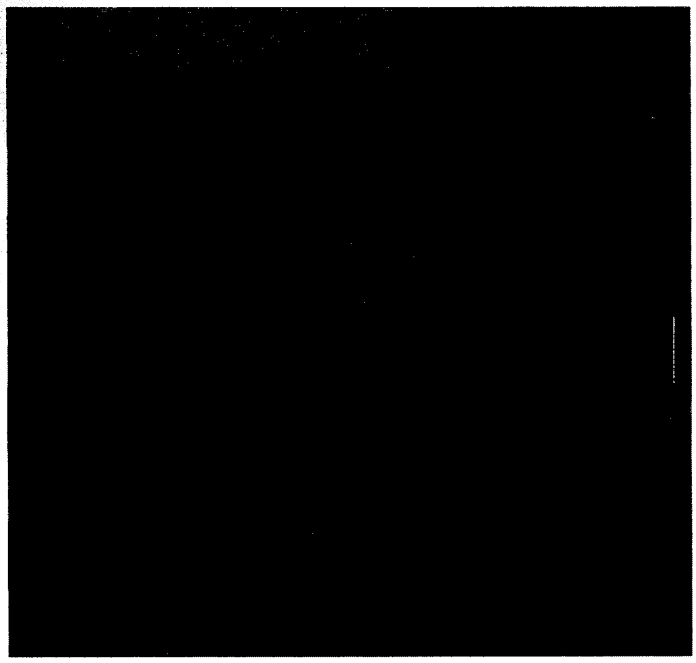
KEY WORDS OF MODERN ANTIFUNGAL THERAPY

CYTOCHROME P450

OR WHAT'S IN A NAME...



The metabolism of fungi is almost identical to that of other eukaryotic organisms, such as humans. Therefore, trying to design a systemic drug that kills fungi without harming their human host means searching for infinitesimal differences in metabolic pathways.

Selective precision for the metabolic pathways in fungi, as distinct from those in humans, remains the key determinant for any systemic antimycotic, regardless of its point of biochemical interaction. This precision has been achieved to an exceptional degree with itraconazole, alias Sporanox*, because it selectively inactivates the fungal cytochrome P450 only.

Figure 1 is a simplified illustration of one of the pathways for the enzymatic ergosterol synthesis in fungal cell membranes. (Ergosterol is essential for the structural cohesion of these membranes). Pharmacologically one can disrupt this process at two distinct points. The first is where squalene is made into an oxide. Alternatively, one can interfere where lanosterol is converted into ergosterol, by inactivating **cytochrome P450** – a chemical catalyst that performs a vital function in the enzymatic reaction. The broadest research experience to date has been gathered with the latter approach. Importantly, in view of the close similarities between the enzymatic processes in fungi and humans, either approach must be highly selective in disrupting the fungal enzyme systems only.

Sporanox*

itraconazole

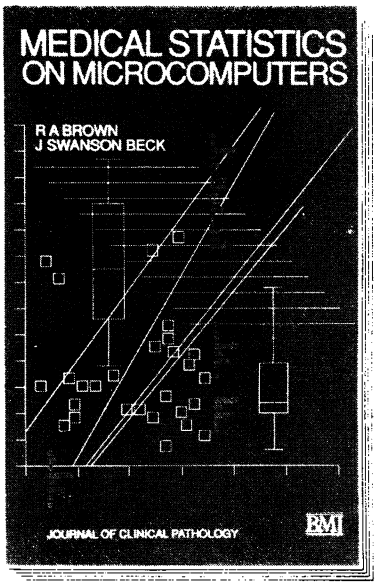
SHORT AND SIMPLE ORAL THERAPY

standard dose in dermatomycoses: 1 capsule (100 mg) once daily for 15 days
standard dose in vaginal candidosis: 2 x 2 capsules (400 mg) for 1 day only

*** Trademarks: SPORANOX, SEMPERA, SISTIZOL, TRISPORAL.**

JANSSEN PHARMACEUTICA
2340 Beerse, Belgium
expertise in antimycotic research

Properties: Sporanox (itraconazole), a triazole derivative, is orally active against infections with dermatophytes (*Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum*), yeasts (*Candida* spp., *Pityrosporum* spp.), *Aspergillus* spp. and various other yeasts and fungi. **Indications:** Sporanox (itraconazole) is indicated for vulvovaginal candidosis, pityriasis versicolor, dermatophytoses, fungal keratitis and oral candidosis. **Dosage and administration:** Vulvovaginal candidosis: 2 capsules (200 mg) morning and evening for 1 day. Pityriasis versicolor: 2 capsules (200 mg) once daily for 7 days. - Tinea corporis, tinea cruris, tinea pedis, tinea manus: 1 capsule (100 mg) daily for 15 days; highly keratinized regions, as in plantar tinea pedis and palmar tinea manus, require 1 capsule (100 mg) daily for 30 days. - Oral candidosis: 1 capsule (100 mg) daily for 15 days. - Fungal keratitis: 2 capsules (200 mg) once daily for 21 days. **Contra-indications:** Sporanox (itraconazole) is contra-indicated during pregnancy. **Warnings and precautions:** Although clinically Sporanox (itraconazole) has not been associated with [illegible] it is advisable not to give this drug to [illegible] known history of liver disease. [illegible] recommended not to breast feed [illegible] (itraconazole). **Drug** [illegible] be given concomitantly [illegible]



UK £8.95; Abroad £10.50; US$25.00
BMA members: £8.45 or £10.00
ACP members: US$21.00

How is no longer a problem — but there's still which and why

The microcomputer revolution has made powerful machines and highly complex programs generally available. This means that users of statistical techniques need no longer be concerned with the arithmetical and algebraic details — the software will take care of all that. What is vital, however, is to understand the ideas and the basic principles of statistical analysis. In *Medical Statistics on Microcomputers* R A Brown and J Swanson Beck show how to get the best use out of microcomputers when analysing data, particularly in the pathology laboratory. They explain the rational basis of various widely applicable statistical methods and also indicate their limitations so that you can make an informed choice. Chapters include:

- Data handling
- Analysis of data from one or two groups
- Comparison of several groups
- Analysis of categorical data
- Statistical methods for diagnostic tests.

Let the BMJ guide you through statistics:

STATISTICS WITH CONFIDENCE — Confidence intervals and statistical guidelines. Martin J Gardner, Douglas G Altman.
Many medical journals, including the *British Medical Journal,* now expect scientific papers submitted to them to contain confidence intervals when appropriate. Why? what are they? and how do you calculate them? *Statistics With Confidence* tells you. A clear explanation of the reasons for using confidence intervals is followed by detailed presentation of methods of calculation, including numerous worked examples and specially compiled tables. To make things even easier, a computer programme, Confidence Interval Analysis (CIA), for calculating confidence intervals, has been specially designed by Martin Gardner and details are available from the Publishing Department, *British Medical Journal* (or the American College of Physicians).
UK £7.95; Abroad £9.50; US$24.00 BMA members £7.45 or £9.00 ACP members US$19.00

STATISTICS AT SQUARE ONE — T D V Swinscow
The statistical testing of data is indispensable in many types of medical investigation and a help on countless occasions in clinical practice. This book provides step by step instruction. Subjects covered include standard deviation, X^2 tests, t tests, non-parametric tests, and correlation. The book includes sections on Fisher's exact probability test and rank correlation. Methods specially adapted to pocket calculators.
UK £3·95; Abroad £5.00; US$13.00 BMA members £3.45 or £4.50 ACP members US$11.00

STATISTICS IN PRACTICE — Sheila M Gore, Douglas G Altman
No doctor can afford to ignore statistics: most modern medical research uses statistics. This important and authoritative book provides clear information on designing studies, applying statistical techniques, and interpreting studies that use statistics. It can be easily understood by those with no statistical training and should be read by all those who want to keep abreast of new developments.
UK £8.95; Abroad £11.00; US$23.00 BMA members £7.95 or £10.00 ACP members US$19.00

EPIDEMIOLOGY FOR THE UNINITIATED — Geoffrey Rose, D J P Barker
Epidemiology has its own techniques of data collection and interpretation and its necessary jargon of technical terms, and in *Epidemiology For The Uninitiated* the authors guide the novice expertly through the theory and practical pitfalls. The second edition of this popular *BMJ* handbook has been revised to include further details of epidemiological methods and some of their more dramatic applications, such as the investigations on the Spanish cooking oil epidemic, and AIDS.
UK £4·95; Abroad £6.00; US$14.00 BMA members £4.45 or £5.50 ACP members US$12.00

ORDER FORM

BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE, *any leading bookseller, or the BMJ/BMA bookshop.*
North America only: AMERICAN COLLEGE OF PHYSICIANS, P.O. Box 7777-R-0270, Philadelphia, PA 19175. In Pennsylvania, add 6% sales tax. Residents of Canada add 7% GST.

Please send me _____ copy/ies of the following BMJ books _____

_____ Membership no. _____

I enclose a cheque for _____ made payable to **British Medical Journal.** Debit my credit card (please tick box)

☐ Visa ☐ American Express ☐ Mastercard Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiry Date _____ Signature _____

NAME _____

ADDRESS _____

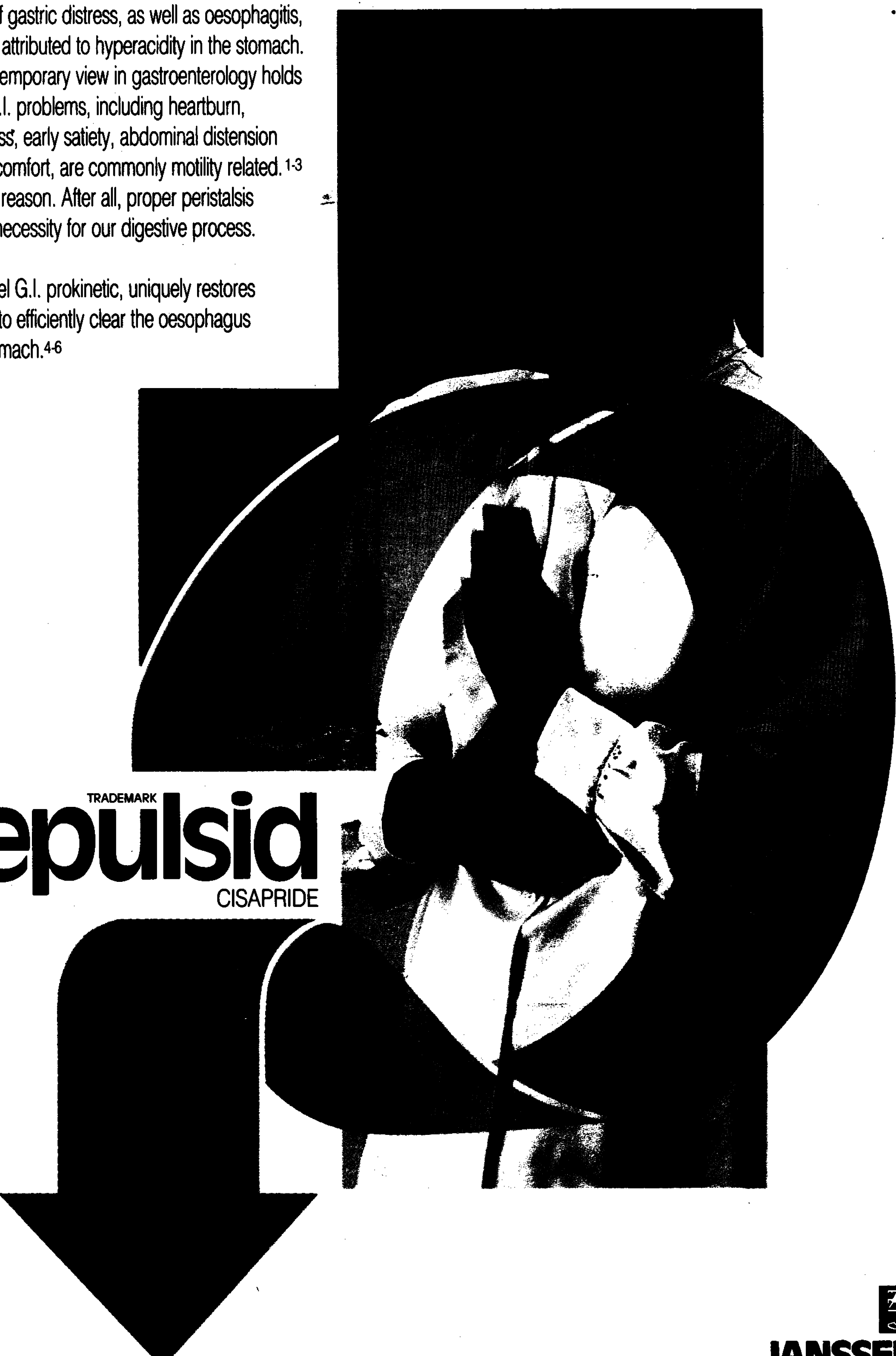
_____ POSTCODE _____

All prices include postage, by air abroad.

gastric distress & oesophagitis
hyperacidity or dysmotility?

Most complaints of gastric distress, as well as oesophagitis, are conventionally attributed to hyperacidity in the stomach. However, the contemporary view in gastroenterology holds that most upper G.I. problems, including heartburn, postprandial fullness, early satiety, abdominal distension and epigastric discomfort, are commonly motility related.[1-3] And this stands to reason. After all, proper peristalsis is a physiological necessity for our digestive process.

Prepulsid, the novel G.I. prokinetic, uniquely restores healthy peristalsis to efficiently clear the oesophagus and empty the stomach.[4-6]



TRADEMARK
Prepulsid
CISAPRIDE

restores upper G.I. motility like no other agent.

JANSSEN
PHARMACEUTICA
B-2340 Beerse, Belgium

expertise in digestive motility

References: 1. Knuff, J.E., *et al.*: Dig. Dis. Sci. 29, 194 (1984). 2. Kahrilas, J.P., *et al.*: Gastroenterology 91, 897 (1986). 3. Malagelada, J.R., *et al.*: Gastroenterol. 88, 1223 (1985). 4. Ceccatelli, P., *et al.*: Gut 29, 631 (1988). 5. Collins, B.J., *et al.*: Hepato-Gastroenterol. 34, 113 (1987). 6. Jian, R., *et al.*: Dig. Dis. Sci. 34, 657 (1989).

Prescribing Information - Prepulsid (cisapride) is a gastro-intestinal prokinetic agent. Prepulsid enhances and co-ordinates gastro-intestinal propulsive motility, thereby preventing stasis and reflux. **Therapeutic indications:** 1. Gastroparesis. 2. Symptoms of X-ray or endoscopy negative upper digestive discomfort. 3. Gastro-oesophageal reflux disorders, including oesophagitis. 4. Intestinal pseudo-obstruction. **Contra-indications:** No absolute contra-indications are known. **Precautions:** *Pregnancy:* Although, in animals, there is no effect on primary fertility, no primary embryotoxic and no teratogenic effect, the anticipated therapeutic benefits should be weighed against the potential hazards before Prepulsid is given during pregnancy, especially during the first trimester. *Nursing mothers:* Although the excretion in breast milk is minimal, nursing mothers are advised not to breast feed while taking Prepulsid. *Driving and machine-operating ability:* Prepulsid does not affect psychomotor function and does not induce sedation or drowsiness. Prepulsid may, however, accelerate the absorption of central nervous system depressants, such as barbiturates and alcohol. Caution should therefore be exercised when Prepulsid is administered with these drugs. **Interactions:** - The acceleration by Prepulsid of gastric emptying may affect the rate of absorption of drugs: absorption of drugs from the stomach may be diminished, whereas absorption of drugs from the small bowel may be accelerated (e.g. benzodiazepines, anticoagulants, paracetamol, H_2-blockers). - In patients receiving anticoagulants, the coagulation times may somewhat increase. It is advisable to check the coagulation time one week after the start of Prepulsid treatment to adapt the anticoagulant dose if necessary. - The effects of Prepulsid on gastro-intestinal motility are, for the most part, antagonized by anticholinergic drugs. - In hepatic and renal insufficiency, it is recommended to halve the initial daily dose. Subsequently, this dose can be adapted, depending on the therapeutic effects or possible side-effects. - In the elderly, steady-state plasma levels are generally higher, due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger patients. - In the case of drugs that require individual titration, it may be useful to monitor plasma levels of such drugs when Prepulsid is associated. **Adverse reactions:** In line with the pharmacological activity of Prepulsid, transient abdominal cramping, borborygmi and diarrhoea may occur. Mild and transient headache or lightheadedness have been reported occasionally. When diarrhoea occurs in babies or infants, the dose should be reduced. There have been isolated reports of convulsive seizures without clearcut relationship to Prepulsid. **Dosage:** - Adults: according to the severity of the condition, 5 or 10 mg of Prepulsid, 2 to 4 times daily, to be taken as tablets or as oral suspension (the full plastic 5-ml spoon contains 5 mg). As a rule the following doses have proven adequate: • less severe conditions: 5 mg t.i.d. (dose can be doubled); • severe conditions (gastroparesis, oesophagitis, refractory constipation): 10 mg t.i.d. to 10 mg q.i.d. (before the 3 main meals and before retiring). - Infants and children: on the average 0.2 mg/kg per intake, 3 to 4 times daily. For the suspension, intakes are indicated on the dosing pipet as a function of body weight.
Full prescribing information available on request.

Note: Prepulsid (cisapride) is not yet available in all countries and not all indications have been approved everywhere.