

Domperidone containing products - QTc prolongation

SPC changes agreed by the Pharmacovigilance WP on 25 January 2006

Section 4.4 Special Warnings and Precautions for Use

Cardiovascular disorders

Data from pre-clinical and epidemiological studies suggest that domperidone may prolong the QT-interval. Cardiac arrhythmias may occur, especially in patients prone to the occurrence of QTc prolongation (e.g. Long QT Syndrome, hypokalaemia and concomitant use of medicinal products known to prolong the QT interval).

A slight increase of QT interval (mean less than 10 msec) was reported in a drug-drug interaction study with oral ketoconazol. Therefore alternative therapeutic options should be considered if antifungal treatment is required (see also section 4.5).

Section 4.5 Interactions

A pharmacokinetic study has demonstrated that the AUC and the peak plasma concentration of domperidone is increased by a factor 3 when oral ketoconazol is administered concomitantly (at steady state). A slight QTc prolonging effect (mean less than 10 msec) of this combination was detected, which was greater than the one seen with ketoconazol alone. The results of this interaction study should be taken into account when prescribing domperidone concomitantly with strong CYP3A4 inhibitors: for example ketoconazol, ritonavir and erythromycin (see also section 5.2).

Section 4.8 Undesirable effects

To be added: under cardiovascular disorders:

Rare: QTc prolongation

Very rare : cardiac arrhythmias

Section 5.3

Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In in vitro experiments on isolated cells transfected with HERG and on isolated guinea pig myocytes, ratios were about 10, based on IC50 values inhibiting currents through ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 20 mg (q.i.d.). Drugs which bind to HERG channels at levels less than 30 times the ratio IC50/effective therapeutic plasma levels ($ETCP_{unbound}$) have a three to four times stronger association with serious ventricular arrhythmias and sudden death as an adverse reaction, compared to drugs which bind to HERG channels at concentrations more than 30 times the therapeutic level. The IC50/ $ETCP_{unbound}$ ratio for domperidone is 0.119 and therefore well above the cut off point for the increased risk of cardiac arrhythmia adverse events.