MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

MEDICINE SAFETY ALERT: INTERACTION BETWEEN KETOCONAZOLE AND DOMPERIDONE AND THE RISK OF QT PROLONGATION

MEDICINE SAFETY ALERT

The Medicines Control Council alerts all health care professionals to safety information regarding the potential risk of interactions when domperidone is administered concomitantly with ketoconazole or possibly with other concomitantly administered medicines.

QT prolongation, ventricular tachyarrhythmias and sudden deaths have been reported following intravenous administration of domperidone in cancer patients. Domperidone has been shown to possess cardiac electrophysiological effects such as prolongation of cardiac repolarisation at normal doses. [1, 2]

The main metabolic pathway of domperidone is via the cytochrome P450 3A4 (CYP3A4) isoenzyme. *In vitro* data indicate that the concomitant use of medicines that significantly inhibit this enzyme may result in increased plasma concentrations of domperidone. Examples of CYP3A4 inhibitors include azole antifungals, macrolide antibiotics (e.g. erythromycin, azithromycin, roxithromycin, clarithromycin), HIV protease inhibitors (e.g. ritonavir) and grapefruit juice.

Co-administration of ketoconazole with domperidone is contraindicated.

Studies in healthy volunteers have identified an interaction between domperidone and ketoconazole, showing a three- to ten- fold increase in maximum plasma concentration (C_{max}) and area under the time-concentration curve (AUC) of domperidone. In one of these studies, ketoconazole was found to inhibit metabolism of domperidone by inhibition of CYP3A4 mediated first pass metabolism, resulting in an approximately three fold increases in C_{max} and AUC, when compared to the administration of domperidone alone.

A QT prolongation (about 10 to 20 msec) was observed when domperidone (10 mg four times daily) was administered concomitantly with ketoconazole (200 mg twice daily) but not for domperidone alone at a dosage of 10 mg four times daily.[3] The QTc prolonging effect of this combination (i.e. with ketoconazole) is not completely understood and cannot be explained solely by domperidone pharmacokinetic data.

The package inserts of domperidone products are in the process of being updated to reflect this important safety information.

Suspected adverse drug reactions associated with domperidone and other medicines can be reported to the National Adverse Drug Event Monitoring Centre. Tel: 021 447-1618 Fax: 021 448-6181

References:

1. Drolet B., Rousseau G., *et al*. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. Circulation. 2000 Oct 17;102(16); 1883-5
2. Martindale 34th Edition
3. Motilium prescribing information.

UPDATE HISTORY

Date	Reason for update	Version & Publication
July 2006	Typographical errors corrected	May06 v1.1 July 2006