U.S. FOOD & DRUG ADMINISTRATION

Psychopharmacologic Drugs Advisory Committee Drug Safety & Risk Management Advisory Committee Joint Meeting on NDA 213378: Olanzapine/Samidorphan for the Treatment of Schizophrenia and Bipolar I Disorder

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Purpose of Today's Meeting

- New Drug Application submitted by Alkermes, Inc.
- ALKS 3831
  - Fixed-dose combination product: olanzapine/samidorphan
  - Samidorphan, opioid receptor antagonist, intended to reduce the weight gain and metabolic adverse reactions commonly associated with olanzapine.

Development Program

- 505(b)(2) pathway
  - Safety and efficacy of olanzapine component of ALKS 3831 supported by demonstration of bioequivalence to approved formulation of olanzapine
  - Applicant asked to show that samidorphan does not interfere with efficacy of olanzapine
  - Effect of samidorphan component on weight gain assessed in dedicated clinical study

Development Program

- Weight mitigation study
  - At least 6 months
  - Coprimary endpoints:
    - % change from baseline in body weight
    - Proportion of subjects with ≥10% weight gain from baseline
  - Metabolic laboratory parameters considered

Development Program

- Study 302: Exploratory
- Study A305: 4-week antipsychotic efficacy
- Study A303: 6-month weight mitigation
- Studies A304 and A306: 12-month open-label safety

Study A305: 4-week efficacy

- Supports that samidorphan does not meaningfully impair the efficacy of olanzapine

Study A303: Weight Mitigation

- Met endpoints
  - Change from baseline weight: -2.38%, p=0.003
  - ≥10% weight gain: 18% ALKS 3831, 30% olanzapine, p=0.003

- Other findings
  - Waist circumference: -2.12 cm (95% CI: -3.35, -0.89)
  - Systolic blood pressure: -2.60 mmHg (95% CI: -4.73, -0.47)

CI=confidence interval

Study A303: Weight Mitigation

- Other findings
  - Metabolic labs: No meaningful difference
    - Cholesterol (HDL, LDL, total cholesterol)
    - Triglycerides
    - Glucose parameters (fasting glucose, hemoglobin A1c, fasting insulin)
  - Quality of life measures: No difference

Open-label Studies: Weight Mitigation

- Studies A304 and A306
  - 12-month open-label
  - ALKS 3831 only (no olanzapine arm)
  - No signal for late surge in weight gain

Samidorphan: Opioid Antagonist Risk

- Can precipitate withdrawal in opioid dependence
  - One hospitalization for samidorphan-precipitated withdrawal
- Inadequate analgesia/block “high”
  - Overdose risk
  - One hospitalization for opioid overdose in ALKS 3831 study
- Epidemiologic data support potential risk
  - Higher rate of opioid use in indicated population than in general population
  - Known co-prescribing of naltrexone and opioids despite contraindication in labeling

FDA Considerations

- Is the weight mitigation clinically meaningful?
- Does weight mitigation, in the absence of a clear signal of metabolic benefit established in studies conducted by the Applicant, address a safety issue?
- How does the apparent benefit weigh against the opioid-antagonist risks of samidorphan?

Questions to the Committees

1. Has the Applicant presented adequate evidence that samidorphan meaningfully mitigates olanzapine-associated weight gain?

2. Has the Applicant adequately characterized the safety profile of ALKS 3831?

3. Is labeling sufficient to mitigate the risks related to the opioid antagonist action of samidorphan?

4. What, if any, additional data are needed to address outstanding issues?


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