DIAGNOSTIC CHALLENGE

A Case of a Blocked Nose

Costa Apostolides, BSc, MD '99, Rachael Smith, BSc, MD '99, and Michele Carr, DDS, MD, MEd

Department of Otolaryngology, Dalhousie University, Halifax, Nova Scotia

One afternoon, during a general ENT clinic at the QEII, you encounter a typical otolaryngologic complaint of a "plugged-up nose". Your patient is a healthy 70-year-old male, Mr. N., who presents with right nasal obstruction worsening over the past year. He states that he has not had any epistaxis or nasal pain, and that his condition was unresponsive to topical steroids (Flonase®). Past medical history includes bowel cancer which was resected several years ago. On social enquiry, you learn that Mr. N. is a retired miner, a past smoker who quit two years ago, and he drinks alcohol socially. Head and neck examination is unremarkable save for a pale, polypoid mass in the right nostril (Figure 1). A CT scan was ordered (Figure 2).

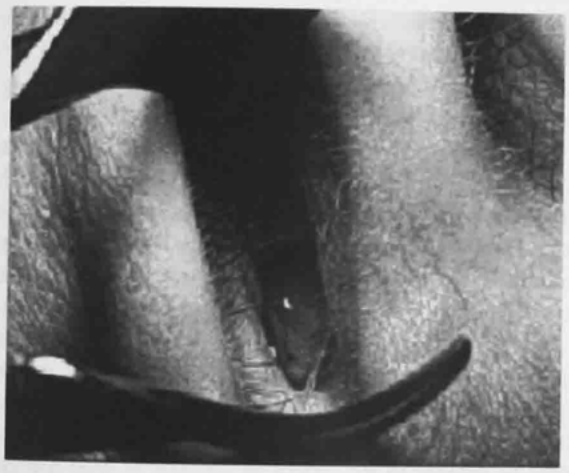

Figure 1
Polypoid mass in right nostril.

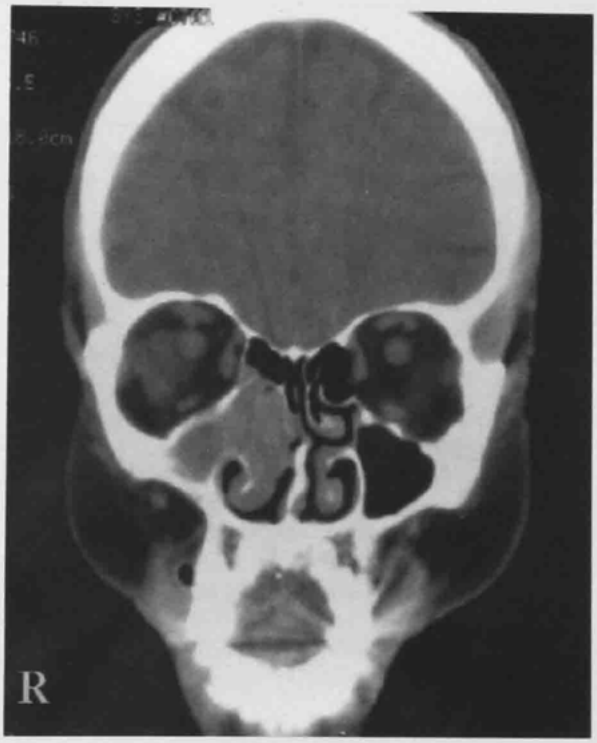

Figure 2
CT scan of head and neck.

Q1: Are the findings on CT consistent with nasal polyps?

Q2: What further diagnostic procedure(s) would you arrange?

Q3: What is the differential diagnosis of nasal obstruction in this age group?

Answers on page 72

A1: The CT scan shows a soft tissue mass filling the right maxillary sinus and anterior ethmoid cells inferiorly, extending into the nasal cavity. There is erosion of the lateral wall of the nose. The middle turbinate is pushed medially and possibly eroded. The other sinuses are normal.

A2: A biopsy would be important to obtain for pathology.

A3:

Table 1.0 Differential diagnosis of nasal obstruction for adults (> 20 years) (1,2).

Common*	
	infection (viral or bacterial)
	allergy (allergic rhinitis, polyps)
	rhinitis medicamentosa
	vasomotor rhinitis
	nasoseptal deformities
	trauma (septal hematoma)
	environmental and occupational irritants
Uncommon**	
	vasomotor rhinitis
	metabolic-endocrine
	pregnancy
	menses
	hypothyroidism
	diabetes mellitus
	drugs (antihypertensives, oral contraceptives, topical decongestants, cocaine)
	chronic sinusitis (bacterial, fungal)
	antrochoanal polyp
	atrophic rhinitis
	septal perforation
	benign neoplasms
	inverting papilloma
	angiofibroma
Rare***	
	malignant neoplasm
	squamous cell carcinoma
	adenocarcinoma
	adenocystic carcinoma
	sarcoma
	malignant melanoma
	esthesioneuroblastoma
	hemangiopericytoma
	granuloma of pregnancy
	foreign body
	rhinolith
	Paget's disease
	midline lethal granuloma
	Wegener's granuloma
	Churg-Strauss syndrome
	sarcoidosis
	superior vena cava syndrome
	Horner's syndrome
	cirrhosis
	uremia
	nonallergic rhinitis with eosinophilia syndrome

*common: nasal diseases in this group are seen daily in a general otolaryngology practice.

**uncommon: one or more cases per year.

***rare: one or more cases in a physician's experience.

DIAGNOSIS- INVERTING PAPILLOMA OF THE NOSE

Inverting papilloma is a relatively uncommon neoplasm of the nasal and paranasal sinus epithelium. It is 25 times less common than ordinary nasal polyps, appearing most often in the fifth to seventh decades of life (3). Many other terms have been used to describe this tumor, such as villiform cancer, epithelial papilloma, Schneiderian papilloma, and papillary sinusitis (4). This is probably due to the variability of histological interpretations of the lesion, as well as a misunderstanding of its behavior since it was first described by Ward in 1854 (5).

These tumors usually arise from the lateral nasal wall with local extensions in the paranasal sinuses, most commonly the maxillary antrum. They are usually firmer, bulkier and more vascular than inflammatory polyps. Non-translucent, inverting papillomas appear red, pale pink, or gray in colour. When viewed microscopically there is a proliferation of the covering epithelium with finger-like invaginates into the underlying stroma (6). The epithelium can be squamous cell, ciliated multilayer columnar cell resembling respiratory epithelium, or transitional.

Symptoms of inverting papilloma are non-specific, but the most common is unilateral nasal obstruction. Others are epistaxis, nasal discharge, sinusitis, nasal polyps, and more rarely, facial pain and proptosis (6,7,8). Interestingly, many patients have a history of nasal surgery prior to diagnosis of inverted papilloma, which may be due to misdiagnosis (6,9).

Radiographic studies include plain films and sinus tomography, but computed coronal tomography is the procedure of choice as it reveals a higher percentage of bone destruction and erosion (6,8). Although radiographic analysis helps to determine the extent of disease, it does not clearly distinguish malignancy from benign disease. For this reason it is important to confirm the diagnosis through biopsy.

The etiology of inverting papilloma is unknown. The most popular theory is that the human papilloma virus (HPV) is involved in the development of these tumors. One study showed the presence of viral DNA sequences in the tumors of 76% of patients with inverting papilloma (6). Further analysis is needed for proof of cause.

It has been found that these neoplasms are best treated with lateral rhinotomy and medial maxillectomy as the recurrence rate is much lower than with other modalities (6,9,10). Other procedures include local excisions (6), midfacial degloving (7,11), Caldwell-Luc operation with ethmoidectomy (9), and endoscopic excision (11).

It is important inverting papilloma be identified and removed as it is not only locally invasive with a tendency toward recurrence, but there is a well- known association with squamous cell carcinoma. Reported incidence of associated carcinoma ranges from 1.7% to 56%, depending upon the study (12).

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ERRATA

Several publishing errors occurred in the December 1997 edition of the *DMJ*. The *DMJ* editorial board sincerely apologizes for these mistakes and any problems they may have caused.

1) Dr. T.J. Marrie's name erroneously appeared on the masthead (page 5) with one 'r' instead of two.

2) The Nova Scotia Medical Society was omitted from the masthead. This has been rectified on the current masthead.

3) An advertisement on page 6 was printed with a number of typographical errors. The corrected advertisment is shown below.

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Manuscripts should be printed on standard 22x28 cm paper. Submissions should be 3000 words (approximately 15 pages double spaced) or less. This word limit does not include references or figures. Longer submissions may be considered with prior permission from the Associate-Editor, Reviews and the Editor-in-Chief. Pages should be numbered consecutively.

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Text, Acknowledgements: These should conform to the *Uniform requirements for manuscripts submitted to biomedical journals* (CMAJ 1994:150:147-154). These are on reserve in Dalhousie University's Kellogg Library under reserve call #971.

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Journal article

1. Johansson E, Aspirisi T. Missing cruciate ligament in congenital short femur. *J Bone Joint Surg* 1983;65A(8):1109-1115.

Chapter in book

2. Hahn JF, Mason L. Low back pain in children. In: Hardy Rw Jr, ed. *Lumbar disc disease*. New York: Raven Press, 1982:217-28. (Seminars in neurological surgery).

Book

3. Katz J. *Common orthopedic problems in pediatric practice*. New York: Raven Press, 1981:125-7.

Tables: Tables should be numbered in the order in which they are referred to in the text. Each should have a brief title. Column headings and descriptive matter in tables should be brief.

Figures: Each figure should be planned to fit into either one or two columns of text. Photographs and illustrations must be black and white and of good quality. Figures should be numbered in the order in which they are referred to in the text. Labelling should be limited to the essential components of a figure. Figure captions should be typed on a separate page at the end of the manuscript. Electronic copies of photographs and illustrations are preferred in TIFF or PICT format, and in separate files. MS PowerPoint (95 or earlier versions) is also acceptable. Attention should be given to be certain the graphics have adequate resolution.

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DIFLUCAN-150 (fluconazole) Capsule 150 mg
THERAPEUTIC CLASSIFICATION: Antifungal

ACTIONS: Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14-α-demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14-α-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

INDICATIONS AND CLINICAL USE: DIFLUCAN-150 (fluconazole) is indicated for the oral treatment of: Vaginal candidiasis (yeast infections due to *Candida*). The diagnosis of vaginal candidiasis should be confirmed by KOH smears and/or cultures before initiating therapy with **DIFLUCAN-150**.

CONTRAINDICATIONS: DIFLUCAN-150 (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing DIFLUCAN-150 to patients with hypersensitivity to other azoles. Coadministration of terfenadine is contraindicated in patients receiving DIFLUCAN (fluconazole) at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study (see **PRECAUTIONS**).

WARNINGS: Anaphylaxis: In rare cases, anaphylaxis has been reported. **Hepatic injury:** In the treatment of systemic infections multiple doses of fluconazole have been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury. **Dermatologic:** In rare cases, during the treatment of systemic infections, patients have developed exfoliative skin disorders during treatment with fluconazole. **Cisapride:** There have been reports of cardiac events including torsades de pointes in patients receiving concomitant administration of fluconazole with cisapride. Patients should be carefully monitored if fluconazole is to be coadministered with cisapride (see **PRECAUTIONS**).

PRECAUTIONS: General: The convenience of the single oral dose **DIFLUCAN-150** (fluconazole) regimen for the treatment of vaginal yeast infections **should be weighed against the acceptability of a higher incidence of drug related adverse events** with DIFLUCAN-150 (26%) versus intravaginal agents (16%) in comparative clinical studies where no difference in efficacy was demonstrated (see **ADVERSE REACTIONS** section). Fluconazole administered in combination with ethinyl estradiol - and levonorgestrel - containing oral contraceptives produced an overall mean increase in ethinyl estradiol and levonorgestrel levels; however, in some patients there were decreases up to 47% and 33% of ethinyl estradiol and levonorgestrel levels, respectively (see **PRECAUTIONS, Drug Interactions** section). The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment may be the result of random variation. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole is a net inducer of ethinyl estradiol or levonorgestrel metabolism. The clinical significance of these effects is presently unknown. **Use in Pregnancy:** There are no adequate and well-controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high dose (400-800 mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). Exposure to fluconazole began during the first trimester in all cases and continued for three months or longer. DIFLUCAN-150 should not be used in pregnant women unless the potential benefit outweighs the potential risk to the fetus. Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25 and 75 mg/kg respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 9.4 x the maximum recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at the 25 mg/kg dose. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg (approximately 10-40 x the recommended human dose) embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition. **Use in Women of Child-bearing Potential:** Since the teratologic effects of fluconazole in humans are unknown, women taking fluconazole for vaginal candidiasis should consider using adequate contraception (see **Use in Pregnancy**). There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high dose (400-800 mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). Exposure to fluconazole began during the first trimester in all cases and continued for three months or longer. Since there are no adequate studies in pregnant women to assess the potential for fetal risk, fluconazole should not be used in pregnant women unless the potential benefit outweighs the potential risk to the fetus. **Use in Nursing Mothers:** Fluconazole is secreted in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended. **Use in Children and Adolescents:** The safety and efficacy of DIFLUCAN-150 mg capsules in the treatment of vaginal candidiasis in patients under 18 years of age have not been established. **Drug Interactions:** Clinically or potentially significant drug interactions between DIFLUCAN-150 and the following agents/classes have been observed. **Oral Contraceptives:** Oral contraceptives were administered as a single dose both before and after the oral administration of fluconazole 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinyl estradiol or levonorgestrel AUC after the administration of fluconazole. The mean increase in ethinyl estradiol AUC was 6% (range: -47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%). Twenty-five normal females received daily doses of both 200 mg fluconazole or placebo for two, ten-day periods. The treatment cycles were one month apart with all subjects receiving fluconazole during one cycle and placebo during the other. The order of study treatment was random. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered on the final treatment day (day 10) of both cycles. Following administration of 200 mg of fluconazole, the mean percentage increase of AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinyl estradiol compared to placebo was 38% (range: -11 to 101%). Both of these increases were statistically significantly different from placebo. **Drugs prolonging the QTc interval:** The use of fluconazole in patients concurrently taking drugs metabolized by the cytochrome P-450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information caution should be used when coadministering DIFLUCAN and such agents. Patients should be carefully monitored. **Terfenadine:** Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. In one study, 6 healthy volunteers received terfenadine 60 mg BID for 15 days. Fluconazole 200 mg was administered daily from days 9 through 15. Fluconazole did not affect terfenadine plasma concentrations. Terfenadine acid metabolite AUC increased 36% ± 36% (range: 7 to 102%) from day 8 to day 15 with the concomitant administration of fluconazole. There was no change in cardiac repolarization as measured by Holter QTc intervals. However, another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that DIFLUCAN taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. Therefore the combined use of fluconazole at doses of 400 mg or higher with terfenadine is contraindicated (see **CONTRAINDICATIONS**). Patients should be carefully monitored if they are being concurrently prescribed fluconazole at multiple doses lower than 400 mg/day with terfenadine. **Astemizole:** Definitive interaction studies with DIFLUCAN have not been conducted. The use of fluconazole may be associated with elevations in serum levels of astemizole. Caution should be used when coadministering DIFLUCAN with astemizole. Patients should be carefully monitored. **Cisapride:** There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were coadministered. Therefore, caution should be used when coadministering fluconazole with cisapride. Patients should be carefully monitored (see **WARNINGS**). **Theophylline:** The pharmacokinetics of theophylline were determined from a single intravenous dose of aminophylline (6 mg/kg) before and after the oral administration of fluconazole 200 mg daily for 14 days in 16 normal male volunteers. There were significant increases in theophylline AUC, C_{max}, and half-life with a corresponding decrease in clearance. The mean ± SD theophylline AUC increased 21% ± 16% (range: -5 to 48%). The C_{max} increased 13% ± 17% (range: -13 to 40%). Theophylline clearance decreased 16% ± 11% (range: -32 to 5%). The half-life of theophylline increased from 6.6 ± 1.7 hours to 7.9 ± 1.5 hours. Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and therapy modified appropriately if signs of toxicity develop. **Cimetidine:** Absorption of orally administered fluconazole does not appear to be affected by gastric pH. Fluconazole 100 mg was administered as a single oral dose alone and two hours after a single dose of cimetidine 400 mg to six healthy male volunteers. After the administration of cimetidine, there was a significant decrease in fluconazole AUC (area under the plasma concentration-time curve) and C_{max}. There was a mean ± SD decrease in fluconazole AUC of 13% ± 11% (range: -3.4 to -31%) and C_{max} decreased 19% ± 14% (range: -5 to -40%). However, the administration of cimetidine 600 mg to 900 mg intravenously over a 4-hour period (from 1 hour before to 3 hours after a single oral dose of fluconazole 200 mg) did not affect the bioavailability or pharmacokinetics of fluconazole in 24 healthy male volunteers. **Antacid:** Administration of Maalox® (20 mL) to 14 normal male volunteers immediately prior to a single dose of fluconazole 100 mg had no effect on the absorption or elimination of fluconazole. **Cyclosporine:** Cyclosporine AUC and C_{max} were determined before and after the administration of fluconazole 200 mg daily for 14 days in eight renal transplant patients who had been on cyclosporine therapy for at least 6 months and on a stable cyclosporine dose for at least 6 weeks. There was a significant increase in cyclosporine AUC, C_{max}, C_{min} (24-hour concentration), and a significant reduction in apparent oral clearance following the administration of fluconazole. The mean ± SD increase in AUC was 92% ± 43% (range: 18 to 147%). The C_{max} increased 60% ± 48% (range: -5 to 133%). The C_{min} increased 157% ± 96% (range: 33 to 360%). The apparent oral clearance decreased 45% ± 15% (range: -15 to -60%). Fluconazole administered at 100 mg daily dose does not affect cyclosporine pharmacokinetic levels in patients with bone marrow transplants. Fluconazole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving fluconazole and cyclosporine. **Warfarin:** There was a significant increase in prothrombin time response (area under the prothrombin time-time curve) following a single dose of warfarin (15 mg) administered to 13 normal male volunteers following oral fluconazole 200 mg administered daily for 14 days as compared to the administration of warfarin alone. There was a mean ± SD increase in the prothrombin time response (area under the prothrombin time-time curve) of 7% ± 4% (range: -2 to 13%). Mean is based on data from 12 subjects as one of 13 subjects experienced a 2-fold increase in his prothrombin time response. Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended. **Hydrochlorothiazide:** Concomitant oral administration of 100 mg fluconazole and 50 mg hydrochlorothiazide for 10 days in 13 normal volunteers resulted in a significant increase in fluconazole AUC and C_{max} compared to fluconazole given alone. There was a mean ± SD increase in fluconazole AUC and C_{max} of 45% ± 31% (range: 19 to 114%) and 43% ± 31% (range: 19 to 122%), respectively. These changes are attributed to a mean ± SD reduction in renal clearance of 30% ± 12% (range -10 to -50%). **Oral Hypoglycemics:** The effects of fluconazole on the pharmacokinetics of the sulfonylurea oral hypoglycemic agents tolbutamide, glipizide, and glyburide were evaluated in three placebo-controlled studies in normal volunteers. All subjects received the sulfonylurea alone as a single dose and again as a single dose following the administration of fluconazole 100 mg daily for 7 days. In these three studies, 22/46 (47.8%) of fluconazole-treated patients and 9/22 (40.1%) of placebo-treated patients experienced symptoms consistent with hypoglycemia. **Tolbutamide:** In 13 normal male volunteers, there was a significant increase in tolbutamide (500 mg single dose) AUC and C_{max} following the administration of fluconazole. There was a mean ± SD increase in tolbutamide AUC of 26% ± 9% (range: 12 to 39%). Tolbutamide C_{max} increased 11% ± 9% (range -6 to 27%). **Glipizide:** The AUC and C_{max} of glipizide (2.5 mg single dose) were significantly increased following the administration of fluconazole in 13 normal male volunteers. There was a mean ± SD increase in AUC of 49% ± 13% (range: 27 to 73%) and an increase in C_{max} of 19% ± 23% (range: -11 to 79%). **Glyburide:** The AUC and C_{max} of glyburide (5 mg single dose) were significantly increased following the administration of fluconazole in 20 normal male volunteers. There was a mean ± SD increase in AUC of 44% ± 29% (range: -13 to 115%) and C_{max} increased 19% ± 19% (range: -23 to 62%). Five subjects required oral glucose following the ingestion of glyburide after 7 days of fluconazole administration. Clinically significant hypoglycemia may be precipitated by the use of fluconazole with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined fluconazole and glyburide use. Fluconazole reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When fluconazole is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary. **Phenytoin:** Phenytoin AUC was determined after 4 days of phenytoin dosing (200 mg daily, orally for 3 days, followed by 250 mg intravenously for one dose) both with and without the administration of fluconazole (oral fluconazole 200 mg daily for 16 days) in 10 normal male volunteers. There was a significant increase in phenytoin AUC. The mean ± SD increase in phenytoin AUC was 88% ± 68% (range: 16 to 247%). The absolute magnitude of this interaction is unknown because of the intrinsically non-linear disposition of phenytoin. Fluconazole increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended. **Rifampin:** Administration of a single oral 200 mg dose of fluconazole after 15 days of rifampin administered as 600 mg daily in 8 healthy male volunteers resulted in a significant decrease in fluconazole AUC and a significant increase in apparent oral clearance of fluconazole. There was a mean ± SD reduction in fluconazole AUC of 23% ± 9% (range: -13 to -42%). Apparent oral clearance of fluconazole increased 32% ± 17% (range: 16 to 72%). Fluconazole half-life decreased from 33.4 ± 4.4 hours to 26.8 ± 3.9 hours. Rifampin enhances the metabolism of concurrently administered fluconazole. Depending on clinical circumstances, consideration should be given to increasing the dose of fluconazole when it is administered with rifampin. **Zidovudine:** Plasma zidovudine concentrations were determined on two occasions (before and following fluconazole 200 mg daily for 15 days) in 13 volunteers with AIDS or ARC who were on a stable zidovudine dose for at least two weeks. There was a significant increase in zidovudine AUC following the administration of fluconazole. The mean ± SD increase in AUC was 20% ± 32% (range: -27 to 104%). The metabolite, GZDV, to parent drug ratio significantly decreased after the administration of fluconazole, from 7.6 ± 3.6 to 5.7 ± 2.2. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. **Drug/Drug Interaction:** Interaction studies with other medications have not been conducted, but such interactions may occur. **Drug/Laboratory Test Interactions:** None known.

ADVERSE REACTIONS: In patients with vaginal candidiasis treated with **DIFLUCAN-150** (fluconazole) as a single oral dose, the adverse events documented in two controlled North American trials were as follows:

	Percent of Patients with Side Effects	
	Fluconazole (n = 448)	Intravaginal Products (n = 422)
Drug Related Side Effects	26.1	15.9
Nausea	6.7	0.7
Abdominal Pain	5.6	1.7
Diarrhea	2.7	0.5
Dyspepsia	1.3	0.2
Headache	12.9	6.6
Application Site Reactions	0.0	4.5
Dizziness	1.3	0.0
Taste Perversion	1.3	0.0
Most of the reported side effects were mild to moderate in severity. Occasional allergic reactions including pruritus and urticaria were reported.		

In marketing experience with single dose fluconazole, rare cases of anaphylactic reaction and angioedema have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Symptoms: There has been one reported case of overdosage with fluconazole. A 42 year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behavior after reportedly ingesting 8200 mg of fluconazole. The patient was admitted to the hospital, and his condition resolved within 48 hours. **Treatment:** In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate. Fluconazole is largely excreted in urine. A three hour hemodialysis session decreases plasma levels by approximately 50%. Mice and rats receiving very high doses of fluconazole, whether orally or intravenously, displayed a variety of nonspecific, agonal signs such as decreased activity, ataxia, shallow respiration, ptosis, lacrimation, salivation, urinary incontinence and cyanosis. Death was sometimes preceded by clonic convulsions.

DOSAGE AND ADMINISTRATION: VAGINAL CANDIDIASIS – ORAL: The recommended dosage of **DIFLUCAN-150** (fluconazole) for vaginal candidiasis is 150 mg as a single oral dose. There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function.

PHARMACEUTICAL INFORMATION: Description: Fluconazole is a white crystalline solid, freely soluble in methanol, soluble in acetone, sparingly soluble in aqueous 0.1M hydrochloric acid and ethanol, slightly soluble in water and saline and very slightly soluble in hexane. Fluconazole is a very weak base with a pKa of 1.76 at 24°C and as a consequence will be essentially nonprotonated at pH values above 3.5. m.p. = 140.3°C. The partition coefficient Log P = ±0.5. **Composition: DIFLUCAN-150:** Each capsule (white) contains 150 mg fluconazole. The capsule also contains the following non-medicinal ingredients: lactose, maize starch, colloidal silicon dioxide, magnesium stearate and sodium lauryl sulphate; the capsule shell contains gelatin and titanium dioxide.

AVAILABILITY OF DOSAGE FORMS: DIFLUCAN-150 Capsules are available as hard white gelatin capsules, marked with Pfizer logo. Each capsule contains 150 mg of fluconazole. Supplied as a unit dose blister (PVC) pack of 1 capsule.

STORAGE: DIFLUCAN-150 Capsules (fluconazole) 150 mg: Store between 15-30°C.

Product monograph available on request.

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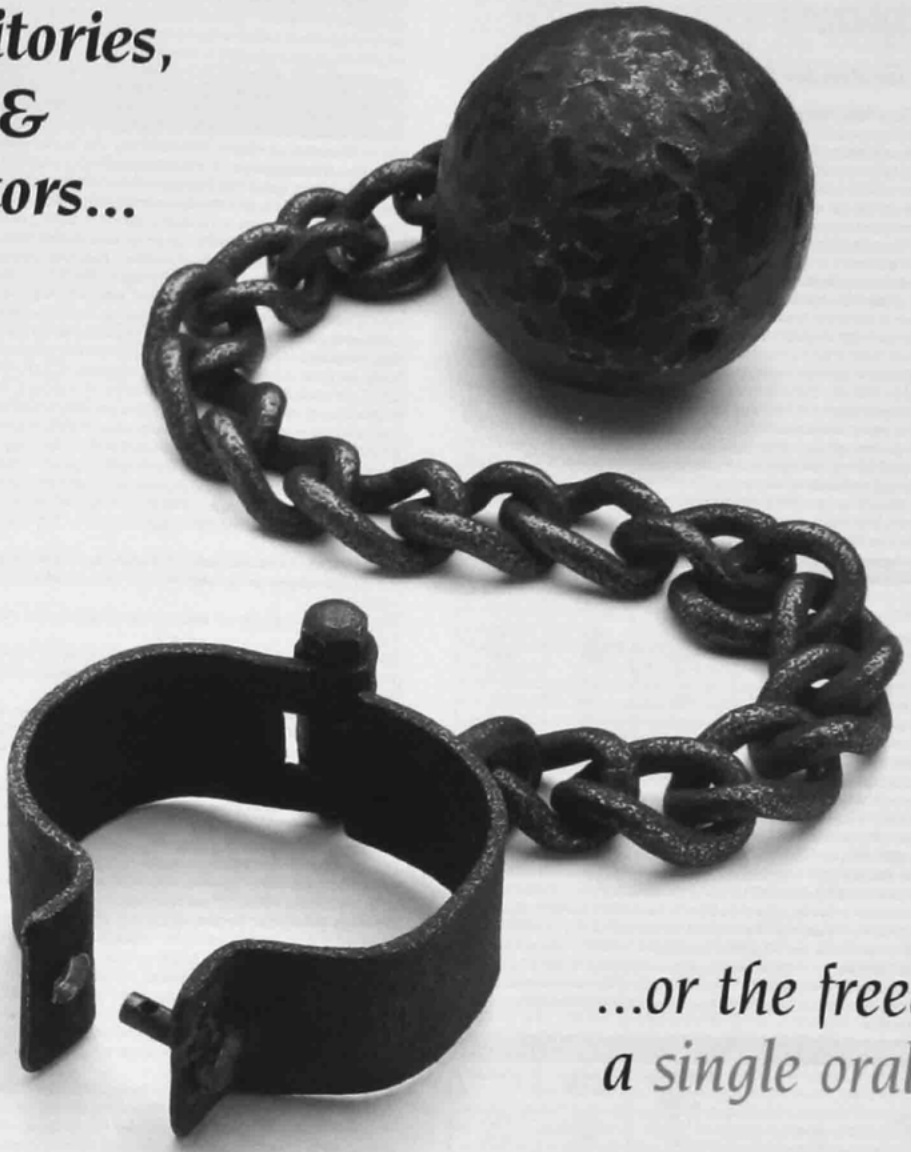
Suppositories, creams & applicators...



...or the freedom of a single oral dose?

Pr Diflucan-150*

(fluconazole / pfizer)

Simple and preferred for vaginal yeast infections.[1†]

In clinical studies of Diflucan-150, the most common side effects were headache, nausea, abdominal pain and diarrhea. Most side effects were mild-to-moderate in nature. The dosing convenience of oral, single-dose Diflucan-150 should be considered in light of the acceptability of its side effect profile relative to that of topical therapies.

†88% of patients preferred Diflucan-150 over creams and vaginal inserts in an open study of 1017 women.

Reference: 1. Phillips RJM et al. An open multicenter study of the efficacy and safety of a single dose of fluconazole 150 mg in the treatment of vaginal candidiasis in general practice. *Br J Clin Pract* 1990;44:219-222.

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We're part of the cure

COPAXONE™
(glatiramer acetate for injection)

20 mg, single use vials for Subcutaneous Injection

Therapeutic Classification: Immunomodulator

PHARMACOLOGY – COPAXONE™ [glatiramer acetate (formerly known as copolymer-1) for injection] is a sterile, lyophilized mixture of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine with an average molar fraction of 0.141, 0.427, 0.095 and 0.338, respectively. The mechanism(s) by which glatiramer acetate exerts its effect on Multiple Sclerosis (MS) is (are) unknown. Pre-clinical study results suggest that glatiramer acetate may modulate immune processes that are currently thought involved in the pathogenesis of MS. In particular, glatiramer acetate has been shown to reduce the incidence and severity of experimental allergic encephalomyelitis (EAE), a condition which may be induced in several animal species through immunization against CNS derived material containing myelin and an often used experimental animal model of MS. Because the immunological profile of glatiramer acetate remains to be fully elucidated, concerns exist about its potential to alter naturally occurring immune responses (See Precautions).

Pharmacokinetics – There is no information regarding the absorption, distribution, metabolism or excretion profile of COPAXONE™ (glatiramer acetate for injection) in humans as appropriate pharmacokinetic studies have not been done. Based on preclinical studies it is assumed that a large fraction of a subcutaneously administered dose of glatiramer acetate would be hydrolyzed locally. Some fraction of injected material is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

Clinical Studies – The efficacy of COPAXONE™ (glatiramer acetate for injection) was evaluated in two similarly designed placebo-controlled trials in patients with relapsing-remitting MS (RR-MS). In both these studies, a dose of 20 mg/day was used. No other dose of glatiramer acetate has been evaluated in this patient population. The first was a pilot study (Trial I) which was conducted at a single-centre and was a double-blind, randomized, matched-pair, parallel group placebo-controlled trial. Fifty patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n = 25) or placebo (n = 25) subcutaneously. The protocol specified primary outcome measure was the proportion of patients who were relapse free during the 2 year duration of the trial, but two additional relevant outcomes were also specified as endpoints: frequency of attacks during the trial, and the change in the number of attacks compared to the rate of attacks in the 2 years prior to study entry. Results from this study (see Table 1) provided preliminary evidence of effectiveness.

Table 1 Outcome	Trial I*		
	Glatiramer acetate n=25	Placebo n=25	p-Value
Mean relapse rate (2 years)	0.6	2.4	0.005
% Relapse free	56%	28%	0.085
Change in Relapse rate	3.2	1.6	0.025
Median Time to first Relapse (days)	>700	150	0.03
% of patients progression free*	80%	52%	0.07

* The primary efficacy measure for Trial I was the proportion of patients who were relapse free during the 2 year duration of the trial (% Relapse Free). Analyses were based on the intent-to-treat population.

* Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months.

Trial II was a multicentre double-blind, randomized, placebo-controlled trial. Two hundred and fifty-one patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n = 125) or placebo (n = 126) subcutaneously. Patients were diagnosed with RR-MS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients had a score of no more than 5 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 5 is defined as one at which a patient is still ambulatory but for whom full daily activities are impaired due to disability; a score of 6 is defined as one at which the patient is still ambulatory but requires assistance and a score of 7 on this scale means that the patient requires a wheelchair. Patients were seen every 3 months for 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the lesion for at least 48 hours). The protocol specified primary outcome measure was the mean two-year relapse rate. Table 2 shows results of the analysis of primary and secondary outcome measures from Trial II based on the intent-to-treat population.

Table 2 Outcome	Trial II*		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean relapse rate (2 years)	1.19	1.68	0.055
% Relapse free	34%	27%	0.25
Median Time to first Relapse (days)	287	198	0.23
% of patients progression free*	78%	75%	0.48
Mean change in EDSS	-0.05	+0.21	0.023

* The primary efficacy measure for Trial II was the mean two-year relapse rate [Mean relapse rate (2 years)]. Analyses were based on the intent-to-treat population.

* Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months.

The effects of glatiramer acetate on relapse severity were not evaluated in either trial.

Both studies showed a beneficial effect of glatiramer acetate on relapse rate, and on this basis glatiramer acetate is considered effective.

INDICATIONS – For use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis to reduce the frequency of relapses. A correlation between a reduction in attack frequency alone and a decreased risk of future disability remains to be established. The safety and efficacy of COPAXONE™ (glatiramer acetate for injection) beyond 2 years have not been adequately studied in placebo-controlled trials. The safety and efficacy of COPAXONE™ in chronic progressive MS have not been evaluated. COPAXONE™ should only be prescribed by clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

CONTRAINDICATIONS – COPAXONE™ (glatiramer acetate for injection) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS – The only recommended route of administration of COPAXONE™ (glatiramer acetate for injection) injection is the subcutaneous route. COPAXONE™ should not be administered by the intravenous route.

Symptoms of Potentially Cardiac Origin – Approximately 26% of COPAXONE™ patients in the multicentre controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain (see Adverse Reactions: Chest Pain). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see Adverse Reactions: Immediate Post-Injection Reaction), many did not. ECG monitoring was not performed during any of these episodes and the pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New Heart Association Class I and II) and thus the risks associated with COPAXONE™ treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown. COPAXONE™ has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see Adverse Reactions: Immediate Post- Injection Reaction). COPAXONE™ has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE™ in such patients.

PRECAUTIONS – Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE™ (glatiramer acetate for injection). The first injection should be performed under the supervision of an appropriately qualified healthcare professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture-resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

Considerations Involving the Use of a Product Capable of Modifying Immune Responses COPAXONE™ is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. There is also no information on whether COPAXONE™ can alter normal human immune responses, such as the recognition of foreign antigens. It is therefore possible that treatment with COPAXONE™ may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Studies in both the rat and monkey have shown that immune complexes are deposited in renal glomeruli. Furthermore, in a controlled trial of 125 patients with relapsing-remitting MS treated for 2 years with 20 mg/day COPAXONE,™ serum IgG levels reached approximately 3 times baseline values in 80% of patients within 3 to 6 months of treatment. These values returned to about 50% greater than baseline during the remainder of treatment. Although COPAXONE™ is intended to attenuate the autoimmune response to myelin, whether chronic treatment with COPAXONE,™ and in consequence, continued alteration of cellular immunity can result in detrimental effects is unknown. Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats are still in progress.

Drug Interactions – Interactions between COPAXONE™ and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE™ with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE™ has not been formally evaluated in combination with Interferon beta. However, 10 patients who switched from therapy with Interferon beta to COPAXONE™ have not reported any serious and unexpected adverse events thought to be related to treatment.

Use in Pregnancy – There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During three clinical trials with COPAXONE,™ seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies.

Nursing Mothers – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE™ should only be considered after careful risk/benefit assessment and be used with caution.

Use in Children – The safety and effectiveness of COPAXONE™ have not been established in individuals below 18 years of age.

Use in the Elderly – COPAXONE™ has not been studied in the elderly (> 65 years old).

Use in Patients with Impaired Renal Function – The pharmacokinetics of COPAXONE™ in patients with impaired renal function have not been determined.

ADVERSE REACTIONS – Approximately 850 MS patients and 50 healthy volunteers have received at least one dose of COPAXONE™ (glatiramer acetate for injection) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE™ in clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), and to over 5 years (28 patients) at a daily dose of 20 mg.

In controlled clinical trials the most commonly observed adverse event associated with the use of COPAXONE™ which occurred at a higher frequency than in placebo treated patients were: injection site reactions, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia. Of a total of 844 patients who could be evaluated for safety, approximately 8% discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness and tremor. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE™ treatment included a case of life threatening serum sickness.

Immediate Post-Injection Reaction – Approximately 10% of Multiple Sclerosis patients exposed to COPAXONE™ in pre-marketing studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE.™ Symptoms experienced could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria. These symptoms were invariably transient, self-limited, did not require specific treatment and in general arose after several months after initiation of treatment, although they may occur earlier in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE.™ Whether these episodes are mediated by an immunologic or non-immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown.

Chest Pain – Approximately 26% of glatiramer acetate patients in the multicentre controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. ECG monitoring was not performed during any of these episodes. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II) therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown. Table 3 lists the adverse experiences after up to 35 months of treatment (> 27 - 33 months: COPAXONE,™ n = 84; Placebo, n = 75; > 33 months: COPAXONE,™ n = 12; Placebo, n = 24) in the multicentre placebo-controlled study (Trial II) in relapsing-remitting Multiple Sclerosis patients that occurred at an incidence of at least 2% among patients who received COPAXONE™ and at an incidence that was at least 2% more than that observed in the same trial for placebo patients regardless of their causal relationship to treatment. No laboratory adverse experiences that met these criteria were reported. It should be noted that the figures cited in Table 3 cannot be used to predict the incidence of side effects during the course of usual medical practice, where patient characteristics and other factors differ from those that prevailed in the clinical trials. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Other events which occurred in at least 2% of patients but were present at equal or greater rates in the placebo group included:

Body as a whole – Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis and malaise.

Digestive System – Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth.

Musculoskeletal – Myasthenia and myalgia

Nervous System – Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder.

Respiratory System – Pharyngitis, sinusitis, increased cough and laryngitis.

Skin and Appendages – Acne, alopecia, and nail disorder

Special Senses – Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness.

Urogenital System – Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 92% of patients were Caucasian, which is representative of the population of patients with Multiple Sclerosis. In addition, the vast majority of patients treated with COPAXONE™ were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups. Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE™. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE™ and placebo groups in blinded clinical trials. No patient receiving COPAXONE™ withdrew from any trial due to abnormal laboratory findings.

Table 3. Adverse Experiences ≥ 2% Incidence and ≥ 2% Above Placebo

Adverse Experience	COPAXONE™ (n=125) n	%	Placebo (n=126) n	%
Body as a Whole				
Injection Site Pain	83	66.4	46	36.5
Asthenia	81	64.8	78	61.9
Injection Site Erythema	73	58.4	17	13.5
Injection Site Pruritus	48	38.4	5	4.0
Flu syndrome	38	30.4	34	27.0
Injection Site Inflammation	35	28.0	9	7.1
Back pain	33	26.4	28	22.2
Chest pain	33	26.4	13	10.3
Injection Site Mass	33	26.4	10	7.9
Injection Site Induration	25	20.0	1	0.8
Injection Site Welt	19	15.2	5	4.0
Neck pain	16	12.8	9	7.1
Face Edema	11	8.8	2	1.6
Injection Site Urticaria	9	7.2	0	.0
Injection Site Hemorrhage	8	6.4	4	3.2
Chills	5	4.0	1	0.8
Cyst	5	4.0	1	0.8
Injection Site Reaction	4	3.2	1	0.8
Injection Site Atrophy	3	2.4	0	.0
Abscess	3	2.4	0	.0
Cardiovascular				
Vasodilatation	34	27.2	14	11.1
Palpitation	14	11.2	6	4.8
Migraine	9	7.2	5	4.0
Syncope	8	6.4	4	3.2
Digestive				
Nausea	29	23.2	22	17.5
Vomiting	13	10.4	7	5.6
Anorexia	6	4.8	3	2.4
Gastroenteritis	6	4.8	2	1.6
Oral Moniliasis	3	2.4	0	.0
Tooth Caries	3	2.4	0	.0
Hemic and Lymphatic				
Lymphadenopathy	23	18.4	12	9.5
Ecchymosis	15	12.0	12	9.5
Metabolic and Nutritional				
Peripheral Edema	14	11.2	7	5.6
Weight gain	7	5.6	0	.0
Edema	5	4.0	1	0.8
Musculo-Skeletal				
Arthralgia	31	24.8	22	17.5
Nervous System				
Hypertonia	44	35.2	37	29.4
Tremor	14	11.2	7	5.6
Agitation	7	5.6	4	3.2
Confusion	5	4.0	1	0.8
Nystagmus	5	4.0	2	1.6
Respiratory				
Rhinitis	29	23.2	26	20.6
Dyspnea	23	18.4	8	6.3
Bronchitis	18	14.4	12	9.5
Skin and Appendages				
Sweating	15	12.0	10	7.9
Erythema	8	6.4	4	3.2
Skin Disorder	5	4.0	2	1.6
Skin Nodule	4	3.2	1	0.8
Wart	3	2.4	0	.0
Special Senses				
Ear Pain	15	12.0	12	9.5
Eye Disorder	8	6.4	1	0.8
Urogenital System				
Urinary Urgency	20	16.0	17	13.5
Vaginal Moniliasis	16	12.8	9	7.1
Dysmenorrhea	12	9.6	9	7.1
Unintended Pregnancy	4	3.2	0	.0
Impotence	3	2.4	0	.0

Other Adverse Events Observed During All Clinical Trials – COPAXONE™ has been administered to approximately 900 individuals during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. The frequencies presented represent the proportion of the 860 individuals exposed to COPAXONE™ who had data available for this determination. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and those not reasonably related to drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: Frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a whole – *Frequent:* Injection site edema, injection site atrophy, and abscess ***Infrequent:*** Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma and photosensitivity reaction.

Cardiovascular – *Frequent:* Hypertension. ***Infrequent:*** Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive – *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration and duodenal ulcer.

Endocrine – *Infrequent:* Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal – *Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

Hemic and Lymphatic – *Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional – *Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal – *Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous – *Frequent:* Abnormal dreams, emotional lability, and stupor. ***Infrequent:*** Ataxia, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, paranoid reaction, paraplegia, psychotic depression and transient stupor.

Respiratory – *Frequent:* Hyperventilation. ***Infrequent:*** Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages – *Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy and warts. ***Infrequent:*** Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses – *Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital – *Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, and vaginal hemorrhage. ***Infrequent:*** Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE – Overdose with COPAXONE™ has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE™ at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE™ at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow-up several hours later produced no report of adverse experiences from either patient.

DOSAGE AND ADMINISTRATION – *COPAXONE™ should only be prescribed by clinicians who have experience in the diagnosis and management of Multiple Sclerosis.* The recommended dose of COPAXONE™ (glatiramer acetate for injection) for the treatment of relapsing-remitting MS is a daily injection of 20 mg given subcutaneously.

Instructions for Use – To reconstitute lyophilized COPAXONE™ for injection, use a sterile syringe and needle to transfer 1.1 mL of the diluent supplied, Sterile Water for injection, into the COPAXONE™ vial. Gently swirl the vial of COPAXONE™ and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist before use if it contains particulate matter. Use within 8 hours after reconstitution. Withdraw 1.0 mL of the solution into a sterile syringe fitted with a new 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include arms, abdomen, hips, and thighs. A vial is suitable for single use only; unused portions should be discarded.

COMPOSITION – COPAXONE™ (glatiramer acetate for injection) is a sterile, lyophilized drug product, intended for subcutaneous injection following reconstitution with Sterile Water for injection. Each vial of lyophilized drug product contains 20 mg glatiramer acetate, plus a 2 mg overage to allow for losses in reconstitution and transfer, and 40 mg mannitol. Each vial of Sterile Water for injection contains 1.0 mL of Sterile Water for injection plus a 0.2 mL overage to allow for losses in reconstitution and transfer.

STABILITY AND STORAGE RECOMMENDATIONS – Vials of lyophilized COPAXONE™ should be stored under refrigeration (2 - 8°C). The vials of diluent should be stored at room temperature.

Reconstituted Solutions – To reconstitute lyophilized COPAXONE™ prior to injection, use a sterile syringe and 25-gauge needle to transfer the diluent supplied, Sterile Water for injection, into the COPAXONE™ vial. Gently swirl the vial of COPAXONE™ and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist if it contains particulate matter. Soon after the product is completely dissolved, withdraw 1.0 mL of the solution into a sterile syringe fitted with a new 27-gauge needle and inject the solution subcutaneously. A vial is suitable for single use only; unused portions should be discarded. The reconstituted solution should not be left longer than 8 hours at room temperature.

Parenteral Products – COPAXONE™ should be reconstituted only with the provided diluent, Sterile Water for injection.

Vial Size	2 mL
Volume of Diluent to be Added	1.1 mL
Volume to be Injected	1.0 mL
Nominal Concentration per mL	20 mg

AVAILABILITY OF DOSAGE FORMS – COPAXONE™ (glatiramer acetate for injection) is supplied as a 20 mg dose of sterile lyophilized glatiramer acetate with mannitol, packaged in single use 2 mL vials. A separate vial, containing 1.1 mL of diluent (Sterile Water for injection) plus 0.1 mL of overage of diluent is included for each vial of drug. COPAXONE™ is available in packs of 32 amber vials of sterile lyophilized material for subcutaneous injection. The diluent (Sterile Water for injection) for COPAXONE™ is supplied in packs of 32 clear vials. Product Monograph available upon request.

References

1. Johnson, KP et al, Extended use of glatiramer acetate (COPAXONE™) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability, Neurology, vol. 50, 3:701-709, March 1998. **2.** Johnson, KP et al, Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis, Neurology, 45:1268-1275, July 1995. **3.** COPAXONE™ Product Monograph, Teva Marion Partners Canada.

COPAXONE™
(glatiramer acetate for injection)

SHARED SOLUTIONS™

1-800-283-0034

TEVAMARION™ PARTNERS

www.tevamarion.com

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PAAB
CCPP

SUSTAINED EFFICACY

Kate's physician chose COPAXONE™ because it keeps working.†[1,2] Kate isn't giving in to MS.*

Kate H.
Burlington, Ontario

PROVEN COMPLIANCE

Claire's physician chose COPAXONE™ because it's generally well-tolerated.[1,2,3] It's one she could start on and stay with.*

Claire S.
La Salle, Québec

For information on **Shared Solutions,™** a free patient support program for healthcare professionals and their patients:
1-800-283-0034
info@tevamarion.com

1-800-283-0034

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COPAXONE™
(glatiramer acetate for injection)

† mean number relapses (24 mos) COPAXONE™ 1.19: Placebo 1.68 (p=0.007)[2]
*Not actual patient case study.

COPAXONE™ (immunomodulator) is indicated for reduction of the frequency of relapses in ambulatory patients with relapsing-remitting multiple sclerosis. A correlation between reduction in attack frequency alone and decreased risk of future disabilities remains to be established. Safety and efficacy beyond 2 years have not been adequately studied in placebo-controlled trials. Safety and efficacy in chronic progressive MS have not been evaluated. The most commonly observed adverse events (>20%) include (not all adverse events were related to treatment): injection site reactions (2.4%-66.4% depending on reaction), vasodilation (27.2%), chest pain (26.4%), hypertonia (35.2%), asthenia (64.8%), flu syndrome (30.4%), back pain (26.4%), nausea (23.2%), arthralgia (24.8%), rhinitis (23.2%).

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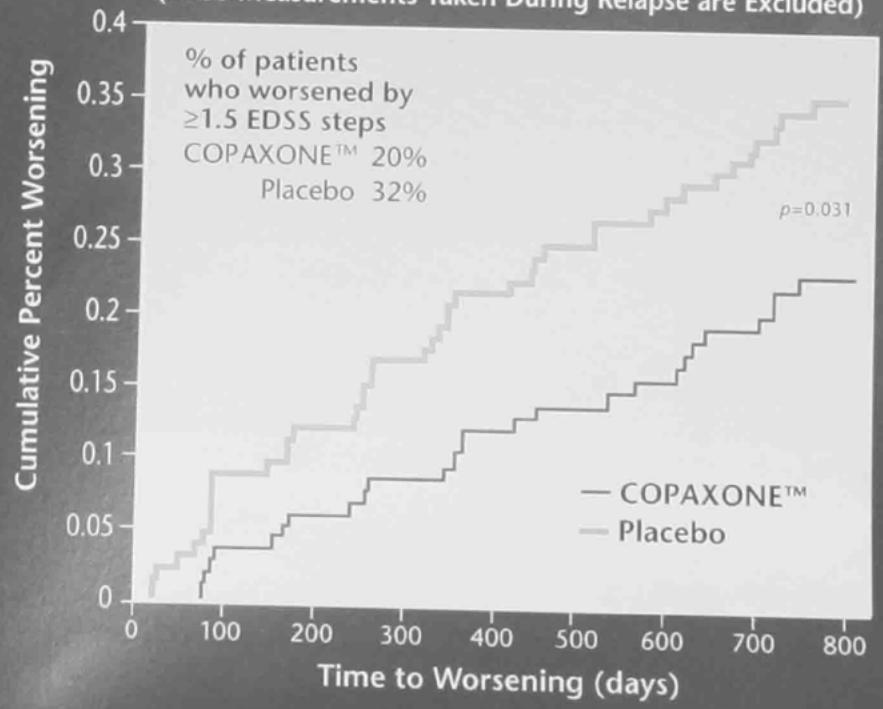
In relapsing-remitting multiple sclerosis:

Why are neurologists choosing PrCOPAXONE™?

(glatiramer acetate for injection)

Effect of COPAXONE™ on neurologic function in randomized, placebo-controlled trial. (n=251)

(EDSS Measurements Taken During Relapse are Excluded)

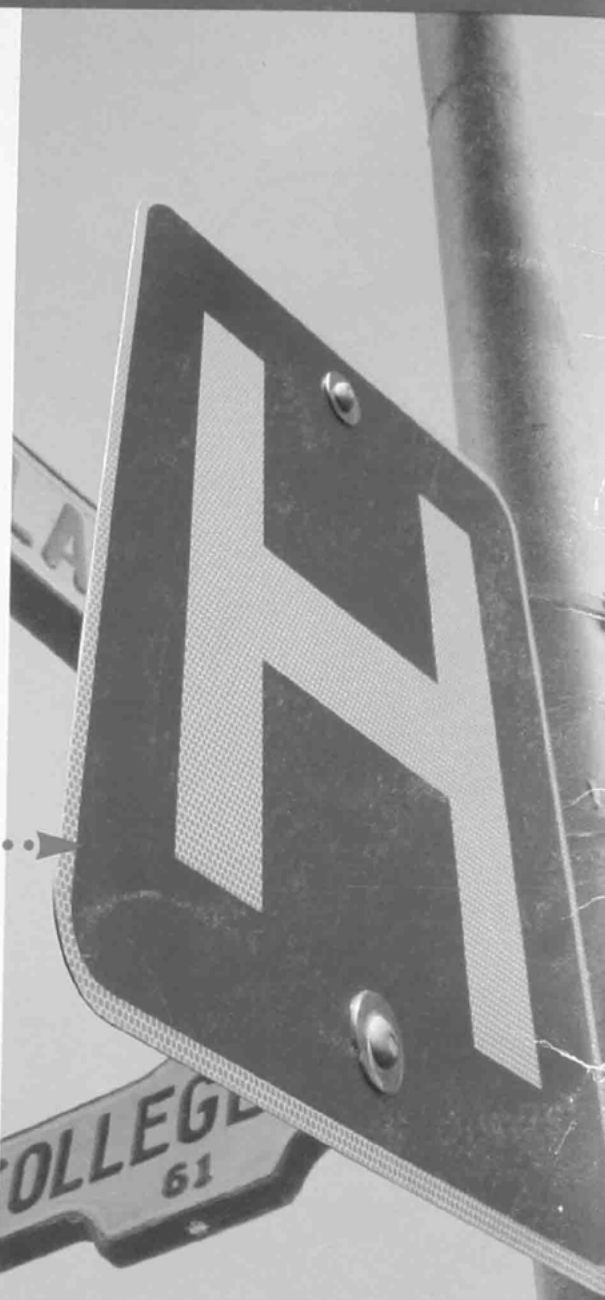


Adapted from Johnson, KP et al.[1]

The body of evidence continues to grow for triple therapy in CHF...

PrLANOXIN® in combination with an ACE inhibitor and diuretic (triple therapy) proves more beneficial than dual therapy (ACE inhibitor and diuretic) in CHF*

HELP REDUCE YOUR CHF PATIENTS' CHANCES OF COMING HERE



- *Reduced risk of hospitalization due to worsening heart failure*[1]
- *Delayed progression of disease in mild to moderate CHF*[2]
- *Improved feeling of general well-being with fewer symptoms*[2]
- *Greater exercise tolerance and endurance*[2]
- *Proven safety profile*[1†]

*DIG study: 6,800 patients with mild (68%), moderate (30%), or severe (2%) CHF.[1] RADIANCE study: NYHA Class II-III CHF.[2]
†Only 2% hospitalized for suspected toxicity in the digoxin group vs. 1% in the placebo group. Suspected toxicity was 11.9% in the digoxin group versus 7.9% in the placebo group. Among these patients, 16.5% in the digoxin group were hospitalized versus 11.4% in the placebo group.[1] Overall in clinical trials only 1-4% of patients experienced adverse reactions considered serious.[3]
Digoxin dosage should be individualized and based upon clinical assessment of each patient.[3]

P LANOXIN®
digoxin

A classic therapy improving today's health outcomes in CHF

GlaxoWellcome

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