Introduction

FTR, a prodrug of tamsivir (TMR), is a first-in-class gp120-directed attachment inhibitor approved in the United States, Europe, and elsewhere at a dose of 600 mg twice daily (BID) in combination with other ARVs for adults with multidrug-resistant HIV-1 who are otherwise unable to construct a suppressive ARV regimen due to resistance, prior intolerance, or safety concerns.\(^1\)

In preclinical studies in dogs, FTR and TMR minimally prolonged the QT interval (∼8 to 18 msec) at maximum observed TMR concentrations ≥3600 ng/mL.\(^2,3\)

- Mean peak plasma TMR concentration with FTR 600 mg BID in highly treatment-experienced participants in the phase 3 BRIGHT study was 1770 ng/mL.\(^4\)
- A thorough QTc/QT interval study in healthy volunteers demonstrated that a supratherapeutic dose of FTR 2400 mg BID was associated with a mean (upper 90% CI) Fridericia-corrected QT (QTcF) prolongation of 4.3 (6.3) msec.\(^2\)
- With FTR 600 mg BID, model-derived upper 90% CIs of QTcF prolongation at maximum TMR concentration were ≤3.2 and ≤5.0 msec for administration alone or with cobicistat 150 mg QD, respectively, suggesting that QT interval effects ≥10 msec are unlikely to occur with the therapeutic FTR dose.\(^2\)

Because QTc prolongation is primarily a concentration-dependent effect and FTR is partially metabolized by cytochrome P450 3A4, we examined potential drug-drug interactions (DDIs) between FTR, pharmacokinetic enhancers, and other agents commonly used in HIV associated with QTc prolongation or TdP risk.

Key Takeaways

- Guideline recommendations, the University of Liverpool HIV Drug Interactions database, and data from phase 2b/3 fosetamivir (FTR) clinical studies were used to assess corrected QT interval (QTc) prolongation risk with FTR and other co-administered agents.
- FTR should be used with caution in patients with a history of QT interval prolongation when co-administered with a drug that has a known risk of Torsades de Pointes (TdP) or in patients with relevant pre-existing cardiac disease.

Results

QTc Prolongation in FTR Clinical Studies

- A plasma TMR concentration of 7500 ng/mL intersects with the clinically important QTc prolongation threshold of 10 msec (upper bound of the 90% CI), which is ~4-fold greater than the mean peak plasma TMR concentration with FTR 600 mg BID in the phase 3 BRIGHT study (1770 ng/mL).\(^4\)
- Through 96 weeks with FTR 600 mg BID in the BRIGHT study, 7.37% (2%) participants discontinued for protocol-defined QTcF prolongation ≥450 msec; all were non-serious events.
- Although discontinued from the study, 6 participants remained on FTR through the named patient program (NPP 207214); none experienced a symptomatic cardiovascular event or documented ventricular tachyarrhythmia.

Guidance for Monitoring QTcProlongationWith FTR Co-administration

- A systematic evaluation of the University of Liverpool HIV Drug Interactions database showed no significant or reported high potential for QTc prolongation when FTR is co-administered with medications commonly used in HIV (Table 1) or other ARVs (Table 2).
- No interaction was expected with and no guidance for monitoring QTcF prolongation was specified for co-administration of FTR with INSTIs, NRTIs, or doravirine.

The combinations of greatest concern with FTR co-administration include several antiarrhythmics due to potential additive QTcF prolongation risk and are not recommended when FTR + boosted PIs or FTR + RPV are used.

Table 1. FTR Co-administration With Medications Commonly Used in HIV

<table>
<thead>
<tr>
<th>ARV</th>
<th>Data and guideline recommendation</th>
<th>Guidance for monitoring QTc prolongation risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPV</td>
<td>↔ TMR probe; no dose adjustment needed</td>
<td>QTC prolongation is unlikely to occur with FTR + RPV</td>
</tr>
<tr>
<td>DRV</td>
<td>↔ TMR probe; ↔ RPV expected; no dose adjustment needed</td>
<td>Use FTR and RPV with caution when co-administered with drugs with a known TdP risk</td>
</tr>
<tr>
<td>ETV</td>
<td>TMR AUC ≥ 50%; ↔ ETR; no dose adjustment needed</td>
<td>Use FTR with caution when co-administered with drugs with a known TdP risk</td>
</tr>
<tr>
<td>DRV/c</td>
<td>TMR AUC ≥ 50%; ↔ DRV; no dose adjustment needed</td>
<td>Use FTR with caution when co-administered with drugs with a known TdP risk</td>
</tr>
<tr>
<td>DRV/r</td>
<td>TMR AUC ≥ 50%; ↔ DRV; COBI expected; no dose adjustment needed</td>
<td>Use FTR with caution when co-administered with drugs with a known TdP risk</td>
</tr>
</tbody>
</table>

Conclusions

- When combined with other ARVs, FTR does not require dose adjustment and QTc prolongation is unlikely to occur.
- Clinically significant interactions may occur with agents with known TdP risk and any such agents should be used with caution when co-administered with FTR + boosted PIs or FTR + RPV.

References


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