.0
75	0.07	0.04	0.07	0.03	1.0
90	0.04	0.03	0.04	0.02	1.0
105	0.03	0.02	0.03	0.01	1.0
120	0.03	0.02	0.03	0.01	1.0
150	0.02	0.01	0.02	0.01	1.0
165	0.02	0.01	0.02	0.01	1.0
240	0.01	0.00	0.00	0.00	0.0

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Table #3
Mean Plasma Concentrations of Misoprostol
Following an Oral Dose of 400 μg (Fed Study)
Treatment A: Misoprostol Tablets, 2 x 200 μg, Lot # N0071A (Fed)
Treatment B: Cytotec® Tablets, 2 x 200 μg, Lot #OC695 (Fed)
Treatment C: Misoprostol Tablets, 2 x 200 μg, Lot # N0071A (Fasted)

Time (minutes)	Plasma Conc. (ng/mL), Mean, S.D.							
	Treatment A		Treatment B		Treatment C		Ratio A/B	Ratio A/C
0	0.00	0.00	0.00	0.00	0.00	0.00	0.0	0.0
3	0.03	0.03	0.02	0.02	0.07	0.07	1.5	0.4
6	0.06	0.05	0.06	0.06	0.24	0.22	1.0	0.3
9	0.11	0.06	0.09	0.09	0.45	0.34	1.2	0.2
12	0.12	0.07	0.14	0.14	0.52	0.31	0.9	0.2
15	0.17	0.10	0.15	0.15	0.58	0.28	1.1	0.3
20	0.17	0.11	0.17	0.17	0.57	0.21	1.0	0.3
30	0.15	0.08	0.15	0.15	0.43	0.19	1.0	0.3
40	0.14	0.07	0.14	0.14	0.26	0.12	1.0	0.5
50	0.14	0.06	0.13	0.13	0.17	0.07	1.1	0.8
60	0.14	0.05	0.13	0.13	0.12	0.05	1.1	1.2
70	0.16	0.06	0.14	0.14	0.08	0.04	1.1	2.0
80	0.15	0.07	0.15	0.15	0.06	0.03	1.0	2.5
90	0.15	0.07	0.15	0.15	0.05	0.02	1.0	3.0
105	0.14	0.05	0.14	0.14	0.03	0.02	1.0	4.7
120	0.14	0.05	0.13	0.13	0.02	0.01	1.1	7.0
150	0.13	0.05	0.11	0.11	0.02	0.01	1.2	6.5
180	0.1	0.05	0.10	0.10	0.01	0.00	1.0	10.0
240	0.06	0.04	0.07	0.07	0.00	0.00	0.9	0.0
300	0.03	0.02	0.02	0.02	0.00	0.00	1.5	0.0
360	0.02	0.01	0.02	0.02	0.00	0.00	1.0	0.0

Table #4
Misoprostol Pharmacokinetic Parameters
Single Dose Fasting Study, 400 μg Dose
Treatment A: Misoprostol Tablets, 2 x 200 μg, Lot # N0071A
Treatment B: Cytotec® Tablets, 2 x 200 μg, Lot #OC695

Plasma Parameters	Cmax (ng/mL)		Tmax (hours)		Kel (1/hours)	
Treatment	A	B	A	B	A	B
MEAN	0.55	0.60	23.56	19.78	0.03	0.03
CV%	41.39	38.68	74.86	43.28	33.52	31.69

Plasma Parameters	T1/2 (hours)		AUCt (ng/mL-hours)		AUCi (ng/mL-hours)	
Treatment	A	B	A	B	A	B
MEAN	26.94	27.14	20.14	20.40	20.74	21.10
CV%	46.09	12.61	29.27	26.99	28.67	26.30

Table #5
Summary Statistics for Misoprostol
Single Dose Fasting Study, 400 μg Dose
Treatment A: Misoprostol Tablets, 2 x 200 μg, Lot # N0071A
Treatment B: Cytotec® Tablets, 2 x 200 μg, Lot #OC695

PK Parameter	Geometric Mean		Ratio	90% C.I.
(Treatment)	A	B	A/B	
LnAUCt (ng·hr/mL)	19.34	19.66	0.98	91.76-105.43
LnAUCi (ng·hr/mL)	19.95	20.39	0.98	91.77-104.29
LnCmax (ng·hr/mL)	0.505	0.549	0.92	80.45-105.39

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Table #6
Misoprostol Pharmacokinetic Parameters
Single Dose Fed Study, 400 μg Dose
Treatment A: Misoprostol Tablets, 2 x 200 μg, Lot # N0071A (Fed)
Treatment B: Cytotec® Tablets, 2 x 200 μg, Lot #OC695 (Fed)
Treatment C: Misoprostol Tablets, 2 x 200 μg, Lot # N0071A (Fasted)

Plasma Parameters	Cmax (ng/mL)			Tmax (hours)			Kel (1/hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	0.24	0.23	0.71	50.65	71.17	17.96	0.01	0.01	0.03
CV%	33.14	39.11	40.60	81.15	89.57	37.38	30.18	33.63	32.63

Plasma Parameters	T1/2 (hours)			AUCt (ng/mL-hours)			AUCi (ng/mL-hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	58.55	60.15	27.29	31.91	30.75	22.76	33.75	32.97	23.31
CV%	31.36	61.26	43.76	26.27	33.84	34.54	25.62	30.13	33.91

Table #7
Summary Statistics for Misoprostol
Single Dose Fed Study, 400 μg Dose
Treatment A: Misoprostol Tablets, 2 x 200 μg, Lot # N0071A (Fed)
Treatment B: Cytotec® Tablets, 2 x 200 μg, Lot #OC695 (Fed)
Treatment C: Misoprostol Tablets, 2 x 200 μg, Lot # N0071A (Fasted)

PK Parameter	Geometric Mean		Ratio
(Treatment)	A	B	A/B
LnAUCt (ng·hr/mL)	30.95	29.30	1.06
LnAUCi (ng·hr/mL)	32.76	31.78	1.03
LnCmax (ng·hr/mL)	0.23	0.22	1.06

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Table #8
Results of In Vitro Dissolution Testing
Test Product: Misoprostol Tablets by Zenith Goldline Pharmaceuticals
Reference Product: Cytotec® Tablets by Searle

FDA Method: [redacted] **Apparatus II at** [redacted]
FDA Specification: NLT [redacted] **(Q) in 20 minutes**

100 μg strength

Sampling Times (min.)	Test Product Lot #N0070			Reference Product Lot #7K321		
	Mean %	Range	% CV	Mean %	Range	% CV
2	70	[redacted]	9.7	81	[redacted]	9.4
5	81	[redacted]	6.9	92	[redacted]	5.8
10	87	[redacted]	5.6	95	[redacted]	3.9
15	92	[redacted]	3.5	96	[redacted]	2.7
20	93	[redacted]	5.4	97	[redacted]	4.4

200 μg Strength

Sampling Times (min.)	Test Product Lot # N0071			Reference Product Lot #OC695		
	Mean %	Range	% CV	Mean %	Range	% CV
2	74	[redacted]	10.1	75	[redacted]	9.2
5	83	[redacted]	5.8	85	[redacted]	7.5
10	91	[redacted]	3.7	91	[redacted]	3.4
15	95	[redacted]	2.4	94	[redacted]	2.9
20	97	[redacted]	1.9	96	[redacted]	2.2

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Figure 1

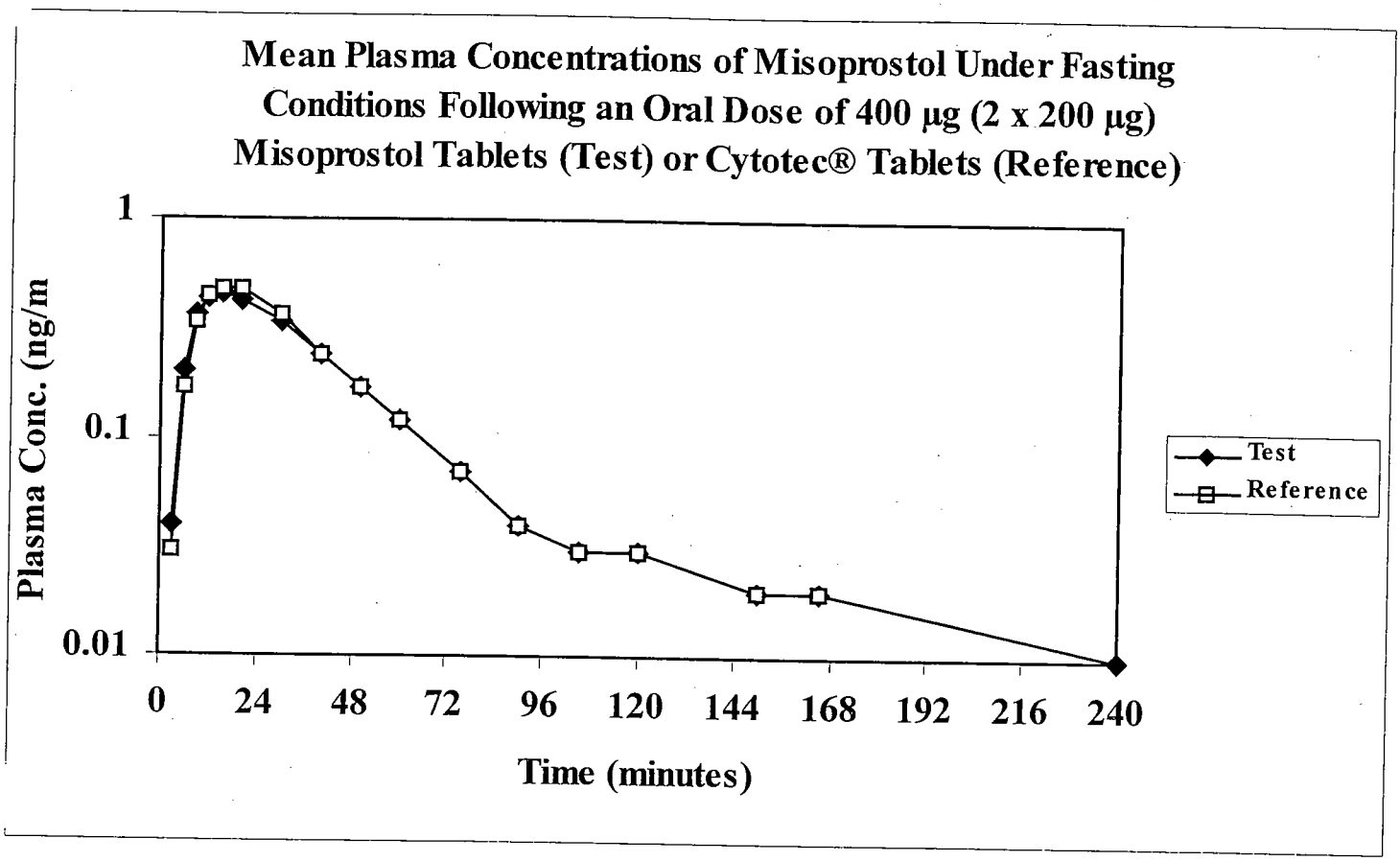

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Figure 2

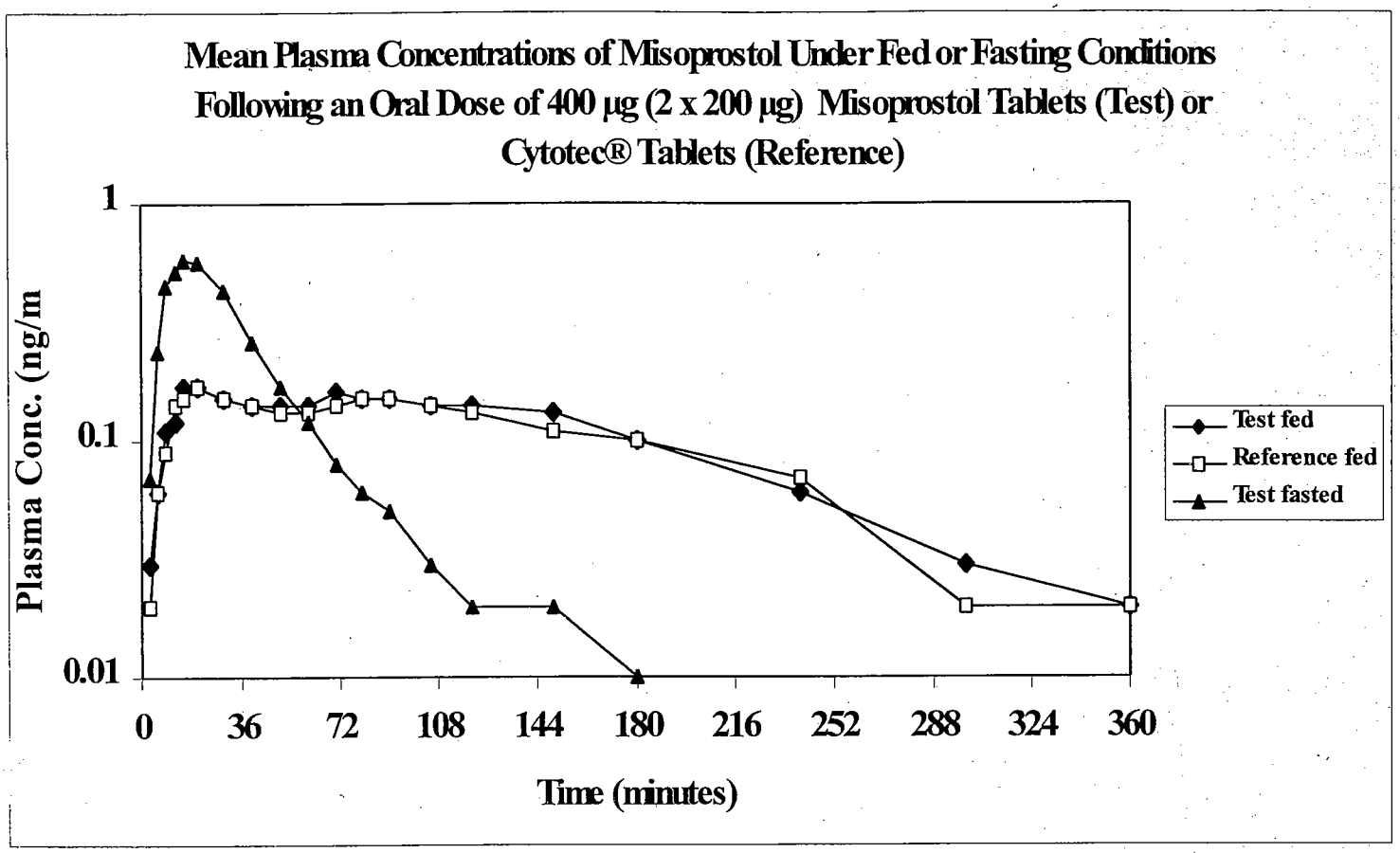

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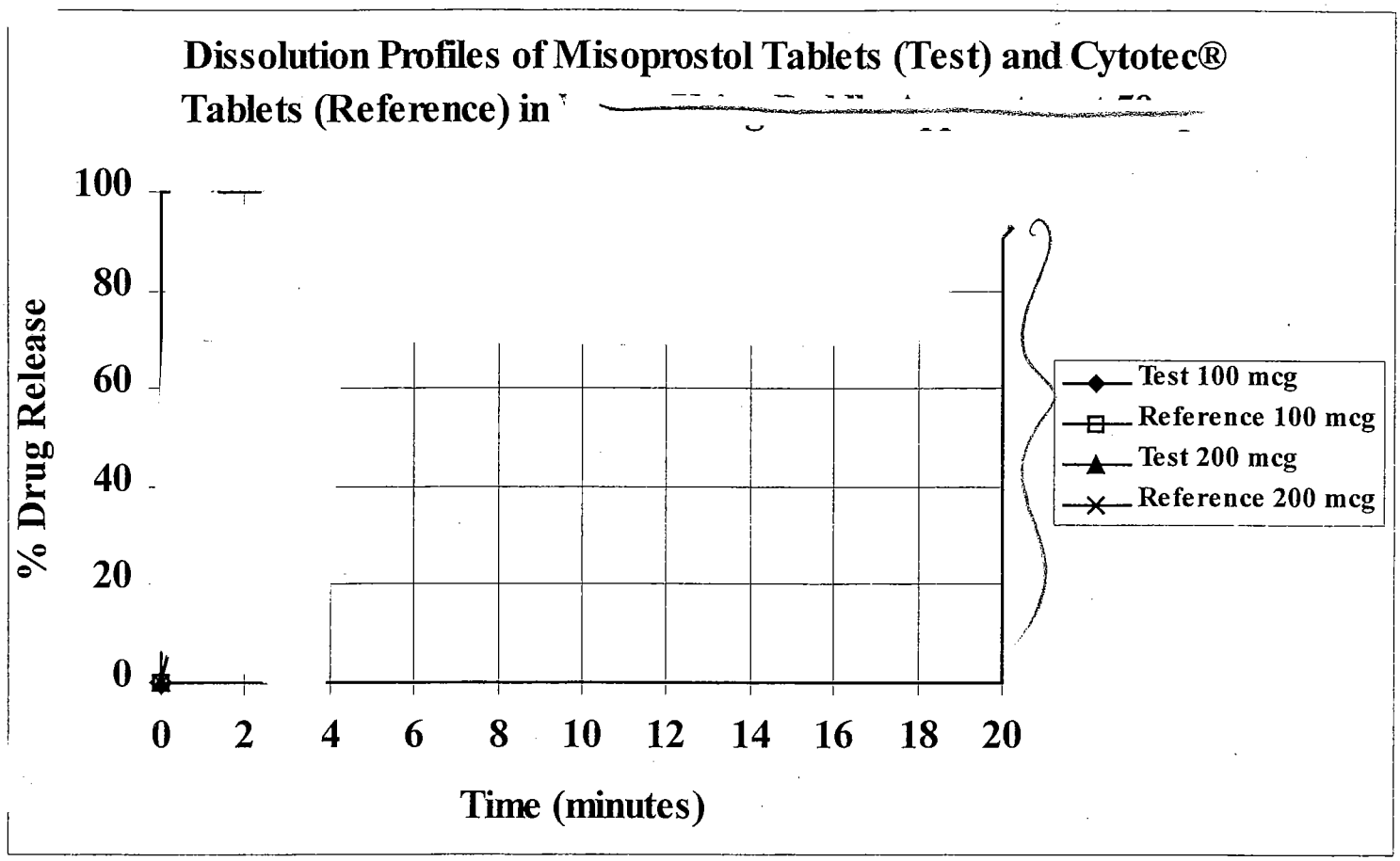
Figure 3



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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-095 APPLICANT: Zenith Goldline Pharmaceuticals
DRUG PRODUCT: Misoprostol Tablets
100 and 200 μg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs.

The dissolution testing should be conducted in [redacted] using USP 24 apparatus II (paddle) at [redacted] The test product should meet the following dissolution specifications:

Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA # 76-095
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: B. Davit

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Printed in final on 4/13/2001

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale MSK 4/13/01
HFD-658/ B. Davit BMD 4/13/01
HFD-650/ D. Conner 4/20/01
HFD-617/ S. Mazzella

Bioequivalency- Acceptable Submission Date: 28 December, 2000

OK 1) Fasting Study (STF) Strength: 200 µg
Clinical: Outcome: AC
Analytical:

OK 2) Food Study (STP) Strength: 200 µg
Clinical: Outcome: AC
Analytical:

OK 3) Dissolution Waiver (DIW) Strength: 100 µg
Outcome: AC

OK 4) Amendment dated 3/29/01 Strength: 200 µg
Outcome: AC

Outcome Decisions: AC- Acceptable

Winbio comments: STF – Acceptable
STP – Acceptable
STF – Acceptable
DIW – Acceptable

SOP

Redacted 12

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-095

ADMINISTRATIVE DOCUMENTS

Active Ingredient Search Results from "Rx" table for query on "MISOPROSTOL."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020607		Yes	DICLOFENAC SODIUM; MISOPROSTOL	Tablet, Delayed Release; Oral	50MG; 0.2MG	ARTHROTEC	SEARLE
020607		Yes	DICLOFENAC SODIUM; MISOPROSTOL	Tablet, Delayed Release; Oral	75MG; 0.2MG	ARTHROTEC	SEARLE
019268		No	MISOPROSTOL	Tablet; Oral	0.1MG	CYTOTEC	SEARLE
019268		Yes	MISOPROSTOL	Tablet; Oral	0.2MG	CYTOTEC	SEARLE

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Search results from the "Rx" table for query on "019268."

Active Ingredient:	MISOPROSTOL
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	CYTOTEC
Applicant:	SEARLE
Strength:	0.2MG
Application Number:	019268
Product Number:	001
Approval Date:	Dec 27, 1988
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	MISOPROSTOL
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	CYTOTEC
Applicant:	SEARLE
Strength:	0.1MG
Application Number:	019268
Product Number:	003
Approval Date:	Sep 21, 1990
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	Click Here

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Patent and Exclusivity Search Results from query on 019268 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019268	001	4301146	JUL 29,2000	

Exclusivity Data

There is no unexpired exclusivity for this product.

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Patent and Exclusivity Terms

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ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: ANDA 76095/000
Stamp: 02-JAN-2001
Regulatory Due:
Applicant: ZENITH GOLDLINE
140 LEGRAND AVE
NORTHVALE, NJ 07647
Priority:
Org Code: 600

Action Goal:
District Goal: 02-DEC-2001
Brand Name:
Estab. Name: MISOPROSTOL
Generic Name:
Dosage Form: (TABLET)
Strength: 0.1 MG & 0.2 MG

Application Comment:
FDA Contacts: K. SHERROD (HFD-640) 301-827-5849 , Project Manager
B. ARNWINE (HFD-645) 301-827-5849 , Team Leader

Overall Recommendation:
Establishment:

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment: COMPANY PROVIDED 2 DMF NUMBERS.
1. DMF#
2. DMF# (on 08-FEB-2001 by P. PATEL (HFD-615) 301-827-5862)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-FEB-2001				PATELP

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:) (on 08-FEB-2001 by P. PATEL (HFD-615) 301-827-5862)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-FEB-2001				PATELP

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment: on 08-FEB-2001 by P. PATEL (HFD-615) 301-827-5862)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-FEB-2001				PATELP

Establishment:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities:
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	08-FEB-2001				PATELP

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Printed by Paras Patel

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 08-Feb-2001 09:41am
From: EES Questions
EESQUESTIONS
Dept:
Tel No: 301-827-0062

TO: Paras Patel (PATELP)

CC: Paras Patel (PATELP)
Subject: RE: [redacted] site

I added the firm, no CFN.

Mimi

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ON ORIGINAL

Printed by Paras Patel

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 06-Feb-2001 03:50pm
From: Paras Patel
PATELP
Dept: HFD-615 MPN2 E113
Tel No: 301-827-5862 FAX 301-594-1174

TO: EES Questions (EESQUESTIONS)

CC: Paras Patel (PATELP)
Subject: [redacted] site

Hello,
The following site could not be found in EES.

DMF: [redacted]

Site: [redacted]

Thanks.. Paras Patel

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Components and Composition Statements:

B. Quantitative Composition:

Quantitative Statement of the Composition of the Drug Product

	Misoprostol Tablets 100mcg	**Misoprostol Tablets 200mcg**
Components	mg / Tablet Batch #: N0070	mg / Tablet Batch #: N0071
*Misoprostol	[redacted]	[redacted]
Microcrystalline Cellulose, [redacted]	[redacted]	[redacted]
Sodium Starch Glycolate, NF	[redacted]	[redacted]
Hydrogenated Vegetable Oil, NF	[redacted]	[redacted]

Inactive ungrad

Redacted 3

Page(s) of trade secret and /or confidential commercial information

This review supercedes the previous review.

REVIEW OF PROFESSIONAL LABELING

DIVISION OF LABELING AND PROGRAM SUPPORT / LABELING REVIEW BRANCH

ANDA Number: 76-095 Date of Submission: December 28, 2000

Applicant: Zenith Goldline Pharmaceuticals, Inc. Est. Name: Misoprostol Tablets, 0.1 mg and 0.2 mg

Labeling Deficiencies:

1. CONTAINER (100's and 250's)

   a. To resolve your question regarding the warning statements on the container closure, we have consulted the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) who reviewed and approved the reference listed drug. We have also asked DGCDP whether the unit of use bottles of 60's, 100's, and 120's were conditions of approval. We defer final comment on the above issues pending DGCDP's response.

   b. We encourage you to differentiate the two different strengths from each other by using contrasting colors and/or boxing, or any other means.

   c. Add a picture on the principal display panel depicting that the product is not for pregnant women as presented on the RLD container labels.

2. INSERT

   a. Please note that there are numerous and significant differences between your proposed insert labeling and the referenced listed drug (RLD) insert labeling approved June 22, 2000. Please also note that there are pending labeling issues with the RLD labeling that we will update you on as soon as they are resolved. Please review the attached RLD insert labeling, revise your proposed insert labeling accordingly, and submit in draft.

   b. Please clarify the scoring of the tablets. It appears that the description of the scoring of the tablets is not consistent in the application.

3. PATIENT INFORMATION LEAFLET

   a. Please see INSERT comment (a).

   b. Add a Spanish version of the patient information to the PATIENT INFORMATION LEAFLET in addition to the English version as a Spanish version was approved for the RLD.

Please revise your labeling as instructed above and submit 4 draft package insert labeling for a tentative approval. Please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission [illegible] differences annotated and explained.

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ATTACHMENT

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		?	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?	X		
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	

Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		?	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. **MODEL LABELING:** NDA 19-268/S-031, Cytotec by Searle, approved June 22, 2000.
2. **INACTIVE INGREDIENTS:** Consistent with application. See page 24, Vol 1.1.
3. **PATENTS/EXCLUSIVITIES:** No unexpired patents and exclusivities.
4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - **NDA:** Store at or below 25^{0}C (77^{0}F), in a dray area.
   - **ANDA: Store at controlled room temperature 15^0-30^{0}C (59^0-86^{0}F) in a dry area (see USP).**
5. **DISPENSING STATEMENT COMPARISON:**
   NDA: "Pharmacist: Dispense in this unit-of-use, child-resistant container with Patient Leaflet attached."
   ANDA: "Pharmacist: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required). Firm will be asked to include "with the Patient Leaflet".
6. **PACKAGE CONFIGURATION**
   - **NDA:** 100 mcg unit of use bottles of 60's and 120's and carton of 100's unit dose, 200 mcg unit of use bottles of 60's and 100's and carton of 100's unit dose.
   - **ANDA:** 100 mcg and 200 mcg bottles of 100's and 250's.
7. **CONTAINER/CLOSURE:** —/CRC - Firm will be asked to include "WARNING NOT FOR PREGNANT WOMEN" on the cap as presented in the cap of the RLD.
8. **FINISHED DOSAGE FORM**
   - **NDA:** 100 mcg is unscored. 200 mcg tablet appears to be scored.
   - **ANDA:** The 100 mcg is unscored and 200 mcg tablets are scored. The application sometime describes the 100 mcg tablet as having "breakline". Firm is asked to clarify the scoring configuration.
9. Mr. Bob Avery left a voice mail requesting clarification regarding whether or not they need to add the "WARNING NOT FOR PREGNANT WOMEN" statement on the container closure. After consulting with Alice Kacuba, PM of Cytotec, I called Mr. Avery on August 13, 2001, and left a voice mail informing him that the statement needs to be added to the container closure and also added that additional information may be forthcoming regarding unit of use bottles as we investigate further into the condition of approval of Cytotec. I called Mr. Avery on August 17, 2001 and left a message informing him that we will send him a written response shortly.
10. Alice Kacuba also informed use that the Spanish/English version of the patient information leaflet was approved after the division requested it. We will ask the generic applicants to do the same.

Date of Review: 8/17/01 Date of Submission: 12/28/00
Primary Reviewer: Koung Lee Date:
Team Leader: Charlie Hor Date:

cc: ANDA: 76-095
DUP/DIVISION FIL
HFD-613/KLee/CHoppes (no cd)
V:\FIRMSNZ\ZENITH\LTRS&REV\76095.NA1.LABELING
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT / LABELING REVIEW BRANCH

ANDA Number: 76-095 Date of Submission: September 7, 2001

Applicant: IVAX Pharmaceuticals Inc. Est. Name: Misoprostol Tablets, 0.1 mg and 0.2 mg

Labeling Deficiencies:

1. GENERAL

Your company's name was changed from "Zenith Goldline" to "IVAX Pharmaceutical Inc." Please revise your labels and insert labeling to reflect the change or explain.

2. CARTON (100's)

Revise the outpatient use statement to read "If dispensed for outpatient use, a child-resistant container should be utilized with a patient leaflet attached."

3. BLISTER PACKAGE (10's)

We encourage you to add a picture depicting that the product is not for pregnant women on each unit dose label if space permits.

4. INSERT

a. CLINICAL PHARMACOLOGY

Insert "was" between "ulcer" and "demonstrated" in the last sentence of the second to the last paragraph.

b. PRECAUTIONS (Pregnancy)

Replace "—" with "have" in the second sentence of the first paragraph.

5. PATIENT INFORMATION LEAFLET (Spanish Text)

a. Replace "—" with médico" in the second paragraph.

b. Revise the entire third paragraph to be consistent with the revisions made in the English text.

c. Replace "—" with "tomarlo" in the first sentence of the fourth paragraph.

d. Replace "—" with "los" in second sentence and "posilidad" with "posibilidad" in the last paragraph of the fifth paragraph.

e. Replace "—" with "generalmente" and "—" with "usualmente" in the first sentence of the sixth paragraph.

f. Replace "—" with "llame" in the last sentence of the sixth paragraph.

g. Replace "—" with "recetado" and "—" with "específico" in the first sentence of the eighth paragaph.

h. Replace "—" with "pudiera" in the last sentence of the eighth paragraph.

i. Replace "—" with "efectos" in the first sentence of the ninth paragraph.

Please revise your label and labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval. Please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. **MODEL LABELING:** NDA 19-268/S-031, Cytotec by Searle, approved June 22, 2000.
2. **INACTIVE INGREDIENTS:** Consistent with application. See page 24, Vol 1.1.
3. **PATENTS/EXCLUSIVITIES:** No unexpired patents and exclusivities.
4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - **NDA:** Store at or below 25^{0}C (77^{0}F), in a dray area.
   - **ANDA: Store at controlled room temperature 15^0-30^{0}C (59^0-86^{0}F) in a dry area (see USP).**
5. **DISPENSING STATEMENT COMPARISON:**
   NDA: "Pharmacist: Dispense in this unit-of-use, child-resistant container with Patient Leaflet attached."
   ANDA: "Pharmacist: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required). Firm will be asked to include "with the Patient Leaflet".
6. **PACKAGE CONFIGURATION**
   - **NDA:** 100 mcg unit of use bottles of 60's and 120's and carton of 100's unit dose, 200 mcg unit of use bottles of 60's and 100's and carton of 100's unit dose.
   - **ANDA:** 100 mcg and 200 mcg bottles of 100's and 250's.
7. **CONTAINER/CLOSURE:** [redacted]/CRC - Firm will be asked to include "WARNING NOT FOR PREGNANT WOMEN" on the cap as presented in the cap of the RLD.
8. **FINISHED DOSAGE FORM**
   - **NDA:** 100 mcg is unscored. 200 mcg tablet appears to be scored.
   - **ANDA:** The 100 mcg is unscored and 200 mcg tablets are scored. The application sometime describes the 100 mcg tablet as having "breakline". Firm is asked to clarify the scoring configuration.
9. Mr. Bob Avery left a voice mail requesting clarification regarding whether or not they need to add the "WARNING NOT FOR PREGNANT WOMEN" statement on the container closure. After consulting with Alice Kacuba, PM of Cytotec, I called Mr. Avery on August 13, 2001, and left a voice mail informing him that the statement needs to be added to the container closure and also added that additional information may be forthcoming regarding unit of use bottles as we investigate further into the condition of approval of Cytotec. I called Mr. Avery on August 17, 2001 and left a message informing him that we will send him a written response shortly.
10. Alice Kacuba also informed use that the Spanish/English version of the patient information leaflet was approved after the division requested it. We will ask the generic applicants to do the same.

11. Consult Result

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL TEAM LEADER CONSULT REVIEW
CYTOTEC (MISOPROSTOL) TABLETS: CONSULT ANDA 76-095
(3 QUESTIONS) FROM GENERIC (SEPTEMBER 4, 2001)

Note: The questions are reproduced in bold letters, the answers in regular font

[redacted]

Hugo Gallo-Torres, M.D., Ph.D.
Medical Team Leader
HFD- 180

My Response

Thanks for the quick response to our consult.

If you do not agree with the recommendations we plan to send to the generic firms, please let us know. Again, we thank you for your prompt response.

Koung

Dr. Gallo-Torres' response

Kuong: I agree .

Hugo E. Gallo-Torres

12. Firm's September 7, 2001 amendment included "

[ ]

Date of Review: October 5, 200 /S/ Date of Submission: September 7, 2001
Primary Reviewer: Koung Lee Date: 11/07/01
Team Leader: Charlie Hoppes Date:

cc: ANDA: 76-095
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSNZ\ZENITH\LTRS&REV\76095.NA2.LABELING
Review

/S/ 11/7/01

APPEARS THIS WAY
ON ORIGINAL

Memo contains CCI

Redacted 6

pages of trade secret and /or confidential commercial information

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 76095/000**
Stamp: **02-JAN-2001** Regulatory Due:
Applicant: **ZENITH GOLDLINE**
140 LEGRAND AVE
NORTHVALE, NJ 07647

Priority:
Action Goal:
Brand Name:
Established Name: **MISOPROSTOL**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **0.1 MG & 0.2 MG**

Org Code: **600**
District Goal: **02-DEC-2001**

FDA Contacts: **K. SHERROD (HFD-640) 301-827-5849 , Project Manager**
B. ARNWINE (HFD-645) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 22-OCT-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **02-AUG-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-FEB-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **18-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: [redacted]

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **9612162**
NORTON WATERFORD LTD

WATERFORD, , EI

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-OCT-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT / LABELING REVIEW BRANCH

Superseded by approval summary April 23, 2002 submission

ANDA Number: 76-095 Date of Submission: November 3, 2001

Applicant: IVAX Pharmaceuticals Inc. Est. Name: Misoprostol Tablets, 0.1 mg and 0.2 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? Yes
- Container Labels: (100's and 120's) Satisfactory in FPL submitted on 11/3/01.
- Carton Labels: (100's) Satisfactory in FPL submitted on 11/3/01.
- Blister Lables: (10's) Satisfactory in FPL submitted on 11/3/01.
- Professional Package Insert Labeling: Satisfactory in FPL submitted on 11/3/01.
- Patient Information Leaflet: Satisfactory in FPL submitted on 11/3/01.
- Revisions needed post-approval: Yes
  Patient Information Leaflet

  a. First sentence of the first paragraph should read "...porque [redacted] haber cambios."

  b. Revise the third paragraph as follows:

     i. Revise the second sentence to read [redacted]

     ii. Revise the third sentence to read [redacted]

     iii. Revise the fourth sentence to read [redacted]

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Cytotec
- NDA Number: 19-268
- NDA Drug Name: Cytotec
- NDA Firm: Searle
- Date of Approval of NDA Insert and supplement #: June 22, 2000;S-031
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? NO
- Basis of Approval for the Container Labels:Side by Side
- Basis of Approval for the Carton Labeling: Based on Container Label

FOR THE RECORD:

1. **MODEL LABELING:** NDA 19-268/S-031, Cytotec by Searle, approved June 22, 2000.
2. **INACTIVE INGREDIENTS:** Consistent with application. See page 24, Vol 1.1.
3. **PATENTS/EXCLUSIVITIES:** No unexpired patents and exclusivities.
4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - **NDA:** Store at or below 25°C (77°F), in a dray area.
   - **ANDA: Store at controlled room temperature 15°-30°C (59°-86°F) in a dry area (see USP).**
5. **DISPENSING STATEMENT COMPARISON:**
   NDA: "Pharmacist: Dispense in this unit-of-use, child-resistant container with Patient Leaflet attached."

ANDA: "Pharmacist: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required). Firm will be asked to include "with the Patient Leaflet".

6. **PACKAGE CONFIGURATION**
   - **NDA:** 100 mcg unit of use bottles of 60's and 120's and carton of 100's unit dose, 200 mcg unit of use bottles of 60's and 100's and carton of 100's unit dose.
   - **ANDA:** 100 mcg and 200 mcg bottles of 100's and 250's.
7. **CONTAINER/CLOSURE:** HDPE/CRC - "WARNING NOT FOR PREGNANT WOMEN" on the cap as presented in the cap of the RLD.
8. **FINISHED DOSAGE FORM**
   - **NDA:** 100 mcg is unscored. 200 mcg tablet appears to be scored.
   - **ANDA:** The 100 mcg is unscored and 200 mcg tablets are scored. The application sometime describes the 100 mcg tablet as having "breakline". Firm is asked to clarify the scoring configuration.
9. Mr. Bob Avery left a voice mail requesting clarification regarding whether or not they need to add the "WARNING NOT FOR PREGNANT WOMEN" statement on the container closure. After consulting with Alice Kacuba, PM of Cytotec, I called Mr. Avery on August 13, 2001, and left a voice mail informing him that the statement needs to be added to the container closure and also added that additional information may be forthcoming regarding unit of use bottles as we investigate further into the condition of approval of Cytotec. I called Mr. Avery on August 17, 2001 and left a message informing him that we will send him a written response shortly.
10. Alice Kacuba also informed use that the Spanish/English version of the patient information leaflet was approved after the division requested it. We will ask the generic applicants to do the same.
11. Consult Result

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL TEAM LEADER CONSULT REVIEW
CYTOTEC (MISOPROSTOL) TABLETS: CONSULT ANDA 76-095
(3 QUESTIONS) FROM GENERIC (SEPTEMBER 4, 2001)

Note: The questions are reproduced in bold letters, the answers in regular font

Dr. Gallo-Torres' response
Kuong: I agree .

Hugo E. Gallo-Torres

12. [ ]

13. **Spanish Version of the Patient Information Leaflet -** Alice Kacuba stated that the Spanish version of the patient information leaflet was requested and approved by the new drug division but was not able to find a copy of it. Alice was kind enough to go to a local pharmacy to pick up a copy. After reviewing it, I noticed it was not updated. A few months later after IVAX amended their application, I asked Ms. Lillie Golson to get me a copy of the patient information leaflet for Cytotec. Again it was not updated. I searched the internet and was not able to find an updated Spanish version of the patient information leaflet so I asked Dr. Lizzie Sanchez and Dr. Edwin Ramos to review IVAX's Spanish translation of the updated patient information leaflet. They found it acceptable however requested a few minor changes. Their comments will be relayed to IVAX. Considering that New Drugs does not have a copy of an approved updated Spanish translation of the patient information leaflet, we decided that Drs. Sanchez and Ramos review and comment on IVAX's translation is sufficient until the new drug division approves an updated version.

Date of Review: January 15, 2002 — Date of Submission: November 3, 2001
Primary Reviewer: Koung Lee — Date: 1/22/02
Team Leader: Charlie Hoppes — Date:

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cc: ANDA: 76-095
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
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Review

/S/ 1/22/02

APPEARS THIS WAY
ON ORIGINAL

Patent and Exclusivity Search Results from query on 019268 003.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019268	003	4301146	JUL 29,2000	

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY
(Supersedes Approval Summary of November 30, 2001 Submission)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT / LABELING REVIEW BRANCH

ANDA Number: 76-095 Date of Submission: April 23, 2002

Applicant: IVAX Pharmaceuticals Inc. Est. Name: Misoprostol Tablets, 0.1 mg and 0.2 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? Yes
- Container Labels: (100's and 120's) FPL submitted on 11/30/01 are acceptable for approval.
- Carton Labels: (100's) FPL submitted on 11/30/01 is acceptable for approval.
- Blister Lables: (10's) FPL submitted on 11/30/01 is acceptable for approval.
- Professional Package Insert Labeling(PE1283 Revised 04/02): FPL submitted on 4/23/02 is acceptable for approval.
- Patient Information Leaflet: FPL submitted on 4/23/02 is acceptable for approval. (combined with PI)
- Revisions needed post-approval: Yes

1. INSERT (CLINICAL PHARMACOLOGY)

   a. Replace "prevent" with "r [redacted]" in the last sentence of the first paragraph in the "Pharmacodynamics" subsection.

   b. Replace [redacted] " with "reduce the risk of" in the first sentence in the "Clinical Studies" subsection.

2. Patient Information Leaflet

   First sentence of the first paragraph should read "...porque [redacted] haber cambios."

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Cytotec
- NDA Number: 19-268
- NDA Drug Name: Cytotec
- NDA Firm: Searle
- Date of Approval of NDA Insert and supplement #: April 17, 2002;S-037
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? NO
- Basis of Approval for the Container Labels:Side by Side
- Basis of Approval for the Carton Labeling: Based on Container Label

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		?	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X

Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)	X		
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?	X		
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., Iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		?	
Failure of DESCRIPTION to meet USP Description and Solubility Information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. **MODEL LABELING:** NDA 19-268/S-037, Cytotec by Searle, approved April 17, 2002.

2. **INACTIVE INGREDIENTS:** Consistent with application. See page 24, Vol 1.1.
3. **PATENTS/EXCLUSIVITIES:** No unexpired patents and exclusivities.

Patent Data

No	Expiration	Use Code	Use	File
		There are no unexpired patents for this product in the Orange Book Database		

Exclusivity Data

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - **NDA:** Store at or below 25^{0}C (77^{0}F), in a dray area.
   - **ANDA: Store at controlled room temperature 15^0-30^{0}C (59^0-86^{0}F) in a dry area (see USP).**
5. **DISPENSING STATEMENT COMPARISON:**
   NDA: "Pharmacist: Dispense in this unit-of-use, child-resistant container with Patient Leaflet attached."
   ANDA: "Pharmacist: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
6. **PACKAGE CONFIGURATION**
   - **NDA:** 100 mcg unit of use bottles of 60's and 120's and carton of 100's unit dose, 200 mcg unit of use bottles of 60's and 100's and carton of 100's unit dose.
   - **ANDA:** 100 mcg and 200 mcg bottles of 100's and 120's.
7. **CONTAINER/CLOSURE:** HDPE/CRC - "WARNING NOT FOR PREGNANT WOMEN" on the cap as presented in the cap of the RLD.
8. **FINISHED DOSAGE FORM**
   - **NDA:** 100 mcg is unscored. 200 mcg tablet appears to be scored.
   - **ANDA:** The 100 mcg is unscored and 200 mcg tablets are scored. The application sometime describes the 100 mcg tablet as having "breakline". Firm is asked to clarify the scoring configuration.
9. Mr. Bob Avery left a voice mail requesting clarification regarding whether or not they need to add the "WARNING NOT FOR PREGNANT WOMEN" statement on the container closure. After consulting with Alice Kacuba, PM of Cytotec, I called Mr. Avery on August 13, 2001, and left a voice mail informing him that the statement needs to be added to the container closure and also added that additional information may be forthcoming regarding unit of use bottles as we investigate further into the condition of approval of Cytotec. I called Mr. Avery on August 17, 2001 and left a message informing him that we will send him a written response shortly.
10. Alice Kacuba also informed use that the Spanish/English version of the patient information leaflet was approved after the division requested it. We will ask the generic applicants to do the same.
11. Consult Result

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL TEAM LEADER CONSULT REVIEW
CYTOTEC (MISOPROSTOL) TABLETS: CONSULT ANDA 76-095
(3 QUESTIONS) FROM GENERIC (SEPTEMBER 4, 2001)

Note: The questions are reproduced in bold letters, the answers in regular font

too long a delay between visits to the physician's office and refills.

Hugo Gallo-Torres, M.D., Ph.D.
Medical Team Leader
HFD- 180

My Response

Dr. Gallo-Torres' response
Kuong: I agree .

Hugo F. Gallo-Torres

12.

13. **Spanish Version of the Patient Information Leaflet -** Alice Kacuba stated that the Spanish version of the patient information leaflet was requested and approved by the new drug division but was not able to find a copy of it. Alice was kind enough to go to a local pharmacy to pick up a copy. After reviewing it, I noticed it was not updated. A few months later after IVAX amended their application, I asked Ms. Lillie Golson to get me a copy of the patient information leaflet for Cytotec. Again it was not updated. I searched the internet and was not able to find an updated Spanish version of the patient information leaflet so I asked Dr. Lizzie Sanchez and Dr. Edwin Ramos to review IVAX's Spanish translation of the updated patient information leaflet. They found it acceptable however requested a few minor changes. Their comments will be relayed to IVAX. Considering that New Drugs does not have a copy of an approved updated Spanish translation of the patient information leaflet, we decided that Drs. Sanchez and Ramos review and comment on IVAX's translation is sufficient until the new drug division approves an updated version.

14. The updated Spanish version submitted on April 23, 2002, only included revision to the third paragraph. It was reviewed by Drs. Edwin Ramos, Lizzie Sanchez and Damaris Maldonado of OGD and was found to be acceptable.

From: Ramos, Edwin
Sent: Monday, April 29, 2002 10:55 AM
To: Lee, Koung U
Subject: RE: Help with Spanish Translation

Sent: Monday, April 29, 2002 11:52 AM
To: Lee, Koung U

From: Lee, Koung U
Sent: Monday, April 29, 2002 11:32 AM
To: Sanchez, Aida L
Subject: RE: Help with Spanish Translation

Do you mean it's okay to approve as is and have Ivax make the changes in a supplement. Thanks Lizzie.

Koung

-----Original Message-----
From: Sanchez, Aida L
Sent: Monday, April 29, 2002 11:26 AM
To: Lee, Koung U
Subject: RE: Help with Spanish Translation

It is fine to wait.

Lizzie

-----Original Message-----
From: Lee, Koung U
Sent: Monday, April 29, 2002 11:23 AM
To: Sanchez, Aida L; Ramos, Edwin; Maldonado, Damaris
Cc: West, Robert L; Rickman, William P
Subject: RE: Help with Spanish Translation

Koung

Para evitar el riesgo de úlceras inducidas por AINE, no tome Misoprostol dura
embarazo (consulte los cuadros de ADVERTENCIAS). Misoprostol puede provocar
veces incompletos, dando lugar a hemorragias peligrosas que pueden requerir
cirugía), partos prematuros o malformaciones del feto. Es importante evitar quec
durante el tratamiento con este medicamento y durante un mínimo de un mes o u
después de dejar de tomarlo.
Misoprostol ha sido asociado a desgarros uterinos al tomarlo después de la o
embarazo. El desgarro del útero puede producir graves hemorragias, histerector
la madre o del feto.

-----Original Message-----
From: Sanchez, Aida L
Sent: Monday, April 29, 2002 11:14 AM
To: Lee, Koung U; Ramos, Edwin; Maldonado, Damaris
Cc: West, Robert L; Rickman, William P
Subject: RE: Help with Spanish Translation

Koung:

The third sentence I would translate:

Es importante evitar durante el tratamiento con este medicamento y durante un minimo de un mes o un ciclo menstrual despues de dejar de tomarlo.

The last two sentences of the English paragraph were not translated:

Lizzie

-----Original Message-----
From: Lee, Koung U
Sent: Monday, April 29, 2002 10:46 AM
To: Sanchez, Aida L; Ramos, Edwin; Maldonado, Damaris
Cc: West, Robert L; Rickman, William P
Subject: Help with Spanish Translation
Importance: High

Koung

<< OLE Object: Picture (Metafile) >>

Do not take Cytotec to reduce the risk of NSAID induced ulcers if you are pregnant (See boxed WARNINGS). Cytotec can cause abortion (sometimes incomplete which could lead to dangerous bleeding and require hospitalization and surgery), premature birth, or birth defects. 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 has been reported to cause the uterus to rupture (tear) when given after the eighth week of pregnancy. Rupture (tearing) of the uterus can result in severe bleeding, hysterectomy, and/or maternal or fetal death.

Date of Review: April 29, 2002
Primary Reviewer: Koung Lee
Team Leader: Lillie Golson

Date of Submission: April 23, 2002
Date: 4/29/02
Date: 4/29/02

/S/

cc: ANDA: 76-095
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSNZ\ZENITH\LTRS&REV\76095.AP2.LABELING
Review

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

DATE: May 21, 2002

PRODUCT NAME: Misoprostol Tablets, 0.1 mg and 0.2 mg

ANDA NUMBER: 76-095

FIRM NAME: IVAX Pharmaceuticals, Inc.

NAME(s) OF PERSON(s) WITH
WHOM CONVERSATION WAS HELD: Patricia Jaworski

PARTICIPANT'S TELEPHONE: (201) 767-1700 ext. 323

BACKGROUND: The deputy director (Div. II) requested that the applicant revise their Impurities specifications on stability to — for Single Other Impurity and — for Total Unknown Impurities.

NAME OF OGD REPRESENTATIVE: Karen Bernard, Ph.D.

I phoned Pat Jaworski and reqeusted that she revise her stability specifiations for Impurities. Specifically the unknown impurities should be revised to — for Single Other Impurity and — for

Ms. Jaworski agreed to revise the impurity limits and submit revised stability protocols and specification sheets.

I thanked her and requested that she fax the information as soon as possible.

Karen Bernard
/S/ 5/21/02

West, Robert L

From: Hassall, Rita R
nt: Monday, July 08, 2002 4:12 PM
: West, Robert L; Parise, Cecelia M
Cc: Buehler, Gary J
Subject: RE: CITIZEN PETITION OR CONTROLLED CORRESPONDENCE ON MISOPROSTOL TABLETS (CYTOTEC)?

According to the controlled doc system, there are no open controls on misoprostol. There does not appear to be a CP, either.

Rita

-----Original Message-----
From: West, Robert L
Sent: Monday, July 08, 2002 3:40 PM
To: Parise, Cecelia M; Hassall, Rita R
Cc: Buehler, Gary J
Subject: CITIZEN PETITION OR CONTROLLED CORRESPONDENCE ON MISOPROSTOL TABLETS (CYTOTEC)?

Cec/Rita:

Any pending C.P.'s or controlled correspondence on Misoprostol Tablets (Cytotec/Searle)?

We have an approval package ready to go.

Thanks,

ob

APPEARS THIS WAY
ON ORIGINAL

Document Name: \\ocs04\EXECSEC\Wp\BETHC\INFO ADVISORIES\Misoprostol Cytotec generic.doc

Draft: 7/8/02: MHess/CDER
Edit: 7/9/02: BClarke
JLocke

APPEARS THIS WAY
ON ORIGINAL

Park, Nicole

From: West, Robert L
Sent: Wednesday, April 17, 2002 3:17 PM
To: Lee, Koung U
Cc: Park, Nicole
Subject: RE: CDER Weekly Report

Well, at least we're up to the minute!

Bob

-----Original Message-----
From: Lee, Koung U
Sent: Wednesday, April 17, 2002 3:14 PM
To: West, Robert L
Cc: Park, Nicole
Subject: RE: CDER Weekly Report

I just received the new approved labeling. Apparently it was just approved an hour ago. There are significant changes which includes safety information. It appears that Ivax will need to make the changes before approval. I'll send the new labeling to Ivax in a few minutes and ask them how long it will take. Thanks.

Koung

-----Original Message-----
From: West, Robert L
Sent: Wednesday, April 17, 2002 3:05 PM
To: Lee, Koung U
Cc: Park, Nicole
Subject: RE: CDER Weekly Report

Thanks, Koung. I'm sure it will be here well before Frank completes the first-generic CMC audit.

Bob

P.S. nicole: Please place a copy of these eMail messages inside the orange folder accompanying the approval package.

Thanks,

Bob

-----Original Message-----
From: Lee, Koung U
Sent: Wednesday, April 17, 2002 2:58 PM
To: West, Robert L
Subject: RE: CDER Weekly Report

I informed Alice Kacuba a few weeks that we were in the process of approving the first generic Misoprostol application and she said nothing was going on with Cytotec. I'll follow up with her and ask for the labeling changes. They should have an electronic version which I'll send to IVAX via E-mail. I'll get this rolling today.

Most likely, the changes will be significant enough to require Ivax to change and supply FPL ASAP.

Koung

-----Original Message-----
From: West, Robert L
Sent: Wednesday, April 17, 2002 2:46 PM
To: Lee, Koung U
Cc: Park, Nicole
Subject: FW: CDER Weekly Report

Koung:

I see from the current Weekly Report that labeling changes were recently approved for Misoprostol (Cytotec). It doesn't indicate the dosage form.

We currently have ANDA 76-095 for Ivax's Misoprostol Tablets on the approvals matrix.

Do we need Ivax to supply revised FPL? If so, can you request Ivax to submit the revised FPL while the application continues to go through the sign-off process? Since it is a first generic, there will be plenty of time to adjust the package accordingly when it hits Frank's office.

Thanks,

Bob

-----Original Message-----
From: CDEREXSEC
Sent: Wednesday, April 17, 2002 2:36 PM
To: CDER-ALL-HANDS; CDER-WKLY-RPT
Subject: CDER Weekly Report

The CDER Weekly Report has been posted on the OCD Intranet Page at
http://cdernet.cder.fda.gov/ocd/wkrpt.htm

Please note that asterisked items (in red) are NOT to be disclosed. Please do NOT discuss these issues with anyone outside of the agency.

Anne
Anne M. Henig
CDER Executive Operations Staff
301-594-5471

DIVISION REVIEW SUMMARY

ANDA: 76-095

DRUG PRODUCT: Misoprostol Tablets

FIRM: IVAX Pharmaceuticals

DOSAGE FORM: Tablets

STRENGTH: 100 and 200 mcg

CGMP STATEMENT/EIR UPDATE STATUS:
EER is acceptable on 10/22/01.

BIO INFORMATION:
The Division of Bioequivalence have found the application to be acceptable. The review was completed on 4/20/01 by M.Gokhale. Chuang.

VALIDATION-DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)
Non-USP product, methods validation was performed by Phila-DO and found acceptable on 11/21/01.

STABILITY-ARE CONTAINERS USED IN THE STUDY IDENTICAL TO THOSE USED IN THE CONTAINER SECTION?

The revised future stability protocol the firm proposes is as follows:

Test		Specification
Appearance	(in house)	White round, FBE tablet, marked with an hourglass and a "100" on one side and "4430" on reverse (100 mcg) White round, FBE tablet, marked with an hourglass and a "200" on one side and "4431" on reverse (200 mcg)
Physical Evaluation		Satisfactory odor and color
Dissolution (USP)		Q = [redacted] released after 20 min
Assay (in-house)		[redacted] of label

(in-house [redacted]) NMT [redacted]
NMT [redacted]
NMT [redacted] Single largest other impurity
NMT [redacted] Total Impurities

[redacted] (in-house) NMT [redacted]

The firm included 3 months of accelerated data (40°C/75% RH) for the bottles of 100 and 250 fill container (CRC) for the 100 mcg and 200 mcg strength, and room temperature stability data for the bulk package for both lots #N0070 and N0071.

All data met specifications although some data points for dissolution were untested. See below under #4. As a result of these inconsistent data and a revision of dissolution methodology, the firm is proposing a 24 month expiration dating period for the bottles and 12 months for the drums. The unit dose packages will have a 15 month expiration dating period. See chart below under comments.

Also included is a future stability commitment, in accordance with FDA Guidelines.

LABELING
The labeling review is acceptable on 1/~~18~~ 22/02.

STERILIZATION VALIDATION
NA

DEMONSTRATION BATCH
A description of the manufacturing process and process flow chart is included beginning on page 0463. An equipment list (with comparison between biobatch and commercial batches) is also included.

[redacted]

Blank batch records are included for future production batches. The firm is proposing a commercial batch size of [redacted] units for the 100 mcg tablets and [redacted] for the 200 mcg tablets. No blank packaging records were included. A reprocessing statement is also included.

The firm manufactured 2 exhibit batches. Lot #N0070 (100 mcg) and Lot #N0071 (200 mcg). A common [redacted] was used (lot no. N0069) for [redacted] into the 100 mcg and 200 mcg tablets. Executed Packaging records were also included.

The batch reconciliation data for lot #N0070 showed that [redacted] tablets were actually manufactured from a theoretical yield of [redacted] tablets. These were packaged as follows: [redacted] into bottles of 100, 30,120 into bottles of 250s and [redacted] packaged. Total tablets packaged were [redacted]

The batch reconciliation for lot#N0071 (200 mcg tablets) showed that [redacted] tablets were actually manufactured out of a theoretical batch yield of [redacted] tablets. Packaging reconciliation showed that [redacted] tablets were packaged into bottles of 100, 30,120 tablets were packaged into bottles of 250s and [redacted] tablets were packaged in [redacted]
Total tablets packaged were [redacted]

PROPOSED PRODUCTION BATCH-MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The process is the same. See above.

RECOMMENDATION: Approve

SIGNATURE: DATE: March 14, 2002

Endorsements:
HFD-640/KBernard/3/15/02 /S/ 4/2/02
HFD-645/RBrown/3/29/02 /S/ 4/8/02

v:\firmsam\IVAXPHARM\ltrs&rev\76-095ds
F/T by: dss/4/1/02

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 76095/000**
Stamp: **02-JAN-2001** Regulatory Due:
Applicant: **IVAX PHARMS**
140 LEGRAND AVE
NORTHVALE, NJ 07647

Priority:
Action Goal:
Brand Name:
Established Name: **MISOPROSTOL**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **0.1 MG & 0.2 MG**

Org Code: **600**
District Goal: **02-DEC-2001**

FDA Contacts: **K. SHERROD (HFD-640) 301-827-5849 , Project Manager**
B. ARNWINE (HFD-645) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 22-OCT-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **02-AUG-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-FEB-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **18-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: [redacted]

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **9612162**
NORTON WATERFORD LTD

WATERFORD, , EI

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-OCT-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

APPEARS THIS WAY
ON ORIGINAL

Patent and Exclusivity Search Results from query on 019268 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

APPEARS THIS WAY
ON ORIGINAL

Application Number Search Results from "Rx" table for query on "19268."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
019268		No	MISOPROSTOL	Tablet; Oral	0.1MG	CYTOTEC	GD SEARLE LLC
019268		Yes	MISOPROSTOL	Tablet; Oral	0.2MG	CYTOTEC	GD SEARLE LLC

Thank you for searching the Electronic Orange Book

Return to Electronic Orange Book Home Page

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-095

CORRESPONDENCE

notified ps 2/1/02

IVAX Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

JAN 22 2002

ORIG AMENDMENT

N/Am

Via Federal Express

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
Chemistry

Re: ANDA # 76-095
Misoprostol Tablets, 100 mcg and 200 mcg

Dear Mr. Buehler:

Reference is made to our pending Abbreviated New Drug Application dated December 28, 2000, for Misoprostol Tablets, 100 mcg and 200 mcg, and to the Agency's letter dated November 29, 2001 (copy in Reference). Pursuant to 21 CFR 314.120, we are amending our application by responding to the deficiencies cited in that letter. This response is designated as a "MINOR AMENDMENT".

A. CHEMISTRY DEFICIENCIES

1. [ ]

[ ]

[ ]

JAN 24 2002

2/12/02

Redacted 6

Page(s) of trade secret and /or confidential commercial information

Configuration	Accelerated Status	Room Temperature Status	Expiration dating proposed
	methodology		
200 mcg, bulk	Not applicable	12 months acceptable	12 months

For our bottle presentations, we will be marketing the 200 mcg, 100's package size in the same container closure system as the currently submitted 250 count size, as indicated in our September, 2001 amendment. Although the accelerated data for the 200 mcg 100's is inconclusive, we do have acceptable data for the 200 mcg 250 count size, and therefore are seeking 24 month expiration dating for the 200 mcg 100's count in the same container closure system.

For the unit dose configuration, where we are proposing an expiration dating period less than 24 months, we propose to increase the expiration date as additional stability data on these batches is generated. We will submit the data in a Changes Being Effected in 30 days supplement (CBE – 30).

As observed on stability, and as previously documented on page 0217 of Section VI of the original ANDA submission, use of the paddle method for our products' formulations results in variable compliance at S1 or S2 where the baskets apparatus has been shown to produce more consistent data. As a consequence, we will be submitting our comments on the draft USP monograph for the tablets, as published in Pharmacopoeial Forum Volume 26 (5) Sept-Oct 2000, to the appropriate USP scientific staff. Our comments will indicate that the ~~paddle~~ method should be chosen as the appropriate method.
DoSe

If the dissolution method in the draft monograph is subsequently found to be unsuitable by USP for misoprostol formulations, it is our intention to submit an amendment to our application to revert back to use of the Apparatus I methodology. However, please be assured that until such a time that we submit a supplement to use Apparatus I, we will continue to use the FDA requested method of Apparatus II.

APPEARS THIS WAY
ON ORIGINAL

A concerted effort has been made to ensure that this amendment contains all of the information required by the Office of Generic Drugs. Should you have any questions or require additional information, please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Thomas O'Connor for

Patricia Jaworski, Associate Director
Regulatory Affairs, New Product Submissions

cc: District Office

..EARS THIS WAY
ON ORIGINAL

1 tr

Redacted 3

Page(s) of trade secret and /or confidential commercial information

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

MAY 2 4 2002

VIA FACSIMILE
Karen Bernard & Nicole Park
Fax No.: 301-443-3839

Via Federal Express

ORIG AMENDMENT
N/AM

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

Re: ANDA 76-095 for Misoprostol Tablets
0.1 mg and 0.2 mg

Dear Mr. Buehler:

Reference is made to our pending Abbreviated New Drug Application for Misoprostol Tablets, 0.1 mg and 0.2 mg and to the telephone communication from Agency representatives of May 21, 2002. Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc. is amending the application by responding to the request made by the Agency.

The Agency instructed IVAX Pharmaceuticals, Inc., to update the Stability Specification/Test Method and Stability Protocol to reflect a tightened "largest single unknown impurity" at NLT [redacted] and to include a specification for "total unknown impurities" at NMT [redacted]

	Stability Specification Currently Proposed by IVAX	Stability Specification Requested by Agency
[redacted]	NMT [redacted] w/w	NMT [redacted] w/w
[redacted]	NMT [redacted] w/w	NMT [redacted] w/w
[redacted]	NMT [redacted] w/w	NMT [redacted] w/w
Largest Single Unknown Impurity	NMT [redacted] w/w	NMT [redacted] w/w
Total Unknown Impurities		NMT [redacted] w/w
Total Impurities	NMT [redacted] w/w	NMT [redacted] w/w

In response to the Agency's comments, we submit the following documentation with this letter. In each case, changes made to the document since they were last submitted to the Agency in the Minor Amendment of January 22, 2002 are stated.

RECEIVED
MAY 2 8 2002
OGD/CDER

Misoprostol Tablets 0.1 mg and 0.2 mg Stability Specifications/Test Methods

Summary of Changes from Document Nos:
T1079/04 to T1079/05 (0.1 mg)
T1078/04 to T1078/05 (0.2 mg)

Drug Product	Effective	Change (to all documents)	Supercedes
Misoprostol Tablets 0.1 mg	May 23, 2002	1. Update to USP 25 2. Procedural detail for Assay, Related Substances, and Dissolution Sample and Standard preparations improved. 3. Revised Related Substances Specification at the Agency's request (Telephone contact of May 21, 2002) Largest Single Unknown Impurity tightened to NMT [redacted] % Total Unknown Impurities NMT [redacted] added	T1079/04
Misoprostol Tablets 0.2 mg			T1078/04

The updated Stability Specifications/Test Methods (IVAX Pharmaceuticals Ireland document numbers T1079/05 and T1078/05 for the 0.1 mg and 0.2 mg formulations respectively) are enclosed as **Exhibit #1.**

APPEARS THIS WAY
ON ORIGINAL

Misoprostol Tablets 0.1 mg and 0.2 mg Pre-Approval Stability Protocols

Summary of Changes from Document Nos:
00-TSP-014/03 to 00-TSP-014/04 (CRC [redacted]. Bottle and [redacted] pack configurations)
00-TSP-016/03 to 00-TSP-016/04 ([redacted] Aluminium Blister pack configurations)

Stability Protocol	Effective	Change (to all documents)	Supercedes
CRC [redacted]. Bottle and [redacted] pack configurations	May 23, 2002	1. Revised Related Substances Specification at the Agency's request (Telephone contact of May 21, 2002) Largest Single Unknown Impurity tightened to NMT [redacted] %	00-TSP-014/03
[redacted] Aluminium Blister pack configurations		Total Unknown Impurities NMT [redacted] added	00-TSP-016/03

The updated Pre-Approval Stability Protocols (IVAX Pharmaceuticals Ireland document numbers 00-TSP-014/04 and 00-TSP-016/04 for the bottle/[redacted], and blister pack configurations respectively) are enclosed as **Exhibit #2.**

APPEARS THIS WAY
ON ORIGINAL

In addition, to the requested revised documents, IVAX Pharmaceuticals, Inc. are providing the Agency with updated Finished Product Specifications/Test Methods in order to include a limit for Total Unknown Impurities in line with the Stability Specifications. The changes are summarized below:

	Finished Product Specification Currently Proposed by IVAX	Revised Finished Product Specification
	NMT % w/w	NMT % w/w
	NMT % w/w	NMT % w/w
	NMT % w/w	NMT % w/w
Largest Single Unknown Impurity	NMT % w/w	NMT % w/w
Total Unknown Impurities		NMT % w/w
Total Impurities	NMT % w/w	NMT % w/w

Misoprostol Tablets 0.1 mg and 0.2 mg Finished Product Specifications/Test Methods

Summary of Changes from Document Nos:
T1076/04 to T1076/05 (0.1 mg)
T1077/04 to T1077/05 (0.2 mg)

Drug Product	Effective	Change (to all documents)	Supercedes
Misoprostol Tablets 0.1 mg	May 23, 2002	1. Update to USP 25 2. Procedural detail for Assay, Related Substances, Content Uniformity and Dissolution Sample and Standard preparations improved. 3. Revised Related Substances Specification at the Agency's request (Telephone contact of May 21, 2002) Largest Single Unknown Impurity tightened to NMT Total Unknown Impurities NMT added	T1076/04
Misoprostol Tablets 0.2 mg			T1077/04

The updated Finished Product Specifications/Test Methods (IVAX Pharmaceuticals Ireland document numbers T1076/05 and T1077/05 for the 0.1 mg and 0.2 mg formulations respectively) are enclosed as **Exhibit #3.**

IVAX Pharmaceuticals, Inc. has made a concerted effort to ensure that this amendment contains all of the information required by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

PJ/AA/GO

APPEARS THIS WAY
ON ORIGINAL

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
Telephone: 201-767-1700
www.IVAXPharmaceuticals.com

MAY 24 2002

Via Federal Express

Food and Drug Administration
5600 Fishers Lane, Rm. 1364
Rockville, MD 20857

Attn: Ms. Irma Rivera, Program Specialist

TELEPHONE AMENDMENT

Re: ANDA 76-095 for Misoprostol Tablets, 0.1 mg and 0.2 mg

Dear Ms. Rivera:

In accordance with 21 CFR §314.96(b) regarding submission of a field copy of the technical section of any amendment to an unapproved Abbreviated New Drug Application, we are forwarding a true and accurate copy of our TELEPHONE AMENDMENT to the above referenced ANDA.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

PJ/GO

IVAX
Pharmaceuticals, Inc.

140 Legrand Avenue
Northvale, New Jersey • 07647
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Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N|AF

ORIG AMENDMENT
FPL

APR 23 2002

LABELING AMENDMENT

Re: ANDA 76-095 for Misoprostol Tablets, 0.1 mg and 0.2 mg

Dear Mr. Buehler:

Reference is made to our pending Abbreviated New Drug Application for Misoprostol Tablets, 0.1 mg and 0.2 mg and to the Agency's electronic mail communication of April 19, 2002. Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc. is amending the application by revising the product labeling in accordance with the recently approved supplemental application (NDA 19268/S-037) filed by the reference listed drug manufacturer, Pharmacia Corporation.

Additionally, to facilitate review of this submission, and in accordance with 21 CFR Part 314.94(a)(8)(iv), we have provided side-by-side comparisons of our revised labeling versus our last submitted labeling, with all differences annotated and explained. Twelve (12) copies (six [6] copies each in the archival and review copies) of our revised insert labeling and the side-by side comparisons can be found in **Exhibit 1** of this amendment.

IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this amendment contains all of the information required by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

PJ/JL

RECEIVED
APR 24 2002
OGD / CDER

IVAX
Pharmaceuticals, Inc.

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Via Federal Express

ORIG AMENDMENT
N/AF

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 0 3 2001

NOV 3 0 2001

LABELING AMENDMENT

Re: ANDA 76-095 for Misoprostol Tablets
0.1 mg and 0.2 mg

Dear Mr. Buehler:

Reference is made to our pending Abbreviated New Drug Application for Misoprostol Tablets, 0.1 mg and 0.2 mg and to the Agency's facsimile correspondence dated November 7, 2001 (copy provided in **Reference**). Pursuant to 21 CFR Parts 314.96 and 314.120, IVAX Pharmaceuticals, Inc. (formerly known as Zenith Goldline Pharmaceuticals, Inc.), is amending the application by responding to the request made by the Agency.

As indicated above, the firm name, Zenith Goldline Pharmaceuticals, Inc., has changed. This represents a name change only, and does not involve a change or transfer of ownership of the ANDA referenced above. IVAX Pharmaceuticals, Inc., continues to be a wholly-owned subsidiary of IVAX Corporation, Miami, Florida.

In response to the Agency's comments, we submit the following:

A. LABELING DEFICIENCY

1. GENERAL:

Your company's name was changed from "Zenith Goldline" to "IVAX Pharmaceuticals, Inc." Please revise your labels and insert labeling to reflect the change or explain.

Response:

We have revised our container labels and insert labeling for this product to reflect our firm's name change from Zenith Goldline Pharmaceuticals, Inc. to IVAX Pharmaceuticals, Inc. Twelve (12) copies of our Final Printed labels and samples of our unit dose cartons are provided herewith as **Exhibit 1** (six (6) copies each in the Archival and Review copies). Twelve (12) copies of our Final Printed insert/patient leaflet labeling are provided herewith as **Exhibit 2** (six (6) copies each in the Archival and Review copies).

over, please

2. *CARTON (100's):*

Revise the outpatient use statement to read "if dispensed for outpatient use, a child-resistant container should be utilized with a patient leaflet attached."

Response:

We have revised our unit dose carton labeling to reflect the change to the outpatient use statement to read, "if dispensed for outpatient use, a child-resistant container should be utilized with a patient leaflet attached." Copies of our Final Printed unit dose carton labeling are included herewith in **Exhibit 1**.

3. *BLISTER PACKAGE (10's):*

We encourage you to add a picture depicting that the product is not for pregnant women on each unit dose label if space permits.

Response:

Due to space constraints on our unit dose blister mats, the addition of the aforementioned picture would not be feasible. Adding the image to each blister package would render the contents of the graphic indiscernible, due to the degree of scale-down necessary to suit the restricted space available. Please note that the graphic being discussed is included on our Final Printed unit dose carton labeling, copies of which are included herewith in **Exhibit 1**.

4. *INSERT:*

   a. *CLINICAL PHARMACOLOGY*

      Insert "was" between "ulcer" and "demonstrated" in the last sentence of the second to the last paragraph.

   b. *PRECAUTIONS (Pregnancy)*

      Replace "____" with "have" in the second sentence of the first paragraph.

5. *PATIENT INFORMATION LEAFLET (Spanish Text):*

   a. ***Replace "____" with "médico" in the second paragraph.***

   b. ***Revise the entire third paragraph to be consistent with the revisions made in the English text.***

   c. ***Replace "____o" with "tomarlo" in the first sentence of the fourth paragraph.***

   d. ***Replace "____ with "los" in the second sentence and "posilidad" with "posibilidad" in the last sentence of the fifth paragraph.***

   e. ***Replace "____" with "generalmente" and "____ with "usualmente" in the first sentence of the sixth paragraph.***

   f. ***Replace "____" with "llame" in the last sentence of the sixth paragraph.***

   g. ***Replace "____o" with "recetado" and "____" with "específico" in the first sentence of the eighth paragraph.***

   h. ***Replace "____" with "pudiera" in the last sentence of the eighth paragraph.***

   i. ***Replace "____ with "efectos" in the first sentence of the ninth paragraph.***

Response:

We have made all of the grammatical revisions requested in items 4(a) through 5(i), above. Copies of our Final Printed insert/patient leaflet labeling are provided herewith as **Exhibit 2**.

over, please

To facilitate review of this submission, and in accordance with 21 CFR §314.94(a)(8)(iv), we have provided side-by-side comparisons of all labeling proposed in this amendment versus the last submitted labeling, with all differences annotated and explained. These side-by-side labeling comparisons are provided herewith as **Exhibit 3**.

IVAX Pharmaceuticals, Inc., has made a concerted effort to ensure that this amendment contains all of the information required by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

PJ/JL

APPEARS THIS WAY
ON ORIGINAL

notd PS
9/13/01

IVAX
Pharmaceuticals, Inc.

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Via Federal Express

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CENTER FOR DRUG
SEP 10 2001
EVALUATION AND RESEARCH

N/Am

SEP 07 2001

MINOR AMENDMENT
Chemistry, Labeling and Bioequivalence

Re: ANDA # 76-095
Misoprostol Tablets, 0.1 mg and 0.2 mg

Dear Mr. Buehler:

Reference is made to our pending Abbreviated New Drug Application dated December 28, 2000, for Misoprostol Tablets, 100 mcg and 200 mcg, and to the Agency's letter dated May 22, 2001 (copy in Reference). In addition, reference is made to the Labeling Comments provided in the Agency's letter of August 20, 2001 (copy in Reference). Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the deficiencies cited in these letters. This response is designated as a "MINOR AMENDMENT".

Please note, the firm name, Zenith Goldline Pharmaceuticals, Inc., has changed. This represents a name change only, and does not involve a change or transfer of ownership of the ANDA referenced above. IVAX Pharmaceuticals, Inc. continues to be a wholly-owned subsidiary of IVAX Corporation, Miami, Florida. As a consequence of this evolving process, these company names are used interchangeably throughout this Amendment.

A. CHEMISTRY DEFICIENCIES

1. *Please be advised that the application cannot be approved until deficiencies regarding DMFs #[redacted] and #[redacted] have been addressed satisfactorily by the DMF holders.*

Response:

[redacted] .. provided a full response to the Agency's Deficiency Letters regarding DMF #[redacted] and DMF #[redacted] on August 16, 2001. Copies of the cover letters are included in **Exhibit 1**.

2. *We recommend that you lower the limit for content of the Misoprostol to NMT The results seen for Batch #0F299 also agree with this value.*

Response:

As requested by the Agency, we have tightened the limit for the content of the Misoprostol to NMT .

Specification	Content Specification (%)
Current (T1051/02)	
Proposed (T1051/03)	

Batch analysis data for three recent lots of Misoprostol are summarised below:

Content Specification (%)	Lot # CE-32-184A Norton Waterford Lot # 1F267	Lot # CE-46-016A Norton Waterford Lot # 1F268	Lot # CE-46-044A Norton Waterford Lot # 1F269
NMT	1.1	1.1	1.2

The updated Raw Material Specification/Test Method (Norton Waterford document number T1051/03) is enclosed as **Exhibit 2.**

3. *We also recommend that you lower the specifications for Related Compounds in your active drug substance testing. The data provided for Batch #0F299 do not support the high levels of impurities you are proposing.*

Response:

We acknowledge the Agency's recommendation and have reviewed the batch analysis data for the lot of Misoprostol used in the submission batches, as well as analytical data from three recent lots.

We have reduced the limits for specified impurities to those applied by the drug substance . The changes are summarised below:

Impurity	Specification		
	(2001)	Current Raw Norton Waterford (T1051/02)	Proposed Norton Waterford (T1051/03)
Other Impurities (other than those originating from			
Single Individual			
Total Impurities		*	

USP Misoprostol Related) (Pharmacopoeial Forum Jan-Feb 2000)

= USP Misoprostol Related . (Pharmacopoeial Forum Jan-Feb 2000)
JSP Misoprostol Related , (Pharmacopoeial Forum Jan-Feb 2000)

* Σ Other Imps +
♠ Σ Other Imps
♣ Compound
♦

The updated Material Specification/Test Method (Norton Waterford document number T1051/03) is enclosed as **Exhibit 2.**

APPEARS THIS WAY
ON ORIGINAL

Batch analysis data for the lot used in the submission batches (Norton Waterford Lot # OF299) plus three recent lots of Misoprostol [redacted] are summarised below. The full Norton Waterford test reports for the three recent lots are enclosed as **Exhibit 3.**

Impurity	Proposed Specification	[redacted] Lot # CE-32-044A Norton Waterford Lot # OF299	[redacted] Lot # CE-32-184A Norton Waterford Lot # 1F267
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	ND	ND
Other Impurities (other than those originating from [redacted])			
Single Individual	[redacted]	ND	[redacted]
Total Impurities	[redacted]	ND	[redacted]

ND – None detected

Impurity	Proposed Specification	[redacted] Lot # CE-46-016A Norton Waterford Lot # 1F268	[redacted] Lot # CE-46-044A Norton Waterford Lot # 1F269
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	ND	ND
Other Impurities (other than those originating from [redacted])			
Single Individual	[redacted]	[redacted]	ND
Total Impurities	[redacted]	[redacted]	ND

ND – None detected

4. *We also recommend that you include a Test for Residual Solvents in the Misoprostol Dispersion testing specification.*

Response:

A test and specification for Residual Solvents in Misoprostol [redacted] has now been included in the updated Specification/Test Method (Norton Waterford document number T1051/03), enclosed as **Exhibit 2.**

The specifications, identical to those applied by the drug substance manufacturer, [redacted], are summarised below:

Norton Waterford Specification/Test Method	Residual Solvent Specifications
Current (T1051/02)	None
Proposed (T1051/03)	[redacted] NMT [redacted] [redacted] NMT [redacted] [redacted] NMT [redacted] [redacted] NMT [redacted] [redacted] NMT [redacted]

Batch analysis data for the Misoprostol [redacted], lot used in the submission batches, plus additional data for three recent lots are summarised below:

Solvent	Specification	[redacted] Lot # CE-32-044A Norton Waterford Lot # 0F299
[redacted]	NMT [redacted]	[redacted]
[redacted]	NMT [redacted]	[redacted]
[redacted]	NMT [redacted]	NQ
[redacted]	NMT [redacted]	[redacted]
[redacted]	NMT [redacted]	[redacted]

NQ= Not Quantified (LOQ)

These data are taken from MSL Report No. 258/00, 'Validation of the Norton Procedure NPD-MIS-DP12 for the Determination of Residual Solvents in Misoprostol [redacted] included in Section XV.3 of the original submission.

APPEARS THIS WAY
ON ORIGINAL

Solvent	Specification	Lot # CE-32-184A	Lot # CE-46-016A	Lot # CE-46-044A
		Norton Waterford Lot # IF267	Norton Waterford Lot # IF268	Norton Waterford Lot # IF269
	NMT			
	NMT			
	NMT			
	NMT	0	0	
	NMT			

The Norton Waterford test reports for the three recent lots of Misoprostol HPMC Dispersion (1:100) are enclosed as **Exhibit 3.**

5. *You did not submit a copy of blank packaging records. This information should be included with the blank production records. Please submit.*

Response:

We acknowledge this omission in the original application. Copies of blank packaging records are included as **Exhibit 4.** These comprise two parts, a blank record and draft bills of material for the packaging operations in the high potency manufacturing suite, and a blank record and draft bills of material for the packaging operations (insert labeling and cartoning) in the packaging suite.

6. *Please provide details regarding the holding times you intend to place on production. In accordance with 21 CFR we ask that you define any time limits you intend to impose on production.*

Response:

The following holding times will be applied in routine production, unless subsequently supported by the results from additional validation studies:

Maximum 4 weeks
Tablets: Maximum 6 months

In-process ablets will be stored in the same packaging configuration as outlined in Section XIII (pages 0843-0844) of the original submission i.e. container/closure lined with bags and containing a desiccant.

Redacted 5

Page(s) of trade secret and /or confidential commercial information

12. *The stability data also does not support a Moisture limit of NMT — We also recommend that you lower this level or provide justification for this high specification.*

Response:

As requested by the Agency, we have reviewed the stability batch data and have tightened the limit for the — content in the Stability Specifications/Test Methods to NMT —

Norton Waterford Stability Specification/Test Methodology	— Content Specification (%)
Current (T1079/02 and T1078/02)	—
Proposed (T1079/03 and T1078/03)	—

The updated Stability Specifications/Test Methods for Misoprostol Tablets 100 mcg and 200 mcg (Doc. Nos. T1079/03 and T1078/03 respectively) are enclosed in **Exhibit 8.**

13. *We note that since you are requesting a 6 month expiration date for the — drug product packaged in —, we ask that you submit the results of the room temperature stability testing at the —*

Response:

Updated Stability Summary Sheets, inclusive of results of — stability for the — pack configuration are now enclosed as **Exhibit 9**.

B. *IN ADDITION*

1. *Please be advised that since the drug product is a non-compendial product, methods validation must be performed at the district laboratory.*

Response:

Please be advised that Zenith Goldline Pharmaceuticals, Inc. responded to the Philadelphia Pharmaceutical Laboratory's Methods Validation request by submitting samples on May 1, 2001.

2. *We also refer you to the PF Vol. 26 (5) 2000 pp. 1304-1310 for the drug substance and drug product.*

Response:

Reference is made to pp. 1107-1116 of our original application, which acknowledge the draft monographs published in the Pharmacopeial Forum Volume 26, Number 5.

Ivax Pharmaceuticals, Inc. commits to regularly update its specifications and methodology so as to remain consistent with current USP/NF and subsequent supplements, as they become available for this product.

C. LABELING DEFICIENCIES

Please note all labeling deficiencies identified in the Agency's May 22, 2001 letter have been superceded by the Division of Labeling's review dated August 20, 2001 (copy in "Reference"). Those issues are presented here.

1. CONTAINER (100's and 250's)

a. *To resolve your question regarding the warning statements on the container closure, we have consulted the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) who reviewed and approved the reference listed drug. We have also asked DGCDP whether the unit of use bottles of 60's, 100's and 120's were conditions of approval. We defer final comment on the above issues pending DGCDP's response.*

Response:

To insure appropriate warning statements on the container closure system, Zenith Goldline has replaced the 38mm cap proposed in our original submission with the "38mm [redacted] – Red Innercap with pregnant instructions [redacted] Printed". Technical Drawing for [redacted], Ref. No. 38-2111, is included in **Exhibit 10**. All other pertinent data remains the same as that provided in Section XIII of our original ANDA dated December 28, 2000.

We would like to take this opportunity to inform the Agency that we have revised our proposed package sizes and container labels to comply with the reference listed drug's condition of approval for unit-of-use containers. Specifically, Misoprostol Tablets will be packaged into unit-of-use bottles as follows:

0.1 mg	0.2 mg
Unit of use bottles of 120 tabs: 150cc/38mm	Unit of use bottles of 100 tabs: 150cc/38mm

Please note that the container/closure configuration proposed for the unit of use bottles (150cc/38mm) is the same as that which was proposed in our original submission for the 0.2 mg

strength (bottles of 250s). Therefore, its use for the 0.1 mg strength is supported by the appropriate stability studies. Please refer to Exhibits 11 and 16, in which we have provided revised container labels and updated stability data, respectively.

IVAX Pharmaceuticals, Inc. understands that final comment is pending DGCDP's response.

b. *We encourage you to differentiate the two different strengths from each other by using contrasting colours and/or boxing, or any other means.*

Response:

It is Zenith Goldline Pharmaceuticals' standard practice to use boxing and contrasting colors in our final printed labeling to differentiate the various strengths of the product.

c. *Add a picture on the principal display panel depicting that the product is not for pregnant women as presented on the RLD container labels.*

Response:

Four copies of our draft container labeling, which includes pictorial display indicating that the product is not for pregnant women, is provided in **Exhibit 11**. Side-by-side comparisons of Zenith Goldline's draft labels for both strengths and the innovator's label is also provided in this Exhibit.

2. INSERT

a. *Please note that there are numerous and significant differences between your proposed insert labeling and the referenced listed drug (RLD) insert labeling approved June 22, 2000. Please also note that there are pending labeling issues with the RLD labeling that we will update you on as soon as they are resolved. Please review the attached RLD insert labeling, revise your proposed insert labeling accordingly, and submit in draft.*

Response:

Zenith Goldline has revised the insert labeling according to the RLD insert labeling sent to us by the Division of Labeling on August 20, 2001 (approved June 22, 2000). Four copies of our proposed draft insert labeling are provided in **Exhibit 12**, followed by a side-by-side comparison of our proposed labeling versus our original draft labeling.

b. *Please clarify the scoring of the tablets. It appears that the description of the scoring of the tablets is not consistent in the application.*

Response:

We acknowledge an inconsistency of the scoring description in the application. We confirm that there is a typographical error in the description detailed beneath the header in the Executed Batch Record (document TTM323/01, pages 0567-0592 of the ANDA). This reads "White round F.B.E. Tablet, Marked with "4430" on one side and "Hourglass Logo **Breakline** 100" on Reverse" and should have read ""White round F.B.E. Tablet, Marked with "4430" on one side and "Hourglass Logo 100" on Reverse". The correct description is included in the Blank Batch Manufacturing Record for the intended commercial lots (pages 0466-0525 of our original ANDA), and as part of **Exhibit 5**, "Batch Manufacturing Record", document TTM442/02.

3. PATIENT INFORMATION LEAFLET

a. *Please see INSERT comment (a).*

b. *Add a Spanish version of the patient information to the PATIENT INFORMATION LEAFLET in addition to the English version as a Spanish version was approved for the RLD.*

Combined 3. a. and b. Response:

Zenith Goldline has revised the patient information leaflet according to the RLD insert labeling sent to us by the Division of Labeling on August 20, 2001 (approved June 22, 2000). This new patient information leaflet also includes a Spanish version. Four copies of our proposed draft patient information leaflet are provided in **Exhibit 13**, followed by a side-by-side comparison of both the English and Spanish versions.

D. BIOEQUIVALENCE COMMENTS

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted], using USP 24 apparatus II (paddles) at [redacted]. The test product should meet the following dissolution specifications:

Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivqlency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Response 1:

We acknowledge the Division of Bioequivalence's comments and commit to incorporating the recommended dissolution testing into our stability and quality control programs.

The dissolution testing will be conducted in ——— using USP 24 apparatus II (paddles) at ———. The test product will meet the following dissolution specifications:

Not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

ADDITIONAL INFORMATION

In addition to our responses to the points raised, IVAX Pharmaceuticals, Inc. are seeking approval for an additional container/closure configuration for our 100mcg and 200mcg tablets in unit dose blister packs. In support of this request, we are enclosing the following documentation:

i. Executed Batch Packaging records from the ——— ———. **(Exhibit 14)**.

ii. Stability Protocol - The tablets packed in the ——— aluminum blister pack configuration were taken from a representative composite sample of each tablet batch. The composites were prepared by controlled sampling of each bulk container of each batch **(Exhibit 15)**.

The composite samples were shipped to the packager in the — packaging configuration as outlined in Section XIII (pages 0843-0844) of the original submission i.e. ——— container/closure lined with ——— bags and containing a desiccant.

iii. Stability Data - 3 months accelerated stability data, plus 9 months stability data at room temperature **(Exhibit 16)**. The stability data support a shelf-life of 2 years for the 100mcg and 200mcg tablets in this pack configuration.

iv. Unit Dose Container/Closure System Information **(Exhibit 17)**.

v. Moisture Permeation **(Exhibit 18)**.

vi. Draft Labeling – Blister Mat and Carton Label **(Exhibit 19)**.

A concerted effort has been made to ensure that this amendment contains all of the information required by the Office of Generic Drugs. Should you have any questions or require additional information, please contact our office at your convenience at (201) 767-1700, extension 323 or 146.

Sincerely,

IVAX PHARMACEUTICALS, INC.

Stacy Bate / for

Patricia Jaworski, Associate Director
Regulatory Affairs, New Product Submissions

cc: District Office

K:\Reg\2001 Amendments\Misoprostol\5-22-01 Minor Amendment\Minor Amendment Response.doc

APPEARS THIS WAY
ON ORIGINAL

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

Via Federal Express

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AB BIOAVAILABILITY

MAR 29 2001

TELEPHONE AMENDMENT - Bioequivalence

Re: ANDA 76-095 for Misoprostol Tablets, 100 mcg and 200 mcg

Dear Mr. Buehler:

Reference is made to our pending Abbreviated New Drug Application for Misoprostol Tablets, 100 mcg and 200 mcg, and to the Agency's telephone communication of March 21, 2001. Pursuant to 21 CFR Parts 314.96 and 314.120, we are amending our application by responding to the request made by the Division of Bioequivalence during the telephone discussion.

Specifically, the Agency instructed Zenith Goldine as follows:

> *In regard to the analytical portion of the fed and fasted bioequivalence studies, please provide a copy of the assay method validation report (FB99-48) and copies of the contract research firm's SOPs governing repeat assays and criteria for acceptance.*

Zenith Goldline Pharmaceuticals, Inc., acknowledges the Agency's request, and, in response, we herewith submit the following:

- ——Analytics Report No. FB-99-48, entitled, "Validation of an ——Assay for the quantitation of Misoprostol Acid in Human Plasma". (Exhibit 1)
- ——Analytics SOP No. FB.1008.06, entitled, "Standard Operating Procedure for Reporting Criteria for Reassayed/Replicate Samples". (Exhibit 2)

Zenith Goldline Pharmaceuticals, Inc., has made a concerted effort to ensure that this amendment contains all of the information required by the Office of Generic Drugs. Should you have any questions, or require additional information, please contact our office at your convenience at (201) 767-1700, ext. 323 or 331.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Stacy Bate/for

Patricia Jaworski
Associate Director, Regulatory Affairs
New Product Submissions

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 30 2001
OGD

140 Legrand Avenue, Northvale, New Jersey 07647 ▪ (201) 767-1700 (800)387-0133 Fax (201)767-3804

Miami, FL • Walton, KY • Cidra, PR • St. Croix, U.S.V.I.

ANDA 76-095

Zenith Goldline Pharmaceuticals, Inc.
Attention: Patricia Jaworski
140 Legrand Avenue
Northvale, NJ 07647

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Misoprostol Tablets, 0.1 mg and 0.2 mg

DATE OF APPLICATION: December 28, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 2, 2001

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/ for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Zenith Goldline
PHARMACEUTICALS
Regulatory Affairs

505(j)(2)(A) OK
06-FEB-2001

DEC 28 2000

Gary Buehler
Acting Director, Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 02 2001
OGD

ABBREVIATED NEW DRUG APPLICATION

Re: Misoprostol Tablets, 100 mcg and 200 mcg

Dear Mr. Buehler:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and in compliance with 21 CFR §314.94, Zenith Goldline Pharmaceuticals, herewith submits an Abbreviated New Drug Application (ANDA) for Misoprostol Tablets, 100 mcg and 200 mcg.

Zenith Goldline has organized its ANDA as per the OGD guidance of February 1999. In support of this Application, the information outlined below is provided:

- Table of Contents
- Form FDA 356H
- Basis for Submission
- Patent Certification and Exclusivity Statement
- Comparison between the proposed drug and the reference listed drug (Cytotec® Tablets manufactured by G. D. Searle & Company)
- Draft Labeling (four copies each in the archival [blue] binder, chemistry review [red] binder and the bioequivalency review [orange] binder)
- Certification of Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454)
- *In-vivo* Bioequivalence studies (Fasted and Fed Studies):

1. [redacted] – Single dose, two way, cross-over, bioequivalence study comparing Misoprostol 200 µg Tablets by Zenith Goldline Pharmaceuticals and Cytotec® 200 µg Tablets manufactured by G., D. Searle & Company following administration of a 400 µg dose under fasting conditions.

2. [redacted] – Single dose, three way, cross-over bioavilablity study comparing Misoprostol 200 µg Tablets by Zenith Goldline Pharmaceuticals and Cytotec® 200 µg Tablets manufactured by G. D. Searle & Company following administration of a 400 µg dose under fasting and fed conditions.

The Diskettes are included in the front covers of the Review (orange) binders: Volume 2 of 8 and Volume 6 of 8, respectively.

140 Legrand Avenue, Northvale, New Jersey 07647 ▪ (201) 767-1700 (800)387-0133 Fax (201)767-3804

Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S V.I.

- Chemistry, Manufacturing and Controls Information

- Methods Validation Package: three (3) separately bound and identified copies are provided. Zenith Goldline Pharmaceuticals commits to resolve any issues which might be identified in the methods validation process whether before, or after, ANDA approval.
- Debarment, Conviction and Field Copy Certifications

The archival copy of this application consists of 11 volumes. The chemistry review copy consists of 4 volumes. The bioequivalency review copy consists of 8 volumes.

The exhibit batches for this application were manufactured at Norton Waterford, Waterford, Republic of Ireland.

Please note that the names Misoprostol Tablets 100 mcg and/or Misoprostol Tablets 100 μg are used interchangeably throughout the dossier with Misoprostol 0.1 mg. These refer to the same product. The names Misoprostol Tablets 200 mcg and/or Misoprostol Tablets 200 μg are also interchangeable with Misoprostol 0.2 mg and refer to the same product.

Zenith Goldline Pharmaceuticals requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office. We have made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions or require some additional information please contact our office at your convenience at (201) 767-1700 x 323.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS

Patricia Jaworski, Senior Manager
Regulatory Affairs (New Products)

PJ:go

cc: District Office