

Asthma and Anaphylactoid Reactions to Food Additives

SUSAN M. TARLO, MB, BS, FRCPC
GORDON L. SUSSMAN, MD, FRCPC

SUMMARY

Presumed allergic reactions to hidden food additives are both controversial and important. Clinical manifestations include asthma, urticaria, angioedema, and anaphylactic-anaphylactoid events. Most adverse reactions are caused by just a few additives, such as sulfites and monosodium glutamate. Diagnosis is suspected from the history and confirmed by specific challenge. The treatment is specific avoidance.

RÉSUMÉ

Les présumées réactions allergiques aux additifs alimentaires font l'objet de controverses mais sont importantes. Parmi les manifestations cliniques, on note l'asthme, l'urticaire, l'angio-oedème et les incidents anaphylactiques-anaphylactoides. La plupart des réactions indésirables sont causées par un petit nombre d'additifs, tels les sulfites et le glutamate monosodique. On peut soupçonner ce diagnostic à l'histoire et le confirmer par des tests de provocation spécifiques. Le traitement consiste à éviter l'agent causal.

Can Fam Physician 1993;39:1119-1123.

NUMEROUS AGENTS ARE ADDED to the food we eat: colouring agents, preservatives, antioxidants, flavouring agents, stabilizers, sweeteners, thickening agents, and so on. Only a few of these agents are currently known to play a role in precipitating allergiclike reactions (typically urticaria, angioedema, asthma, and anaphylaxis).

The mechanism of the reaction caused by the best-studied ingested food additives (sulfites, monosodium glutamate, tartrazine, and benzoates) remains unknown, although certain agents, such as gums, can clearly cause a typical immunoglobulin E (IgE)-mediated allergic response. This article discusses the clinical features, diagnosis, and management of asthma, urticaria, and anaphylactic responses caused by common food additives (*Table 1*).

.....
Dr Tarlo is Head of an Allergy Clinic and Occupational Lung Disease Clinic at the Western Division of the Toronto Hospital and is a Research Physician at the Gage Research Institute in Toronto. **Dr Sussman** is Head of the Section of Allergy, Division of Immunology, at Wellesley Hospital and is an Assistant Professor at the University of Toronto.

Sulfites

Sulfiting agents are used mainly as antioxidants in food fresheners and to control microbial growth in fermented beverages (*Table 2*). Studies have suggested that 5% to 10% of asthmatic patients experience an exacerbation of their asthma within 10 to 20 minutes of ingesting sulfites.¹⁻⁴ Severity of reaction ranges from mild symptoms after ingesting a large amount to life-threatening responses after ingesting small amounts.^{5,6} The response most commonly manifests as asthma alone but can include flushing, urticaria, angioedema, tearing, runny nose, abdominal pain, seizures, and anaphylaxis.^{1-4,7,8} Extremely sensitive patients have died from such responses.¹⁻⁴

Sulfites in foods or drinks can be present as sulfur dioxide, sodium sulfite, sodium or potassium metabisulfite, and sodium or potassium bisulfite. Sulfites were commonly used in restaurants to keep salads and uncooked vegetables looking crisp and fresh. However, after one sulfite-related death in Canada, this use was banned. Sulfites can still be used as a whitener for potatoes, grapes, and shrimp. Legislation requiring the nature and concentration of sulfite to be labeled is expected. Today, the most common sources of

sulfites are beer, wine, dried apricots, other dried fruit, frozen french fries, frozen seafood, jams, jellies, and bottled fruit juices.

The mechanism of the asthmatic response to sulfites is unknown. A few sulfite-sensitive patients have positive skin

Some multidose bronchodilator solutions for aerosolization previously contained sulfites as preservatives but no longer do. Freon-propelled inhalers do not contain sulfites. Some injectable solutions, such as epinephrine, do contain sulfites as preservatives, but the amount injected has not been shown to precipitate asthma or anaphylactoid responses.¹⁴

Sulfite sensitivity should be suspected if a patient's history indicates asthma exacerbation within 20 minutes of ingesting foods or beverages. If a definitive diagnosis is necessary, single- or double-blind challenge testing can be carried out.¹⁻⁶ This carries some risk and is contraindicated in patients with a history of very severe response. It should be performed only in a hospital with staff and facilities for resuscitation in the event of a severe reaction, and with the patient's informed consent. As with any challenge of food additives (*Table 3*), a control day with placebo challenge is required (using lactose or, if the patient is lactose intolerant, xylose). The patient should avoid sulfite-containing foods for at least 5 days before challenge.

The challenge should consist of repeated increasing doses of potassium metabisulfite administered at intervals depending on the timing of symptoms recorded in the history (generally every 20 minutes). Powdered metabisulfite or placebo is dissolved in 10 mL of water or juice, and the patient is asked to hold the solution in his or her mouth for 30 seconds before swallowing it. Increasing doses of metabisulfite (eg, 1 mg, 5 mg, 15 mg, 45 mg, 100 mg, or smaller increments in those with severe symptoms) are used for challenge, and the response is monitored by spirometry before, and 20 minutes after, each dose. If the forced expiratory volume in 1 second, or FEV₁, falls 20% or more, the challenge is stopped for the day, and the patient is monitored until clinically improved. An FEV₁ that falls as much as, or more than, 20% more than on the placebo day indicates a positive response to sulfites. Medication use should be consistent both days; guidelines for discontinuing medications should be followed as in other challenges (*Table 3*).

Treatment is by avoidance and patient education on the appropriate management of symptoms caused by inadvertent

Table 1. Common food additives known to cause adverse reactions

ADDITIVE	REACTION
Sulfites	Asthmatic attack
	Anaphylaxis
	Abdominal pain
	Urticaria and angioedema Rhinoconjunctivitis
	Seizure
	Death
Monosodium glutamate	Chinese restaurant syndrome Late and immediate onset asthma
Benzoates, butylated hydroxytoluene, butylated hydroxyanisole	Chronic urticaria
Tartrazine	Asthma Urticaria
Nitrites, nitrates	Gastrointestinal complaints Cyanosis
Aspartame	Urticaria and angioedema

Adapted from Yang.¹

test results to metabisulfite and a positive Prausnitz-Küstner reaction (passive transfer), suggesting an IgE-mediated allergic reaction.¹⁻⁷ Another proposed mechanism is a local response to released sulfur dioxide or sulfite inhalation, as asthmatics have been shown to be particularly responsive to the irritant bronchoconstrictor effect of inhaled sulfur dioxide.⁹⁻¹² However, studies have indicated no clear relationship between inhaled sulfur dioxide, airway responsiveness, and ingested sulfite sensitivity, suggesting that other factors also play a role in the response. Sulfite oxidase deficiency has been identified by fibroblast tissue cultures in sulfite-sensitive patients. Such a deficiency could delay clearance of a sulfite load and magnify the effect of sulfites.¹³

ingestion (using a prepared adrenalin syringe or going to a hospital emergency department).

Monosodium glutamate

Monosodium glutamate (MSG) is added to food to enhance flavour. It is present most frequently in Chinese restaurant food and is also in commercially prepared soups, stews, and other main dishes in quantities of up to 5 g per portion.

The most common manifestation of MSG sensitivity (Chinese restaurant syndrome)^{15,16} occurs 1 to 2 hours after MSG ingestion and is characterized by headache, nausea, sweating, chest tightness, burning, and numbness. Occasionally, severe symptoms mimic angina. Asthma exacerbations have been documented rarely but can occur up to 12 hours after MSG ingestion.^{17,18} Sensitivity to MSG appears to be far less common clinically than sulfite sensitivity. The mechanism is unknown, but the symptoms could be caused by stimulation of irritant receptors in the airways or by a central effect.

If the diagnosis is suspected from the history, a trial of MSG avoidance and specific oral challenge testing can be done. Either MSG (in doses ranging from 500 mg to 3 g) or lactose placebo are given by capsule. The challenge procedure is similar to that for sulfites with a placebo control day, patient blinding, and consent. However, the follow-up time after each dose could be several hours, depending on the timing of previous presumed reaction to MSG noted in the history.

Tartrazine and benzoates

Tartrazine is a yellow dye used in some yellow, orange, and green colours for foods, drinks, and medications. Benzoates are used as preservatives in jams, jellies, pickles, and soft drinks. Studies have reported that these additives exacerbate **asthma, urticaria, and angioedema**, particularly in acetylsalicylic acid-sensitive asthmatics (8% to 44% in some studies).¹⁹⁻²² However, studies during the past 12 years with double-blind challenge testing have shown only rare patients to be truly sensitive to these agents.²³ Thus, an avoidance diet is unjustified for ASA-sensitive asthmatics unless carefully compared with a

normal diet by peak flows, symptom scores, and medication requirements. Apparent improvements with avoidance should be documented by single- or double-blind challenges as described for the other additives before placing patients on long-term, **very restrictive diets**.

The mechanism of the response is unknown, but **tartrazine and benzoate have been reported to stimulate lymphocyte-derived and leukocyte inhibitory factors, suggesting a possible role for cell-mediated immunity.**²⁴

Other ingested food additives

Other food additives, such as spices and gums, can cause IgE-mediated events as in true food allergy (urticaria, angioedema, asthma, or anaphylaxis). When an allergy history suggests reactions to foods containing such agents, skin testing and, where needed, single- or double-blind oral challenges can be helpful.

Aspartame has been reported to precipitate urticaria in a few patients, but to date this has not been proved by double-blind challenge.²⁵⁻²⁷

Antimicrobial drugs

Health and Welfare Canada²⁸ has limited the allowable levels of almost all antibiotics found in milk, poultry, and meat. Although these levels are extremely low (0.01 to 4 ppm maximum residue), they could be responsible for IgE-mediated allergic reactions in susceptible individuals. Patients with suggestive histories should undergo appropriate investigations (skin tests or challenge).

Inhaled food additives

In addition to ingested food additives, inhaled food additives, especially among food-industry workers, can cause or exacerbate rhinitis, conjunctivitis, and asthma. Examples include enzymes, such as fungal amylase used by bakers and in flour manufacture; papain used as a meat tenderizer²⁹; sulfites used to make frozen french fries; and pectin used in jam production.³⁰ Patients who inhale food additives at work may have a history of exacerbation of symptoms during the week with improvement on weekends and holidays.

Investigations should include documentation of a work relationship by serial

They have not realized that those studies showing a rare effect tested patients ON meds with a SMALL amount of dye. Oh yeah - and often they had not even first avoided the dye!!

avoiding tartrazine & other food dyes is sensible not "restrictive"

Table 2. Common sources of food additives

SULFITES

- Wine
- Beer
- Salad bars
- Frozen french fries
- Dried fruit, eg, apricots, white raisins
- Lemon concentrates for cooking or drinks
- Some baked goods

MONOSODIUM GLUTAMATE

- Chinese meals
- Soups
- Stews

TARTRAZINE

- Jams
- Some butter
- Candies
- Cakes
- Tablets

BENZOATES

- Some soft drinks
- Pickles
- Jams
- Jellies
- Cakes

see note
top of
next
parag

peak flow recordings and repeat measurements of airway responsiveness at work and off work; skin testing where feasible (eg, with inactivated papain); and, if needed, specific inhalation challenge in a spe-

ity of a common food additive should be considered and further investigated. A trial of additive avoidance can be used, but it should be carefully monitored and compared with symptoms during a similar period on a normal diet. Blinded challenges can also be helpful. Inhaled food additives should be considered among food workers with symptoms of allergy suggestive of occupational exposure. ■

Requests for reprints to: Dr S.M. Tarlo, Toronto Hospital (Western Division), Edith Cavell Wing, #4008, 399 Bathurst St, Toronto, ON M5T 2S8

References

1. Yang WH, Purchase ECR, Rivington RR. Positive skin tests and Prausnitz-Küstner reactions in metabisulfite sensitive subjects. *J Allergy Clin Immunol* 1986;78:443-9.
2. Yang WH, Purchase ECR. Adverse reactions to sulfites. *Can Med Assoc J* 1985;133:865-8.
3. Yang WH. Adverse reaction to food and food additives. *Allergy* 1989;19:7-20.
4. Dalton-Bunnow MF. Review of sulfite sensitivity. *Am J Hosp Pharm* 1985;42:2220-6.
5. Stevenson DD, Simon RA. Sensitivity to ingested metabisulfites in asthmatic subjects. *J Allergy Clin Immunol* 1981;68:26-32.
6. Stevenson DD, Simon RA. Sulfites and asthma. *J Allergy Clin Immunol* 1984;74:469-72.
7. Prenner BM, Stevens JJ. Anaphylaxis after ingestion of sodium bisulfite. *Ann Allergy* 1976;37:180-2.
8. Schwartz HJ. Sensitivity to ingested metabisulfite: variations in clinical presentation. *J Allergy Clin Immunol* 1983;71:487-9.
9. Sheppard D, Wong WS, Uehara CF, Nadel JA, Boushey HA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980;122:873-8.
10. Bethel RA, Epstein J, Sheppard D, Nadel JA, Boushey HA. Sulfur dioxide induced bronchoconstrictor in freely breathing, exercising, asthmatic subjects. *Am Rev Respir Dis* 1983;128:987-90.
11. Delohery J, Simmul R, Castle WD, Allen DH. The relationship of inhaled sulfur dioxide reactivity to ingested metabisulfite in patients with asthma. *Am Rev Respir Dis* 1984;130:1027-32.
12. Schwartz HJ, Chester EH. Bronchospastic responses to aerosolized metabisulfite in asthmatic subjects: potential mechanisms and clinical implications. *J Allergy Clin Immunol* 1984;74:511-3.

Table 3. Food additive oral challenges

CHALLENGES

- Trial of avoiding the specific additive should show improvement.
- Single- or double-blind challenge testing can be performed.
- Placebo-control day (lactose or, if lactose intolerant, xylose) is required.

CONDITIONS

- If possible, inhaled bronchodilators should be stopped at least 8 hours before each challenge and long-acting theophylline for 48 hours. Cromolyn and nedocromil should be stopped before sulfite challenge.
- Spirometry should be assessed before and at intervals after each dose and the challenge stopped if FEV₁ falls 20% or more. Baseline FEV₁ must be at or greater than 1.5 L or 70% of best.
- Timing between doses is assessed from the history of symptom onset after ingestion.
- Challenges should be performed in hospital with informed consent and facilities for resuscitation.
- A positive challenge is a 20% or more fall in FEV₁ after ingesting the additive compared with the placebo control day.

CONSIDERATIONS

- Consider sulfite sensitivity in patients with intermittent acute exacerbations of asthma within 20 minutes of ingesting wine, beer, dried fruit, or restaurant meals.
- Consider a possible exacerbating role for MSG, tartrazine, and benzoates in patients with severe asthma, urticaria, and angioedema, even without clear, food-related symptoms. An additive avoidance trial might be worthwhile if carefully monitored.
- Before restricting a patient to long-term additive avoidance, carefully document the effects of additive avoidance compared with normal diet by assessing peak flows, symptoms, and medication needs in the absence of other confounding variables.

cialized unit. Treatment, after establishing the diagnosis, is again by avoidance.

Conclusion

Food additives should be considered as possible triggering factors among patients with asthma, urticaria, angioedema, or anaphylaxis. During history-taking all patients should be asked whether meals or drinks appear to precipitate symptoms. If symptoms appear to be provoked by several different foods or drinks, the possibil-

13. Jacobsen DW, Simon RA, Singh M. Sulfite oxidase deficiency and cobalamin protection in sulfite sensitive asthmatics (SSA)[abstract]. *J Allergy Clin Immunol* 1984;73:135.
14. Simon RA. Adverse reactions to drug additives. *J Allergy Clin Immunol* 1984; 74:623-30.
15. Kwok RHM. Chinese restaurant syndrome [letter]. *N Engl J Med* 1968;278:796.
16. Schaumburg HH, Byck R, Gerstl R, Mashman JH. Monosodium L-glutamate: 1+5 pharmacology and role in the Chinese restaurant syndrome. *Science* 1969;163:826-8.
17. Allen DH, Baker GJ. Chinese restaurant asthma. *N Engl J Med* 1981;305:1154-5.
18. Allen DH, Delohery J, Baker G. Monosodium L-glutamate induced asthma. *J Allergy Clin Immunol* 1987;80:530-7.
19. Settupane GA, Pudu-Pakkam RK. Aspirin intolerance. III. Subtypes, familial occurrence and cross reactivity with tartrazine. *J Allergy Clin Immunol* 1975;56:215-21.
20. Tarlo SM, Broder I. Tartrazine and benzoate challenge and dietary avoidance in chronic asthma. *Clin Allergy* 1982; 12:303-12.
21. Stenius BSM, Lemola M. Hypersensitivity to acetylsalicylic acid (ASA) and tartrazine in patients with asthma. *Clin Allergy* 1976; 6:119-29.
22. Spector LS, Warggaard CM, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J Allergy Clin Immunol* 1979;64:500-6.
23. Stevenson DD, Ouimon RA, Lumry WR, Mathison DA. Adverse reactions to tartrazine. *J Allergy Clin Immunol* 1986;78:182-91.
24. Warrington RJ, Sander PJ, McPhillips S. Cell mediated immune responses to artificial food additives. *Clin Allergy* 1986;16:527-33.
25. Kulczycki A. Aspartame-induced urticaria. *Ann Intern Med* 1986;104:207-8.
26. Garriga MM, Berkbile C, Metcalfe DD. A combined single blind, double blind, placebo controlled study to determine reproducibility of the hypersensitivity response to aspartame. *J Allergy Clin Immunol* 1991;87:821-7.
27. Geha R, Buckley CE, Patterson R, Polmar S, Saxon A, Rohr A, et al. Aspartame is no more likely than placebo to cause allergic reactions [abstract]. *J Allergy Clin Immunol* 1992;89:184.
28. Health and Welfare Canada. *Food and Drugs Act and Regulations*. Ottawa: Health and Welfare Canada, April 11, 1991:Table III, Section 15.
29. Flindt MLH. Allergy to alpha-amylase and papain. *Lancet* 1979;1:1407-8.
30. Cohen A, Forse M, Tarlo S. Occupational asthma caused by pectin inhalation in the manufacture of jam. *Chest* 1993;103:309-11.

• • •



THERAPEUTIC CLASSIFICATION Mucosal Protective Agent

INDICATIONS CYTOTEC (misoprostol) is indicated for the prevention of NSAID-induced gastric ulcers. Patients at high risk of developing NSAID-induced complications and who may require protection include: • Patients with a previous history of ulcer disease or a significant gastrointestinal event. • Patients over 60 years of age. • Patients judged to be at risk because of general poor health, severe concomitant medical disease, or patients who are poor surgical risks. • Patients disabled by joint symptoms (e.g., HAQ Disability Index Score >1.5) or those with severe systemic manifestations of arthritis. • Patients taking other drugs known to damage or exacerbate damage to the gastrointestinal tract such as corticosteroids or anticoagulants. • Patients taking a high dosage or multiple NSAIDs, including those available Over-The-Counter. The risk of NSAID-induced complications may be highest in the first three months of NSAID therapy. CYTOTEC is also indicated for the treatment of NSAID-induced gastric ulcers (defined as ≥ 0.3 cm in diameter) and for the treatment of duodenal ulcers.

CONTRAINDICATIONS Known sensitivity to prostaglandins, prostaglandin analogues, or excipients (microcrystalline and hydroxypropyl methylcellulose, sodium starch glycolate and hydrogenated castor oil). Contraindicated in pregnancy. (See CLINICAL PHARMACOLOGY.) Women should be advised not to become pregnant while taking CYTOTEC (misoprostol). If pregnancy is suspected, use of the product should be discontinued.

WARNINGS Women of childbearing potential should employ adequate contraception (i.e., oral contraceptives or intrauterine devices) while receiving CYTOTEC (misoprostol). (See CONTRAINDICATIONS.) **Nursing Mothers:** It is unlikely that CYTOTEC is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, CYTOTEC should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants. **Pediatric Use:** Safety and effectiveness in patients below the age of 18 have not been established.

PRECAUTIONS **Selection of Patients:** Caution should be used when using symptomatology as the sole diagnostic and follow-up procedure, since CYTOTEC (misoprostol) has not been shown to have an effect on gastrointestinal pain or discomfort. Before treatment is undertaken, a positive diagnosis of duodenal ulcer or NSAID-induced gastric ulcer should be made. The general health of the patient should be considered. Misoprostol is rapidly metabolized by most body tissues to inactive metabolites. Nevertheless, caution should be exercised when patients have impairment of renal or hepatic function. (See CLINICAL PHARMACOLOGY: Pharmacokinetics.) **Diarrhea:** Rare instances of profound diarrhea leading to severe dehydration have been reported with an underlying condition such as irritable bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if CYTOTEC is prescribed. **Use in Elderly or Renally Impaired: Considerations for Dosage Adjustment:** In subjects over 64 years of age or those who are renally impaired the pharmacokinetics may be affected, but not to a clinically significant degree. (See DOSAGE AND ADMINISTRATION.) No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 mcg QID) is recommended. **Drug Interactions:** The serum protein binding of misoprostol acid (the active metabolite of misoprostol) was not affected by: indomethacin, ranitidine, dioxin, phenylbutazone, warfarin, diazepam, methyldopa, propranolol, triamterene, cimetidine, acetaminophen, ibuprofen, chlorpropamide, and hydrochlorothiazide. Salicylic acid (300 mcg/mL) lowered the protein binding of misoprostol from 84% to 52%; this is not considered clinically significant since the binding of misoprostol acid is not extensive and its elimination half-life is very short. In laboratory studies, misoprostol has shown no significant effect on the cytochrome P450-linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolized by this system. No drug interactions attributable to misoprostol have been observed to date. (See CLINICAL PHARMACOLOGY.) Some prostaglandins and prostaglandin analogues have the capacity to produce hypotension through peripheral vasodilation. The results of clinical trials to date indicate that CYTOTEC has not produced hypotension at dosages effective in promoting the healing of ulcers. Nevertheless, CYTOTEC should be used with caution in the presence of disease states where hypotension might precipitate severe complications, e.g., cerebral vascular disease or coronary artery disease. Epileptic seizures have been reported with prostaglandins and prostaglandin analogues administered by routes other than oral. Therefore, misoprostol tablets should be used in known epileptics only when their epilepsy is adequately controlled and then only when expected benefits outweigh potential risks. Symptomatic responses to CYTOTEC do not preclude the presence of gastric malignancy.

ADVERSE REACTIONS **Gastrointestinal:** In subjects receiving CYTOTEC (misoprostol) 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea, abdominal pain and flatulence. The average incidences of these events were 11.4%, 6.8% and 2.9%, respectively. In clinical trials using a dosage regimen of 400 mcg bid, the incidence of diarrhea was 12.6%. The events were usually transient and mild to moderate in severity. Diarrhea, when it occurred, usually developed early in the course of therapy, was self limiting and required discontinuation of CYTOTEC in less than 2% of the patients. The incidence of diarrhea can be minimized by adjusting the dose of CYTOTEC, by administering after food, and by avoiding co-administration of CYTOTEC with magnesium-containing antacids. **Gynecological:** Women who received CYTOTEC during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). **Elderly:** There were no significant differences in the safety profile of CYTOTEC in approximately 500 ulcer patients who were 65 years of age or older, compared with younger patients. Confusion has been reported in a small number of patients in our post marketing surveillance of CYTOTEC. **Incidence greater than 1%:** In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving CYTOTEC and may be causally related to the drug: nausea (3.2%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%) and constipation (1.1%). However, there were no clinically significant differences between the incidences of these events for CYTOTEC and placebo.

DOSAGE AND ADMINISTRATION **Treatment and Prevention of NSAID-Induced Gastric Ulcers:** The recommended adult oral dosage of CYTOTEC (misoprostol) for the prevention and treatment of NSAID-induced gastric ulcer is 400 to 800 mcg a day in divided doses. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate, CYTOTEC and NSAIDs are to be taken simultaneously. CYTOTEC should be taken after food. **Duodenal Ulcer:** The recommended adult oral dosage of CYTOTEC (misoprostol) for duodenal ulcer is 800 mcg per day for 4 weeks in two or four equally divided doses (i.e., 200 mcg qid or 400 mcg bid). The last dose should be taken at bedtime with food. Antacids (aluminum based) may be used as needed for relief of pain. Treatment should be continued for a total of 4 weeks unless healing in less time has been documented by endoscopic examination. In the small number of patients who may not have fully healed after 4 weeks, therapy with CYTOTEC may be continued for a further 4 weeks. **Use in Elderly and Renally Impaired: Consideration for Dosage Adjustment:** 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. There was no clear correlation between degree of impairment and AUC. In subjects over 64 years of age the pharmacokinetics may be affected. In both patient groups the pharmacokinetic changes are not clinically significant. No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dosage may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 mcg QID) is recommended.

AVAILABILITY CYTOTEC (misoprostol) 200 mcg tablets are white to off-white, scored, hexagonal with SEARLE 1461 engraved on one side available in bottles of 120 and 500 tablets. CYTOTEC 100 mcg tablets are white to off-white, round tablets with SEARLE engraved on one side and CYTOTEC on the other available in bottles of 100 tablets.

Store below 30°C (86°F).

Pharmacist: Dispense with Patient Insert.

400 Iroquois Shore Road
Oakville, Ontario
L6H 1M5

SEARLE

References: 1. Adapted from Langman, MJS. Peptic Ulcer Complications and the use of Non-Aspirin, Non-Steroidal, Anti-Inflammatory Drugs. *Adverse Drug Reaction Bulletin* 1986;120:488451. 2. Cytotec Product Monograph May 1991. 3. Graham DY, Agrawal NM, Roth SH et al. Prevention of NSAID-induced gastric ulcer with misoprostol. *Lancet* 1988;2:1277-1280. 4. Elliott SL, Yeomans ND, Buchanan RRC, et al. Long term epidemiology of gastropathy associated with nonsteroidal antiinflammatory drugs (NSAID) (abstr). *Clin Exp Rheumatol* 1990; (suppl 4) 8:58. 5. Fries JF, Miller SR, Spitz PW, et al. Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. *Gastroenterology* 1989;96:647-655. 6. Gabriel S, Jaakkimainen L, Bombardier C. Risk of serious gastrointestinal complications related to use of nonsteroidal antiinflammatory drugs A meta-analysis. *Annals of Internal Medicine*. 1991; 115:787-796. Product Monograph Available upon Request

PAAB