Tamoxifen and the risk of variability in clinical response due to CYP2D6 genetic variants or when given with CYP2D6 inhibitors

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SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.4
In the literature it has been shown that CYP2D6 poor metabolisers have a lowered plasma level of endoxifen, one of the most important active metabolites of tamoxifen (see section 5.2).
Concomitant medications that inhibit CYP2D6 may lead to reduced concentrations of the active metabolite endoxifen. Therefore, potent inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided during tamoxifen treatment (see section 4.5 and 5.2).

Section 4.5
Pharmacokinetic interaction with CYP2D6 inhibitors, showing a 65-75% reduction in plasma levels of one of the more active forms of the drug, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine) in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided (see section 4.4 and 5.2).

Section 5.1
CYP2D6 polymorphism status may be associated with variability in clinical response to tamoxifen. The poor metaboliser status may be associated with reduced response. The consequences of the findings for the treatment of CYP2D6 poor metabolisers have not been fully elucidated (see sections 4.4, 4.5 and 5.2)
CYP2D6 genotype
Available clinical data suggest that patients who are homozygote for non-functional CYP2D6 alleles, may experience reduced effect of tamoxifen in the treatment of breast cancer.
The available studies have mainly been performed in postmenopausal women (see sections 4.4 and 5.2)

Section 5.2
Tamoxifen is metabolised mainly via CYP3A4 to N-desmethyl-tamoxifen, which is further metabolised by CYP2D6 to another active metabolite endoxifen. In patients who lack the enzyme CYP2D6 endoxifen concentrations are approximately 75% lower than in patients with normal CYP2D6 activity. Administration of strong CYP2D6 inhibitors reduces endoxifen circulating levels to a similar extent.

PACKAGE LEAFLET

Take special care

- Co-administration with the following drugs should be avoided because a reduction of the effect of tamoxifen cannot be excluded: *paroxetine, fluoxetine (e.g. antidepressants), bupropion (antidepressant or aid to smoking cessation), quinidine (for example used in the treatment of cardiac arrhythmia) and cincalet/cinacalcet (for treatment of disorders of the parathyroid gland).*

Taking other medicines

- *Please inform your doctor if you are taking, or have recently taken any other medicines, even those you have bought without prescription. In particular, you should inform your doctor if you are taking:*
  - *paroxetine, fluoxetine (e.g. antidepressants)*
  - *bupropion (antidepressant or aid to smoking cessation)*
  - *quinidine (for example used in the treatment of cardiac arrhythmia)*
  - *cinacalcet (for treatment of disorders of the parathyroid gland)*