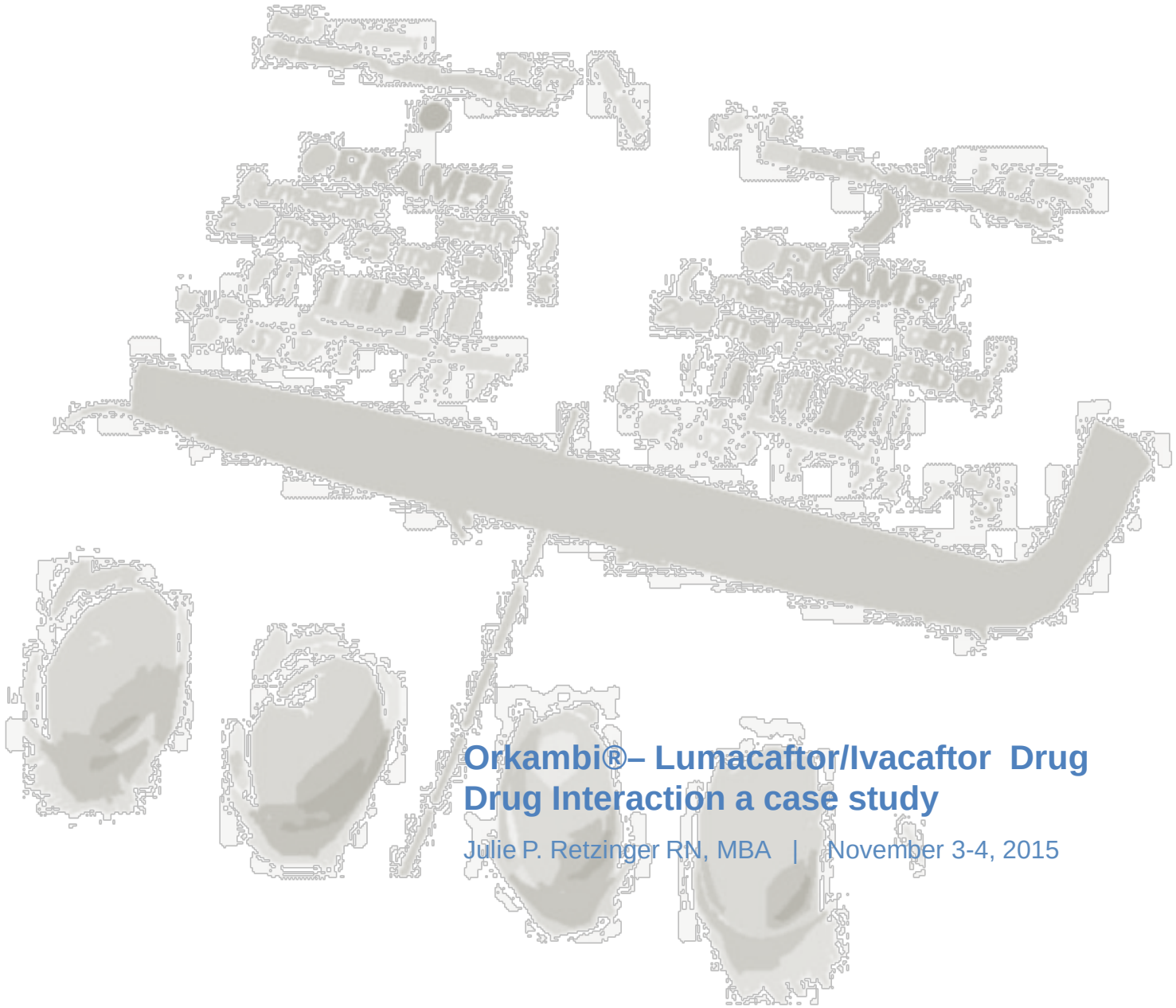

Orkambi®– Lumacaftor/Ivacaftor Drug Drug Interaction a case study

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Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the individual, and do not necessarily represent Vertex Pharmaceutical Inc.

Case Study Outline

- Brief background on Cystic Firbrosis , Kalydeco® (Ivacaftor), and Orkambi®(lumacaftor/Ivacaftor)

- Our approach to PI sections:
  - 2- Dosage and Administration
  - 7- Drug Interactions
  - 12- Clinical Pharmacology
  - Agency interactions/communications during the review cycle

- Table format vs. narrative vs. forest plot

- Conclusions

Background

- Cystic fibrosis (CF) is a chronically debilitating, rare genetic disease with serious morbidity and high premature mortality. CF is caused by absent or defective cystic fibrosis transmembrane conductance regulatory (CFTR) protein which results from mutations in both copies of the CFTR gene (located on chromosome 7).

- Kalydeco® (Ivacaftor) 150 mg tablet, approved 1st to treat only a specific type of mutation (G551D), and later, other gating mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Initial US approval 2012.

- Orkambi® (lumacaftor/ivacaftor) 200mg/125mg tablet–indicated for the treatment of cystic fibrosis (CF) in patients who are homozygous for the *F508del* mutation in the *CFTR* gene. Initial US approval 2015.

Labeling approach – Section 2- Dosage and Administration

- We reviewed our approach to Kalydeco® - wanted to drive a consistent approach and look for the Orkambi® labeling

- **Kalydeco®**
- **2.2 Dosing Information in Adults and Children Ages 6 Years and Older**
- The recommended dose of KALYDECO for both adults and pediatric patients age 6 years and older is one 150 mg tablet taken orally every 12 hours (300 mg total daily dose) with fat-containing food [see Dosage and Administration (2.1)].

Labeling approach – Section 2- Dosage and Administration

- We reviewed our approach to Kalydeco® - wanted to drive a consistent approach and look for the Orkambi® labeling

- **Orkambi®**
- **2.1 Dosing Information in Adults and Children Age 12 Years and Older**
- Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours with fat-containing food.
  - Further examples are given to describe what are appropriate fat containing foods
  - Missed dose information is included
  - Cross referencing to Clinical Pharmacology (12.3) and Patient Counseling Information (17)].

Labeling approach – Section 2- Dosage and Administration

- **2.2 Dosage Adjustment for Patients with Hepatic Impairment**
- **Orkambi®**
- No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A dose reduction to 2 tablets in the morning and 1 tablet in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) is recommended for patients with moderate hepatic impairment (Child-Pugh Class B).

- **Kalydeco®**
- The dose of KALYDECO should be reduced to one tablet or one packet of oral granules once daily for patients with moderate hepatic impairment (Child-Pugh Class B).

Labeling approach – Section 2- Dosage and Administration

- **Orkambi®**
- Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening (lumacaftor 400 mg/ivacaftor 250 mg total daily dose), or less, in patients with severe hepatic impairment after weighing the risks and benefits of treatment

- **Kalydeco®**
- KALYDECO should be used with caution in patients with severe hepatic impairment (Child-Pugh Class C) at a dose of one tablet or one packet of oral granules once daily or less frequently.

Labeling approach – Section 2- Dosage and Administration

- **Orkambi®**
- **2.3 Dosage Adjustment for Patients Taking CYP3A Inhibitors**
- No dose adjustment is necessary when CYP3A inhibitors are initiated in patients already taking ORKAMBI. However, when initiating ORKAMBI in patients currently taking strong CYP3A inhibitors (e.g., itraconazole), reduce ORKAMBI dose to 1 tablet daily (lumacaftor 200 mg/ivacaftor 125 mg total daily dose) for the first week of treatment. Following this period, continue with the recommended daily dose.
- **Kalydeco®**
- **2.6 Dosage Adjustment for Patients Taking Drugs that are CYP3A Inhibitors**
- When KALYDECO is being co-administered with strong CYP3A inhibitors (e.g., ketoconazole), the dose should be reduced to one tablet or one packet of oral granules twice a week. The dose of KALYDECO should be reduced to one tablet or one packet of granules once daily when co-administered with moderate CYP3A inhibitors (e.g., fluconazole). Food containing grapefruit or Seville oranges should be avoided

Labeling approach – Section 7- Drug Interactions

- We reviewed section 7 of Kalydeco® - wanted to drive a consistent approach to our labeling – submitted Section 7 in a narrative format
- **Orkambi®**
- Agency communication
  - "The labeling language for Section 7 (Drug Interactions) should reflect the concomitant medications used in the phase 3 trials. You should submit more specific language addressing the recommendations for common CF concomitant medicines in Section 7 in the label."
  - "In addition, you should include recommendations for managing concomitant administration of the following drug classes in Section 7 of the label:
    - Other antacids/H2 blockers
    - Ibuprofen or other anti-inflammatory drugs
    - Oral hypoglycemic
    - Antidepressants"

Labeling approach – Section 7- Drug Interactions

- Reconsidered our approach due to the Agency request to reflect the concomitant medication used in the phase 3 trials
  - CF population has multiple concomitant medications
  - Needed to determine an appropriate cut off to include concomitant medications
  - Following analysis of the data base we selected a 10% cut-off, we felt this would reflect the most frequently used concomitant medications in the phase 3 studies
  - Additional analysis of the data base regarding representation of the requested drug classes
    - Other antacids/H2 blockers
    - Ibuprofen or other anti-inflammatory drugs
    - Oral hypoglycemic
    - Antidepressants
- Decided to re-submit in a **tabular format** due to the increased number of medications to be added

Labeling approach – Section 7- Drug Interactions

Table 2: Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of ORKAMBI With Other Medicinal Products		
Concomitant drug class: **Drug name**	Effect	Clinical comment
Concomitant Drugs of Most Clinical Relevance		
Anti-allergics: **montelukast**	↔ LUM, IVA ↓ montelukast	No dose adjustment of ORKAMBI is recommended when co-administered with montelukast. No dose adjustment for montelukast is recommended. Employ appropriate clinical monitoring, as is reasonable, when co-administered with ORKAMBI. ORKAMBI may decrease the exposure of montelukast, which may reduce its efficacy.
Antibiotics: **clarithromycin, telithromycin**	↔ LUM ↑ IVA ↓ clarithromycin, telithromycin	No dose adjustment of ORKAMBI is recommended when clarithromycin or telithromycin are initiated in patients currently taking ORKAMBI. Reduce the dose of ORKAMBI for the first week of treatment when initiating ORKAMBI in patients currently taking clarithromycin or telithromycin [see Dosage and Administration (2)]. Consider an alternative to these antibiotics, such as azithromycin. ORKAMBI may decrease the exposures of clarithromycin and telithromycin, which may reduce their efficacy.
erythromycin	↔ LUM ↑ IVA ↓ erythromycin	No dose adjustment of ORKAMBI is recommended when co-administered with erythromycin. Consider an alternative to erythromycin, such as azithromycin. ORKAMBI may decrease the exposure of erythromycin, which may reduce its efficacy.

Labeling approach – Section 7- Drug Interactions

Table 2: Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of ORKAMBI With Other Medicinal Products		
Concomitant drug class: **Drug name**	Effect	Clinical comment
Concomitant Drugs of Most Clinical Relevance		
Anti-allergics: **montelukast**	↔ **LUM, IVA** ↓ **montelukast**	No dose adjustment of ORKAMBI is recommended when co-administered with montelukast. No dose adjustment for montelukast is recommended. Employ appropriate clinical monitoring, as is reasonable, when co-administered with ORKAMBI. ORKAMBI may decrease the exposure of montelukast, which may reduce its efficacy.

Labeling approach – Section 7- Drug Interactions

- **Orkambi® – Under table - Inclusion of negative information**

- No dosage adjustment of ORKAMBI or concomitant drug is recommended when ORKAMBI is given with the following: azithromycin, aztreonam, budesonide, calcium carbonate antacid, ceftazidime, cetirizine, ciprofloxacin, colistimethate, colistin, dornase alfa, fluticasone, ipratropium, levofloxacin, metformin, pancreatin, pancrelipase, salbutamol, salmeterol, sulfamethoxazole and trimethoprim, tiotropium, and tobramycin.

Labeling approach – Section 7- Drug Interactions

- Agency Communication
  - "Section 7 (drug Interactions) was edited in order to improve readability."
  - The drug interaction section was moved back into the narrative format
  - We as a company did not approach the Agency regarding this change – we accepted

Labeling approach – Section 12.3 Pharmacokinetics Drug Interaction Studies

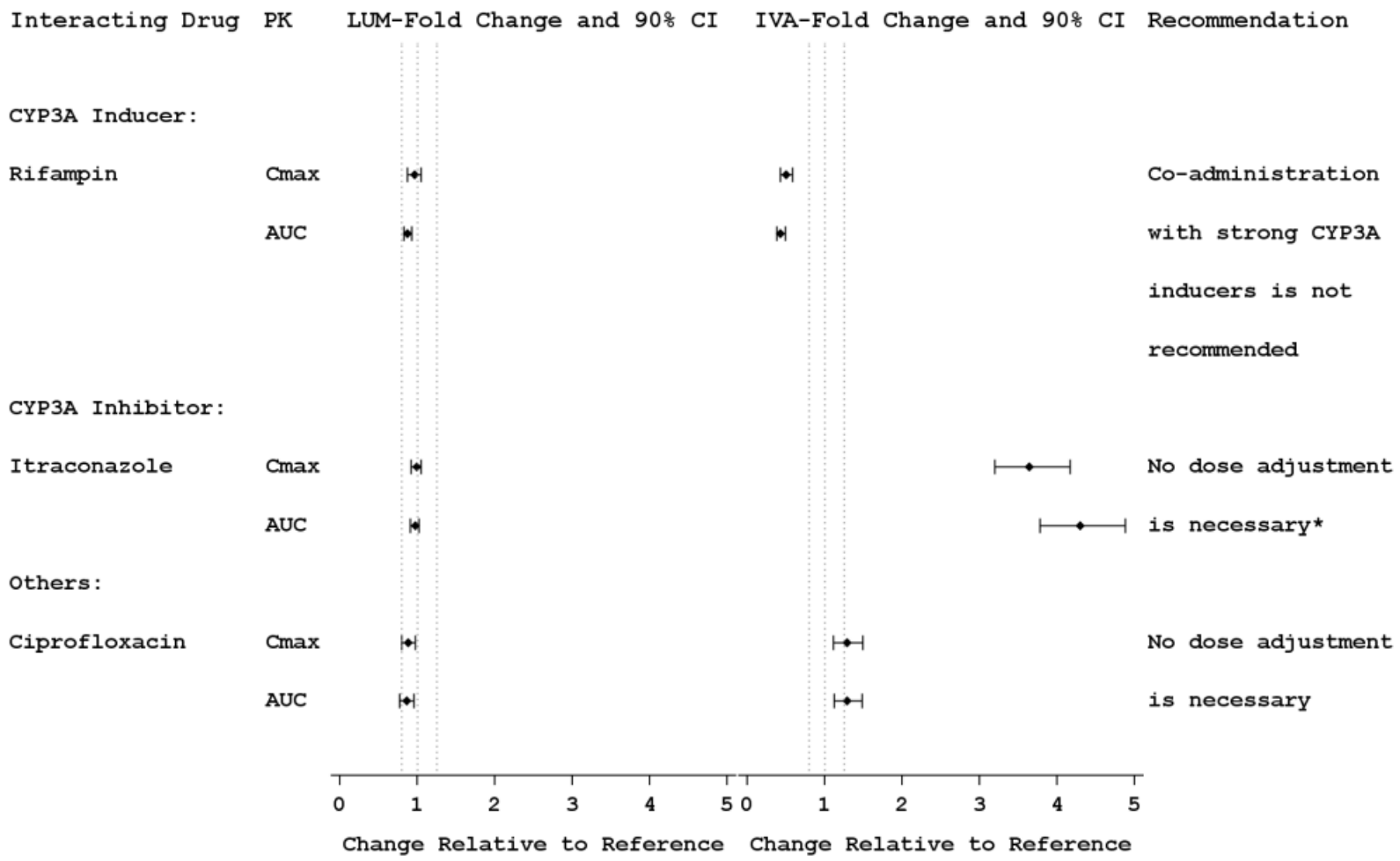
- **Kalydeco®**
- Review of our Kalydeco label – in fact we did include forest plot graphs to represent impact of Kalydeco on other drugs, and impact of other drugs on Kalydeco.

- **Orkambi®**
- We submitted without forest plot representation of these interactions we felt that for this fixed dose combination drug, forest plot(s) could potentially be confusing to the prescriber.

Labeling approach – Section 12.3 Pharmacokinetics Drug Interaction Studies

- **Orkambi®**
  - Agency Communication- please insert forest plot graph to represent impact of extrinsic factor on Lumacaftor and Ivacaftor pharmacokinetics
  - We inserted two forest plot graphs next to each other one for Lumacaftor and one for Ivacaftor
  - This presentation drove readability concerns regarding this critical information

Labeling approach – Section 12.3 Pharmacokinetics Drug Interaction Studies



Labeling approach – Section 12.3 Pharmacokinetics Drug Interaction Studies

- **Orkambi®**
  - Agency Communication – Table 3 (Impact of other Drugs on Lumacaftor 200mg q12h/Ivacaftor 250mg q12h) and Figure 1 are redundant.
  - Choose one or the other for labeling purposes. Our opinion is that, overall, Table 3 is more informative
  - We agreed – forest plot gone but not forgotten

Drug Interaction Table vs. Narrative Format

- When reflecting numerous drug interactions a table allows for a quick and easy reference to find of a particular drug.

- The narrative forces the reader to read the entire section to try to identify a particular drug interaction and to decipher the actual interaction.

- Hence, the table format promotes readability.

To Forest plot or not to Forest plot that is the question ?

- For our particular drug, a fixed dose combination, placing the two Forest plots next to each other was confusing to the reader, and could drive readability issues for the reader

- Forest Plot presentation should be considered very judiciously
  - consider if you are a fixed dose combination

Conclusions

- Work with the Agency regarding your position
- When in doubt request a consult with the Clin. Pharm labeling reviewer
- Tabular Drug Interaction format has been proposed in a number of local labels


THANK YOU