



**Direct Healthcare Professional Communication regarding Fareston®
(toremifene) and prolongation of the QTc interval in a dose-related
manner.**

Dear Healthcare Professional,

The content of this letter has been agreed with the European Authorities. Orion Pharma wishes to inform you that the Summary of Product Characteristics (SPC) will be updated to include new information on prolongation of the QTc interval related to toremifene. The approved therapeutic indication for Fareston 60 mg/day is the first line treatment of hormone dependent metastatic breast cancer in postmenopausal patients.

Summary

Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to toremifene, in the form of QT prolongation. Consequently:

- **Toremifene is therefore contraindicated in patients with:**
 - **Congenital or documented acquired QT prolongation**
 - **Electrolyte disturbances, particularly in uncorrected hypokalaemia**
 - **Clinically relevant bradycardia**
 - **Clinically relevant heart failure with reduced left-ventricular ejection fraction**
 - **Previous history of symptomatic arrhythmias**

- **Toremifene should not be used concurrently with other drugs that prolong the QT interval.**

- **Toremifene should be used with caution in patients with ongoing proarrhythmic conditions (especially elderly patients) such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (including Torsade de Pointes) and cardiac arrest.**

- **If signs or symptoms that may be associated with cardiac arrhythmia occur during treatment with Fareston, treatment should be stopped and an ECG should be performed.**

The product information (Summary of Product Characteristics (SPC)) has been updated (sections 4.3, 4.4, 4.5, 4.8, 4.9 and 5.3) to include this information (see enclosed SPC). A European Commission decision implementing this change is pending.

Further information on the safety concern

Non clinical *in vitro* and *in vivo* studies have evidenced the potential of toremifene and its metabolite to prolong cardiac repolarisation and this can be attributed to the blockade of hERG channels.

Currently, toremifene 20 mg/day and 80mg/day are being studied in prostate cancer indications. Therefore *in vitro* and *in vivo* electrophysiological studies and a QT study



have been sponsored as part of development for the male indications and based on current requirements.

The QT clinical study has been performed in 250 male subjects with a 5-arm parallel design (placebo, moxifloxacin 400 mg, toremifene 20 mg, 80 mg, and 300 mg). The results conclusively demonstrated a strong dose related QTc signal, with the 20 mg dose being positive and the 80 mg dose (21-26 ms) exceeding the threshold (20 ms) for increased likelihood of proarrhythmia. Of note, 4.3% of the subjects also experienced new abnormal U waves with the 80 mg dose. No data regarding the therapeutic dose of 60 mg (used in the current indication) are available. The dose dependency is confirmed by the data on the suprathreshold dose 300 mg (QTc prolongations and occurrence of new abnormal U waves).

Since 1988, Fareston has been granted marketing authorisation in 67 countries. Cumulative exposure is estimated to be over 450 000 patient years. A broad search containing unspecified symptoms, which might represent Torsade de Pointes or QTc prolongation, made in the global Fareston drug safety database yielded 24 individual case safety reports. Most of the cases are doubtful due to the chronology or due to the identification of other possible explanations for the event. However, 6 patients, of whom 2 received 200mg/d, died suddenly and no causes have been identified. Even though most of these 6 cases are poorly documented, it is not possible to exclude a relationship with the product. Additionally, one case of QT prolongation in a hypokaleamic patient receiving toremifene was found.

Call for reporting

Healthcare professionals are reminded to continue to report adverse reactions in accordance with the Medicine and Healthcare products Regulatory Agencies (MHRA) 'Yellow Card' reporting system. In addition, this information may be reported to Orion Pharma (UK) Ltd, Oaklea Court, 22 Park Street, Newbury, Berkshire, RG14 1EA, or by contacting medical information on 01635 520300.

Communication information

If you have any further questions, please also contact our Medical Information department at Orion Pharma (UK) Ltd, Oaklea Court, 22 Park Street, Newbury, Berkshire, RG14 1EA or telephone on 01635 520300.

Please find enclosed a copy of the revised Summary of Product Characteristics (SPC), with changes highlighted in the text (bold), for your information.

Yours sincerely,

Julie Boothe
Medical Affairs Manager