Questions for the Advisory Committee members

Topic 1:

1. The scientific evidence on the metabolism of tamoxifen demonstrates that CYP2D6 is an important pathway in the formation of endoxifen.

Discussion

2. The pharmacologic and clinical evidence are sufficient to demonstrate that endoxifen significantly contributes to the pharmacologic (anti-estrogenic) effect of tamoxifen.

Discussion

3. Does the clinical evidence demonstrate that postmenopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizer are at increased risk for breast cancer recurrence?

If yes, should the tamoxifen label include information about increased risk for breast cancer recurrence in CYP2D6 poor metabolizers prescribed tamoxifen?

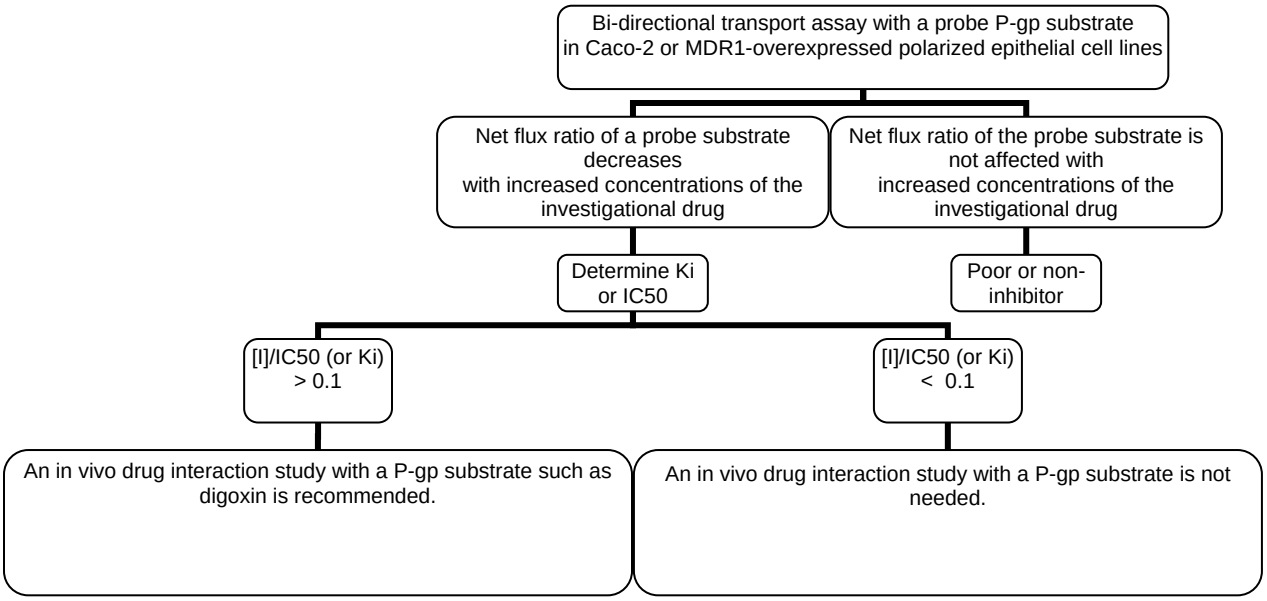
If not, what additional types of clinical evidence will demonstrate that postmenopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizer may be at increased risk for breast cancer recurrence?

4. Is there sufficient scientific and clinical evidence to support revisions of the tamoxifen label that recommends CYP2D6 genotype testing for post-menopausal patients before they are prescribed tamoxifen for adjuvant treatment?

Topic 2

1. Are the criteria for determining whether an investigational drug is an inhibitor of P-gp and whether an in vivo drug interaction study is needed, as described in the following figure, are appropriate?

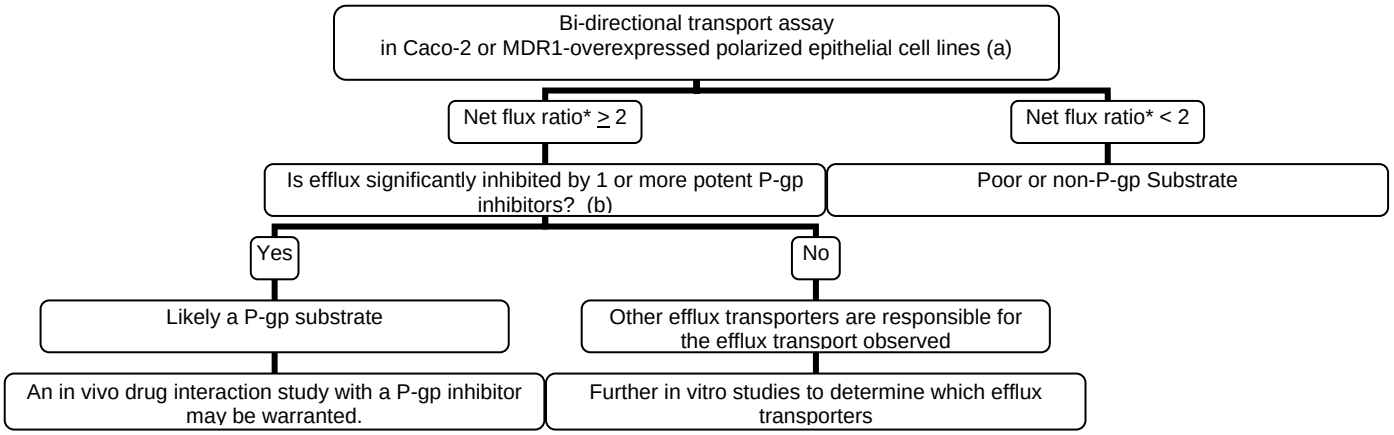
Figure 1. Decision tree to determine whether an investigational drug is an inhibitor for p-gp and whether an in vivo drug interaction study with a P-gp substrate such as digoxin is needed



* For Caco-2 cells, net flux ratio is calculated as (Permeability $_{app, B-A}$/Permeability $_{app, A-B}$); For MDR1-overexpressed cell lines, net flux ratio is calculated as ratio of (Permeability $_{app, B-A}$/Permeability $_{app, A-B}$)$_{MDR1}$ to (Permeability $_{app, B-A}$/Permeability $_{app, A-B,}$)$_{wild-type}$. Note that [I] represents the mean steady-state Cmax value for total drug (bound plus unbound) following administration of the highest proposed clinical dose.

2. Are the criteria for determining whether an investigational drug is a substrate of P-gp and whether an in vivo drug interaction study is needed, as described in the following figure, are appropriate?

Figure 2. Decision tree to determine whether an investigational drug is a substrate for P-gp and whether an in vivo drug interaction study with a P-gp inhibitor is needed



*For Caco-2 cells, net flux ratio is calculated as (Permeability $_{app, B-A}$/Permeability $_{app, A-B}$); For MDR1-overexpressed cell lines, net flux ratio is calculated as ratio of (Permeability $_{app, B-A}$/Permeability $_{app, A-B}$)$_{MDR1}$ to (Permeability $_{app, B-A}$/Permeability $_{app, A-B,}$)$_{wild-type}$.

(a) An acceptable system produces next flux ratios of probe substrates similar to the literature values. A net flux ratio ≥2 for the investigational drug is a positive signal for further evaluation. Note: there is a concern that this value is too liberal and will lead to too may positive results. An alternative is to use a % value (net flux of investigation drug relative to a probe substrate, such as digoxin).

(b) reduction of the flux ratio significantly (> 50%) or to unity

3. If a NME is a P-gp substrate and an in vivo interaction study is indicated, are the inhibitors listed in page 11 (i.e., ritonavir, cyclosporine, verapamil) appropriate?

> 3a. Should different inhibitors be considered, if NME is also a substrate for CYP3A? For example, a strong dual inhibitor of P-gp and CYP3A (e.g., ritonavir)

4. Dose the current knowledge base support the recommendation of drug interaction studies for other transporters such as OATP1B1, MRP2, BCRP, OCTs and OATs?