Alternatives for Rifampin as a CYP3A Inducer in DDI Studies in View of N-Nitrosamine Impurity Issues

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Directors Scientific Affairs, Celerion

14 June 2023
Everyone is Exposed to Some Level of Nitrosamines

<table>
<thead>
<tr>
<th>Cured and Grilled Meats</th>
<th>Vegetables</th>
<th>Dairy Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking Water</td>
<td>Cosmetics</td>
<td>Drugs</td>
</tr>
<tr>
<td>Detergents and Solvents</td>
<td>Plastic and Chemicals</td>
<td>Tobacco</td>
</tr>
</tbody>
</table>
Nitrosamine Impurity Chronology in Marketed Medication

- **2018**
  - Valsartan (NDMA)
  - Losartan & Irbesartan (NDEA)

- **2019**
  - Losartan (N MBA)
  - Ranitidine & Metformin (NDMA)

- **2020**
  - **Rifampin (MNP) & Rifapentine (CPNP)**

- **2021**
  - Varenicline (nitroso-varenicline)

- **2022**
  - Varenicline (nitroso-varenicline)

- **2023**
  - Varenicline (nitroso-varenicline)

**Regulatory Response:**

- EMA Scientific Opinion
  - September

- EMA Guidelines
  - June

- FDA Guidance
  - September

- Risk Assessment Step 1
  - March

- FDA Guidance
  - September

- Risk Assessment Step 2 & 3
  - October

- FDA Workshop
  - May/June

CPNP, 1-cyclopentyl-4-nitrosopiperazine; NMBA, N-nitroso-N-methyl-4-aminobutyric acid; NDEA, N-Nitrosoethylisopropylamine; MNP, 1-methyl-4-nitrosopiperazine

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What are N-Nitrosamines?

Probable or possible human carcinogens

- Chemical compounds with a functional N-nitroso group (\( \geq N-N=O \))
- Nitrosamines are metabolized in the liver (CYP2E1) and can produce DNA reacting agents
  - Cytotoxic
  - Mutagenic
  - Carcinogenic
- ICH M7: Cohort of concern
- Small alkyl compounds (e.g. rifampin impurity, MNP)
- API-derived complexes called Nitrosamine Drug Substance Related Impurities (NDSRIs) (e.g. nitroso-varenicline)
  - Derived from nitrosation of secondary or tertiary amines in drug structure

Figure 1. Generic N-nitrosamine structure

Nitrosamine Source in Marketed Drug

During drug manufacturing, nitrosamines can be formed from reactions of secondary amines with nitrite in acidic conditions.

**During Manufacturing**
- Nitrites – applied to quench azide reactions
- Sodium nitrate and sodium azide impurities with sodium nitrites
- Organic nitrites converted to inorganic nitrites
- Water
- Solvents
- Amines in chemical synthesis, or formed during a reaction

**Post Manufacturing**
- Interaction with excipients
- Packaging – blister pack ink may contain amines
- Degradation products

Regulatory Guidance to Control N-Nitrosamine Impurities

March 31st, 2021

Step 1: Risk assessment

October 1st, 2023

Step 2: Confirmatory testing if risks are identified

Step 3: Reporting changes implemented to prevent or reduce the presence of nitrosamine impurities in drug products in approved and pending NDAs and ANDAs

- EMA Assessment Report: Nitrosamine Impurities in Human Medicinal Products, June 2020

- FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs, February 2021

Graphs redrawn from:

N=860 drugs

- Risk identified: 2%
- No risk: 84%
- Response pending: 16%

N=136 drugs

- No nitrosamine: 61%
- Limit exceeded: 15%
- Limit not exceeded: 22%
- Response pending: 2%
### DDI Substrates and Perpetrators: Impurities Reported

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nitrosamine Detected</th>
<th>Role in DDI Studies</th>
<th>Impact to DDI Studies</th>
<th>Alternatives for DDI Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ranitidine, Nizatidine</strong></td>
<td>NDMA</td>
<td>Acid reducing agent</td>
<td>Removed from market (ranitidine) or recalled (nizatidine)</td>
<td>Famotidine or proton pump inhibitor (esomeprazole or rabeprazole)</td>
</tr>
<tr>
<td><strong>Metformin</strong></td>
<td>NDMA</td>
<td>OCT2, MATE1/2K substrate</td>
<td>No impact</td>
<td>IR-metformin is available for DDI studies and does not contain impurity</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>MNP</td>
<td>1. Strong CYP3A4 inducer 2. OATP1B1/3 inhibitor (single dose)</td>
<td>Batches available for patients only, use alternatives</td>
<td>1. Carbamazepine, efavirenz, lumacaftor, phenytoin 2. Atazanavir &amp; ritonavir, clarithromycin, cyclosporine, gemfibrozil, lopinavir, ritonavir</td>
</tr>
<tr>
<td><strong>Propranolol</strong></td>
<td>nitroso-propranolol</td>
<td>CYP2D6 substrate</td>
<td>Product recalled (CND), but no impact (not an index substrate)</td>
<td>Desipramine, dextromethorphan, nebivolol</td>
</tr>
</tbody>
</table>
N-Nitrosamine Source - Manufacturing Risk

- Rifampin is derived from rifamycin B and is used for treating tuberculosis (TB)
- During manufacturing, addition of AMP can lead to MNP formation
- Thermal degradation may also increase MNP levels

N-nitrosamine: MNP = 1-methyl-4-nitrosopiperazine

AMP = 1-amino-4-methylpiperazine

Acceptable Intake (AI) Limits

- AI limit is a daily exposure to a compound that approximates a 1:100,000 cancer risk after 70 years of exposure.

- Derived from nonclinical TD$_{50}$

- MNP TD$_{50}$ values not considered reliable
  - NDMA applied as a surrogate

- Conversion to parts per million (ppm) is product-dependent and calculated based on a drug’s max daily dose

### Nitrosamine AI Limit (ng/day)$^1$

<table>
<thead>
<tr>
<th>Nitrosamine</th>
<th>AI Limit (ng/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDMA</td>
<td>96</td>
</tr>
<tr>
<td>NDEA</td>
<td>26.5</td>
</tr>
<tr>
<td>NMBA</td>
<td>96</td>
</tr>
<tr>
<td>NMPA</td>
<td>26.5</td>
</tr>
<tr>
<td>NIPEA</td>
<td>26.5</td>
</tr>
<tr>
<td>NDIPA</td>
<td>26.5</td>
</tr>
<tr>
<td>MNP</td>
<td>96 (NDMA surrogate value)</td>
</tr>
</tbody>
</table>

### Calculating MNP AI for Rifampin:

- Rifampin daily dose = 600 mg/day
- MNP ppm = $\frac{96 \text{ ng/day}}{600 \text{ mg/day}} = 0.16$ ppm

[1] Derived from nonclinical TD$_{50}$ values not considered reliable

# MNP Levels in Rifampin

<table>
<thead>
<tr>
<th>Company (Manufacturer)</th>
<th>Product</th>
<th>MNP level (ppm)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akorn</td>
<td>Rx Rifampin 300 mg</td>
<td>1.49-3.20</td>
<td>Discontinuation of manufacture of drug (Sep 2022)</td>
</tr>
<tr>
<td>Akorn</td>
<td>Rx Rifampin 150 mg</td>
<td>2.95-3.47</td>
<td>Filed for bankruptcy (2023)</td>
</tr>
<tr>
<td>Fresenius Kabi</td>
<td>Rx Rifampin Injection 600 mg</td>
<td>0.94</td>
<td>Available (Mar 2023)</td>
</tr>
<tr>
<td>Lannett</td>
<td>Rx Rifampin 300 mg</td>
<td>1.88-2.52</td>
<td></td>
</tr>
<tr>
<td>Lannett</td>
<td>Rx Rifampin 150 mg</td>
<td>2.22-2.43</td>
<td></td>
</tr>
<tr>
<td>Lupin Pharmaceuticals Inc.</td>
<td>Rx Rifampin 300mg</td>
<td>1.31-2.08</td>
<td>Available (Mar 2023)</td>
</tr>
<tr>
<td>Lupin Pharmaceuticals Inc.</td>
<td>Rx Rifampin 150mg</td>
<td>1.52-2.26</td>
<td></td>
</tr>
<tr>
<td>Mylan</td>
<td>Rx Rifampin Injection 600 mg</td>
<td>0.99-2.51</td>
<td>Unavailable (Mar 2023)</td>
</tr>
<tr>
<td>Sandoz/Epic</td>
<td>Rx Rifampin 300 mg</td>
<td>1.86-2.66</td>
<td>Available (Jan 2023)</td>
</tr>
<tr>
<td>Sandoz/Epic</td>
<td>Rx Rifampin 150 mg</td>
<td>2.39-2.76</td>
<td></td>
</tr>
<tr>
<td>Sanofi Pharmaceuticals</td>
<td>Rx Rifampin Injection 600 mg</td>
<td>0.80-1.11</td>
<td>Available (Jun 2021)</td>
</tr>
</tbody>
</table>

2. [https://www.accessdata.fda.gov/scripts/drugshortages/dsp_SearchResults.cfm](https://www.accessdata.fda.gov/scripts/drugshortages/dsp_SearchResults.cfm)
3. [https://eu.usatoday.com/story/money/2023/05/01/akorn-drug-recall/11761785002](https://eu.usatoday.com/story/money/2023/05/01/akorn-drug-recall/11761785002)
The acceptable intake limits are 0.16 parts per million (ppm) for MNP in rifampin and 0.1 ppm for CPNP in rifapentine. The agency will not object to certain manufacturers temporarily distributing rifampin containing MNP below 5 parts per million (ppm). The agency also will not object to certain manufacturers temporarily distributing rifapentine containing CPNP below 14 ppm. FDA will not object to these higher exposures to maintain patient access to these life-saving medications.

Risk of not treating TB outweighs theoretical risk of cancer
Rifampin Use in Healthy Volunteers; Regulatory Positions

**FDA:**
*Per Celerion-Sponsor communication:*

FDA notified 2 of our Sponsors that *using rifampin in healthy subjects is NOT acceptable* and suggested to one of the sponsors to use phenytoin or carbamazepine.

**EMA:**
*Per EMA Committee for medicinal products for human use – Meeting minutes 19-22 Apr 2021:*

The CHMP noted the question from the PKWP on the *use of Rifampicin in Drug Interaction Studies in healthy volunteers* and discussed the recommendation from the Nitrosamine Implementation Oversight Group (NIOG) that *Rifampicin containing nitrosamine above the acceptable intake should not be used* in these studies. The CHMPl was in agreement with the recommendation and adopted the response to PKWP.

**MHRA:**
*Per general Celerion inquire to MHRA:*

The Commission on Human Medicines has advised that that rifampicin should, at present, *not be used in Drug-Drug-Interaction studies healthy volunteers.* Alternative suitable PK-inducers, such as Rifabutin, may be used instead.
Alternative CYP3A Inducers for DDI Studies
Rifampin Replacement Candidates

<table>
<thead>
<tr>
<th>Perpetrator</th>
<th>Drug Type &amp; Indication</th>
<th>Comments</th>
<th>Suitable?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apalutamide</td>
<td>Nonsteroidal antiandrogen</td>
<td>Increased risk of seizure and incidence of fall and fractures</td>
<td>X</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Sodium channel blocker</td>
<td>Dose titration to mitigate AEs and black box warning</td>
<td>✓</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Nonnucleoside rt inhibitor</td>
<td>Listed in ICH M12 Guidance; only moderate inducer</td>
<td>?</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Nonsteroidal antiandrogen</td>
<td>Increased risk of seizure and incidence of fall and fractures</td>
<td>X</td>
</tr>
<tr>
<td>Ivosidenib</td>
<td>Mutant isocitrate-DH1 inhibitor</td>
<td>Multiple doses of ivosidenib not studied in healthy participants (lack of data)</td>
<td>X</td>
</tr>
<tr>
<td>Lumacaftor</td>
<td>CFTR modulator</td>
<td>Only in combination with ivacaftor (Orkambi). Favorable safety profile</td>
<td>?</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Adrenal cytotoxic agent</td>
<td>Occurrence of common AEs &gt;15%</td>
<td>X</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Sodium channel blocker</td>
<td>Narrow therapeutic window, yet preferred perpetrator</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Antimicrobial</td>
<td>MHRA recommendation; not an option listed by FDA</td>
<td>X</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Herbal supplement</td>
<td>Effect varies widely and is preparation-dependent</td>
<td>X</td>
</tr>
</tbody>
</table>

Adapted from FDA Drug-Drug Interactions Table 3.3

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Carbamazepine as Alternative?

- **Anticonvulsant drug**

- **Strong inducer of CYP3A** (via CAR/PXR);
  - Also strong inducer of CYP2B6
  - Weak inducer of CYP2C9
  - Inducer of P-gp

- **Safety concerns:**
  - Risk of **severe cutaneous adverse reactions** with high starting doses (**Black Box warning**)
  - Risk of aplastic anemia & agranulocytosis

- **Risk mitigation measures**
  - Exclude anyone with positive HLAB*1502 allele (~ risk of CBZ hypersensitivity reactions)
  - Dose titration to mitigate AEs
    - 3+3 days 100 / 200 mg BID; ≥7 days 300 mg BID
    - Monitor platelet and WBC counts

- **Sufficient experience with DDI trials in healthy volunteers**

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**In study A, 7 out of twelve subjects completed the study according to protocol. Five subjects discontinued the study due to the emergence of generalized exanthema, a well-known and common side effect of carbamazepine. In three**

Phenytoin as Alternative?

- Anticonvulsant drug

- Strong inducer of CYP3A (via CAR/PXR)
  - Also moderate inducer of CYP1A2 and CYP2C19
  - Inducer of P-gp

- Narrow therapeutic window
  - Safety concerns (e.g. risk of seizures & neurological events)

- Sufficient experience with DDI trials in healthy volunteers

- Long half-life, requiring time to reach Css and maximal CYP3A induction

- Risk mitigation measures
  - Genotyping CYP2C9 and CYP2C19 poor metabolizers
  - Exclude history of seizures, neurological conditions and suicide ideation
  - Exclude WCBP because of prenatal risks
  - If substrate may increase phenytoin levels, monitor phenytoin levels

- Recommended phenytoin regimen: 100 mg TID phenytoin for ≥14 days

Phenytoin Safety Profile

Literature phenytoin DDI studies:
- 16 studies published
- AEs were mild to moderate and transient in nature
- Most common AEs:
  - Skin rash, Dizziness, Headache

Celerion phenytoin DDI experience:
- 8 DDI studies in past 2 yrs
- PHT generally well tolerated
- No dropouts due to phenytoin AEs

Phenytoin-Related AEs from Published DDI Studies

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Number of Study Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blurred Vision</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
</tr>
<tr>
<td>Elevated LFT</td>
<td>6</td>
</tr>
<tr>
<td>GI Symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
</tbody>
</table>

Pagliuanga & van Haarst, 2022 ACCP Poster Presentation.
• Literature review

• Spectrum of substrate reduction in the presence of strong CYP3A inducers

• Overall phenytoin and carbamazepine induce a similar %AUC reduction as rifampin
Case Studies:
PHT and CBZ DDI Studies
Case Study 1 – Phenytoin-Induced CYP3A Activity

DDI study to determine the effect of itraconazole (ITZ) and phenytoin (PHT) on the single dose PK of Drug X

- Drug X is being developed to treat cancer
- Nonclinical data suggests Drug X is a CYP3A substrate
- ITZ is a strong CYP3A4 and P-gp inhibitor
- PHT is a strong CYP3A4 inducer

- 2 Dose levels applied for Drug X:
  - ITZ arm: Low dose Drug X to avoid over-exposure with decreased clearance
  - PHT arm: High dose Drug X for more accurate PK parameters

- 6β-hydroxycortisol / free cortisol as CYP3A endogenous induction biomarker
- Part 2: CYP2C9 and CYP2C19 poor metabolizers excluded
Case Study 1 – Study Design

**Part 1 (ITZ)**
- **Screening**: 29 days
- **Period 1**: Days -1 to 5
  - **Drug X (low dose)**: Day 1
  - **Drug X (low dose)**: Day 4
- **Period 2**: Days -1 to 8
  - **ITZ 200 mg QD**: Days 1-8
- **Follow up**: 14 days after last dose
- **PK**

**Part 2 (PHT)**
- **Screening**: 29 days
- **Period 1**: Days -1 to 4
  - **Drug X (high dose)**: Day 1
  - **Drug X (high dose)**: Day 14
- **Period 2**: Days -1 to 18
  - **PHT100 mg TID**: Days 1-17
- **Follow up**: 14 days after last dose
- **PK**
Case Study 1 - Strong CYP3A Induction with PHT

Case Study 1 - Moderate Induction and Inhibition Effects on Drug X

**ITZ co-administration**
- Moderately increased exposure of Drug X

**PHT co-administration**
- Induced a robust CYP3A induction (confirmed by endogenous biomarker)
- Moderately reduced exposure of Drug X

Co-administration with strong CYP3A inhibitors and inducers has risks

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>ITZ+Drug</th>
<th>PHT+Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Low dose</td>
<td>High dose</td>
</tr>
<tr>
<td>Cmax</td>
<td>↑ 95%</td>
<td>↓ 50%</td>
</tr>
<tr>
<td>AUC$_{0\text{-}\text{inf}}$</td>
<td>↑105%</td>
<td>↓ 60%</td>
</tr>
</tbody>
</table>
Drug Y is being developed for treatment of cardiovascular disease

Nonclinical data suggests Drug Y is a CYP3A and P-gp substrate

ITZ is a strong CYP3A4 & clinical P-gp inhibitor

PHT is a strong CYP3A4 inducer & P-gp inducer

Quinidine (QND) is a clinical P-gp inhibitor

Part 2: CYP2C9 and CYP2C19 poor metabolizers excluded

3-part, open-label, fixed sequence, 2 periods
- Part 1: Period 1 – Drug Y alone; Period 2 – ITZ 200 mg QD (Days 1-6) co-admin with Drug Y (Day 5)
- Part 2: Period 1 – Drug Y alone; Period 2 – PHT 100 mg TID (Days 1-15) with co-admin with Drug Y (Day 14)
- Part 3: Period 1 – Drug Y alone; Period 2 – QND 300 mg (Day 1, t=-1h & 3h), Drug Y (Day 1, t=0h)
Case Study 2 – Dynamic CYP3A Activity, no P-gp Effect

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>ITZ+Drug Y</th>
<th>PHT+Drug Y</th>
<th>QND+Drug Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>↑ 135% (+1.35-fold change)</td>
<td>↓ 65% (-2.8-fold change)</td>
<td>↑ 15%</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</td>
<td>↑ 420% (+4.2-fold change)</td>
<td>↓ 80% (-5-fold change)</td>
<td>↑ 20%</td>
</tr>
</tbody>
</table>

Similar (but inverse) dynamic change with strong CYP3A inhibitor and inducer

Minimal P-pg contribution as demonstrated by QND effect

Co-administration with strong CYP3A inhibitors and inducers may need to be avoided
## Adverse Event (AE) Frequency from Phenytoin Case Studies

All AEs were mild to moderate and transient in nature.

<table>
<thead>
<tr>
<th>AE Frequency:</th>
<th>n = 1</th>
<th>n = 2-5</th>
<th>n &gt; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Study 1</td>
<td>Blurred Vision, Fatigue, GI Symptoms, Nausea</td>
<td>Dizziness, Elevated LFT, Headache, Other</td>
<td>Skin Rash</td>
</tr>
<tr>
<td>Case Study 2</td>
<td>Nausea</td>
<td>Fatigue, GI Symptoms, Skin Rash</td>
<td>Headache</td>
</tr>
</tbody>
</table>
Typical Carbamazepine DDI Study Design

Dose Titration:

Screening: 29 days
Period 1: Days -1 to 4
- CBZ 100 mg BID
  Days 1-3
- CBZ 200 mg BID
  Days 4-6
- CBZ 300 mg BID
  Days 7-23
Drug X: Day 21
Washout
Period 2: Days -1 to 24
Follow up: 14 days after last dose

Adapted from Bolledula et al, Clin Transl Sci. 2022.
Case Study 3 – Carbamazepine CYP3A Induction

Effects of itraconazole and carbamazepine on the pharmacokinetics of nirmatrelvir / ritonavir in healthy subjects

Nirmatrelvir / ritonavir received emergency use authorization by the FDA for COVID-19, full approval May 2023

Nirmatrelvir and ritonavir are both CYP3A substrates; ritonavir acts as PK booster

CBZ Study: Open-label, fixed sequence, 2 periods
- Period 1 – Nirmatrelvir / ritonavir 300/100 mg alone;
- Period 2 – CBZ titration 100 mg BID (Day 1-3), 200 mg BID (Day 4-7), 300 mg BID (Day 8-15) with co-admin nirmatrelvir / ritonavir 300/100 mg (Day 14)
- Exclusion of subjects shown to carry or be positive for HLA-B*1502 and HLA-A*3101

ITZ Study: Open-label, fixed sequence, 2 periods
- Period 1 – Nirmatrelvir / ritonavir 300/100 mg BID (Day 1-3) alone;
- Period 2 – ITZ 200 mg (Day 1-8) with co-admin nirmatrelvir / ritonavir 300/100 mg BID (Day 4-6)
Case Study 3 – Moderate Induction and Inhibition Effect on Nirmatrelvir

CBZ DDI Study Safety Results:

- No deaths, serious adverse events (SAEs) nor severe AEs
- CBZ generally well tolerated
- One participant discontinued from study due to moderate SIADH (Syndrome of Inappropriate secretion of Anti-Diuretic Hormone), related to CBZ in Period 2.
Period 2 Duration by Induction and Treatment Days
PBPK DDI Modeling
Physiologically Based Pharmacokinetic (PBPK) Modeling

- Integration of physiological, system, chemical, and drug-dependent preclinical and clinical information
- Multi-compartment representing organs and blood flow
- Aim to simulate untested clinical scenarios
  - First in human dose exposure
  - Absorption
  - Food effect
  - Drug-drug interaction
  - Formulation
  - Special populations

**PBPK Model-Informed Labeling - Vonoprazan**

- **Potassium-competitive acid blocker**
  - GERD, erosive esophagitis

- **Dual and Triple Pak**
  - Combined with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* infection in adults

- **In vitro**
  - CYP3A4 is primary metabolizing enzyme, minor CYP2D6 and CYP2C19 contribution
  - Inhibits CYP3A

- **Plans for a clinical rifampin DDI study were halted due to nitrosamine issues**

- **Applied PBPK to simulate rifampin and efavirenz CYP3A induction, and inform drug label**

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https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215152Orig1s000,215153Orig1s000IntegratedR.pdf
### Table 113. Predicted and Observed Effects of CYP3A Perpetrators on Vonoprazan PK Following Co-administration of CYP3A Perpetrators With Single or Multiple Doses of Vonoprazan in Healthy Subjects

<table>
<thead>
<tr>
<th>CYP3A inhibitors</th>
<th>Vonoprazan Dosing</th>
<th>$C_{\text{max, inh}}$ (ng/mL)</th>
<th>$\text{AUC}_{0-\text{inf}}$ (ng/mL.h)</th>
<th>$C_{\text{max}}$ Ratio</th>
<th>$\text{AUC}_{0-\text{inf}}$ Ratio</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>500 mg BID 7d</td>
<td>63.7</td>
<td>648</td>
<td>1.35</td>
<td>1.58</td>
<td>Study TAK-438-110</td>
</tr>
<tr>
<td></td>
<td>40 mg SD 0d</td>
<td>72.3</td>
<td>690</td>
<td>1.51</td>
<td>1.78</td>
<td>Sim/obs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.14</td>
<td>1.06</td>
<td>1.12</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>400 mg BID 7d</td>
<td>70.2</td>
<td>538.8*</td>
<td>1.87</td>
<td>1.85*</td>
<td>Study TAK-438/CPH-401</td>
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<tr>
<td></td>
<td>20 mg BID 7d</td>
<td>57.4</td>
<td>403.3*</td>
<td>1.28</td>
<td>1.36*</td>
<td>Sim/obs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.82</td>
<td>0.75</td>
<td>0.67</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg QD 18d</td>
<td>7.32</td>
<td>38.6</td>
<td>0.28</td>
<td>0.20</td>
<td>predicted</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg QD 16d</td>
<td>11.2</td>
<td>52.6</td>
<td>0.28</td>
<td>0.22</td>
<td>predicted</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600 mg QD 18d</td>
<td>14.9</td>
<td>92.2</td>
<td>0.56</td>
<td>0.46</td>
<td>predicted</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600 mg QD 16d</td>
<td>21.6</td>
<td>116</td>
<td>0.54</td>
<td>0.46</td>
<td>predicted</td>
</tr>
</tbody>
</table>

* Predicted 80% reduction

* Predicted 50% reduction

Source: [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215152Orig1s000,215153Orig1s000IntegratedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215152Orig1s000,215153Orig1s000IntegratedR.pdf)
Effect of CYP3A Inducers on Vonoprazan:

Vonoprazan exposures are predicted to be 80% lower when co-administered with a strong CYP3A4 inducer such as rifampicin and 50% lower when co-administered with a moderate CYP3A4 inducer such as efavirenz.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215152s000,215153s000lbl.pdf

But…. Reviewer comments: The analyses may underestimate the induction effects of rifampin and efavirenz on vonoprazan PK. Confidence in induction prediction is low but is not a major concern in this case because the Applicant recommends avoiding co-administration of vonoprazan with strong or moderate CYP3A inducers in the product labelling

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215152Orig1s000,215153Orig1s000IntegratedR.pdf
Nitrosamine Concerns

May 2022
- Vonoprazan approved

Aug 2022
- Detected trace amounts of nitrosamine impurities, n-nitroso-vonoprazan (NVP)¹

Jan 2023
- Market launch delayed as company is working to reduce NVP below acceptable intake level of 96 ng/d¹

Apr 2023
- Root cause analysis and minor reformulation completed²

But…

². https://investors.phathompharma.com/node/8631/pdf
# Drugs Applying PBPK CYP3A Inducer Models Reviewed by the FDA (2018-2019)

<table>
<thead>
<tr>
<th>Drug (NDA)</th>
<th>TA</th>
<th>Inducer Modeled</th>
<th>FDA Assessment¹</th>
<th>Label²: CYP3A Inducers Co-admin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siponimod (209884)</td>
<td>Neurology</td>
<td>RIF and EFZ</td>
<td>Adequate</td>
<td>Strg not recommended</td>
</tr>
<tr>
<td>Prucalopride (210166)</td>
<td>Gastroenterology</td>
<td>RIF</td>
<td>Inadequate (model did not provide verification of RIF on P-gp &amp; BCRP)</td>
<td>None</td>
</tr>
<tr>
<td>Avatrombopag (210238)</td>
<td>Hematology</td>
<td>RIF</td>
<td>Adequate (relevant studies supporting label)</td>
<td>None</td>
</tr>
<tr>
<td>Cannabidiol (210365)</td>
<td>Neurology</td>
<td>Redacted</td>
<td>Inadequate (metabolites not in model)</td>
<td>Consider dose ↑ with Strg</td>
</tr>
<tr>
<td>Encorafenib (210496)</td>
<td>Oncology</td>
<td>RIF</td>
<td>Inadequate (model lacked key clinical data to verify assumptions)</td>
<td>Avoid with Mod. &amp; Strg</td>
</tr>
<tr>
<td>Doravirine (210806)</td>
<td>Anitviral and anti-infective</td>
<td>RIF, EFZ, RIB</td>
<td>Adequate (relevant studies supporting label)</td>
<td>RIF, PHT, CBZ contra-indicated. ↑ dose with RIB</td>
</tr>
<tr>
<td>Apalutamide (210951)</td>
<td>Oncology</td>
<td>RIF</td>
<td>Adequate</td>
<td>None</td>
</tr>
<tr>
<td>Duvelisib (211155)</td>
<td>Hematology</td>
<td>RIF</td>
<td>Adequate</td>
<td>Avoid with Strg</td>
</tr>
<tr>
<td>Ivosidenib (211192)</td>
<td>Hepatology</td>
<td>RIF and EFZ</td>
<td>Adequate</td>
<td>Avoid with Strg</td>
</tr>
<tr>
<td>Upadacitinib (211675)</td>
<td>Anesthesia, Analgesia, Pulm., Allergy, Rheuma.</td>
<td>RIF</td>
<td>Adequate (relevant studies supporting label)</td>
<td>Strg not recommended</td>
</tr>
<tr>
<td>Erdafitinib (212018)</td>
<td>Oncology</td>
<td>RIF</td>
<td>Adequate</td>
<td>Avoid with Strg. ↑ dose with Mod.</td>
</tr>
<tr>
<td>Fedratinib (212327)</td>
<td>Hematology</td>
<td>RIF and EFZ</td>
<td>Inadequate (uncertainties in predicting the net effect coming from CYP3A and CYP2C19)</td>
<td>Avoid with Mod. &amp; Strg</td>
</tr>
<tr>
<td>Alpelisib (212526)</td>
<td>Oncology</td>
<td>RIF</td>
<td>Inadequate (uncertainties in predicting the net effect)</td>
<td>Avoid with Strg.</td>
</tr>
<tr>
<td>Voxelotor (213137)</td>
<td>Hematology</td>
<td>RIF and EFZ</td>
<td>Adequate</td>
<td>Avoid with Mod. &amp; Strg</td>
</tr>
<tr>
<td>Zanubrutinib (213217)</td>
<td>Hematology</td>
<td>EFZ</td>
<td>Adequate (RIF DDI study conducted in HV)</td>
<td>Avoid with Mod. &amp; Strg</td>
</tr>
<tr>
<td>Lefamulin (211672; 211673)</td>
<td>Antiviral and anti-infective</td>
<td>RIF and EFZ</td>
<td>Inadequate (uncertainty in model structure)</td>
<td>Avoid with Mod. &amp; Strg</td>
</tr>
<tr>
<td>Entrectinib (212725; 212726)</td>
<td>Oncology</td>
<td>RIF and EFZ</td>
<td>Adequate</td>
<td>Avoid with Mod. &amp; Strg</td>
</tr>
</tbody>
</table>

1. Adapted from: Zhang et al. JCP 2020. 2. Per drug label. CBZ, carbamazepine; DDI, drug-drug interaction; EFZ, efavirenz; HV, healthy volunteers; Mod, moderate inducer; PHT, phenytoin; RIB, rifabutin; RIF, rifampin; Strg, strong inducer

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Summary

Nitrosamine impurities continues to remain an issue for drugs in development
• DDI studies – effect substrates, inhibitors and inducers
• New drugs coming onto market need to preform risk assessment

Alternative CYP3A inducers needed for DDI studies
• “Clean” rifampin batches yet to be released

Preferred alternatives include PHT & CBZ, while EFZ and LUM could also be considered
• PHT and CBZ demonstrate similar reduction in substrate exposure

PHT is a strong CYP3A inducer with good safety profile
• Holds similar dynamic range on CYP3A as ITZ

Dose titration and special mitigations steps required for CBZ

PBPK may be an alternative approach for well-verified, robust models
Thank You!

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Check out our recent articles on nitrosamine impurities:


Perspective
The Impact of N-nitrosamine Impurities on Clinical Drug Development
Sabina Paglialunga, Aernout van Haarst

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