Psychopharmacologic Drugs Advisory Committee
Drug Safety & Risk Management Advisory Committee
Joint Meeting on NDA 211179
Immediate-Release Amphetamine Sulfate for the Treatment of Attention Deficit Hyperactivity Disorder

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Purpose of Today's Meeting

- New Drug Application submitted by Arbor Pharmaceuticals
- AR19: an immediate-release amphetamine sulfate product formulated with properties intended to deter non-oral abuse
- The Committees will be asked to discuss
  - Overall risk-benefit profile of the product
  - Potential public health impact
  - Whether abuse-deterrence has been demonstrated
- Potentially first stimulant with abuse-deterrent labeling

Efficacy of AR19

- Developed under 505(b)(2) pathway
- Relative bioavailability study
- Adult efficacy study
- The efficacy of AR19 for the treatment of ADHD is not in question and will not be a focus of this meeting.

Terminology

- Misuse
  - intentional use, for *therapeutic* purposes, of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed.
- Abuse
  - intentional, *nontherapeutic* use of a drug, even once, for its desirable psychological or physiological effects.
- Nonmedical Use
  - When discussing epidemiologic data, refers to both *misuse* and *abuse*

AR19 Development Program

- No guidance for abuse-deterrent stimulants
- Applicant followed Agency guidance for opioids
  - We have not yet determined that prescription stimulant products warrant the same regulatory approach

Abuse-Deterrent Formulation

- Immediate-release product with proposed strengths up to 40 mg
- Not intended to deter abuse by the oral route
- Intended to deter intranasal and intravenous abuse
- Potential risk secondary to manipulation for use via unintended routes of administration
- Public health impact

Category I Studies

- Physical Manipulation
  - 82.5 to 98.4% of non-ADF amphetamine reduced to an insufflatable particle size (<500 microns) without pretreatment
  - AR19 40mg
    - Without pretreatment: up to 75.6% reduced to an insufflatable particle size
    - With pretreatment: up to 87.8% reduced to an insufflatable particle size
- Extractability and Syringeability
  - Up to 90% of amphetamine can be extracted from non-ADF amphetamine without pretreatment
  - AR19 40 mg
    - Extraction without pretreatment: up to ~15% amphetamine extracted
    - Extraction with pretreatment: up to ~50% (~20 mg) amphetamine extracted
    - Extraction from multiple capsules was largely not feasible

Intravenous Abuse Potential

- In vitro studies provide data on the amount of amphetamine extracted into a solution suitable for injection
- Interpretation of in vitro studies requires understanding of a dose-response curve for reinforcing effects in human abuse potential studies to determine the minimum reinforcing dose
- Based on the Agency's literature search, a 10 mg amphetamine dose administered in 1 mL over 1 minute is expected to produce reinforcing subjective effects
- In vitro manipulation studies demonstrated that it was possible to form a solution containing 10 mg or greater of amphetamine for intravenous use

Intranasal Abuse Potential

- **Completer population** (n=37); prespecified population
  - Analysis failed the validation test, therefore, not appropriate to analyze the data for this population further
  - 9% is not the prespecified margin (10% margin was prespecified)
- ***Applicant's* modified completer population** (n=36); post-hoc exploratory analysis
  - The Applicant stated that the analysis was validated; however, the Agency did not agree with their statistical approach
- ***Agency's* modified completer population** (n=33); post-hoc exploratory analysis
  - Nominally passed the validation test
  - Primary analysis did not reach nominal statistical significance
  - Responder analysis on the primary endpoint did not reach nominal statistical significance

Relevance to Proposed Deterrence Claims

- Not intended to, and will not, deter abuse by the oral route
- In vitro manipulation studies
  - Feasible to obtain a solution for injection containing a reinforcing dose of amphetamine
- IN HAP study
  - Does not provide convincing evidence that the formulation employed for AR19 has significant abuse-deterrent effects, as compared to amphetamine sulfate, when administered by the IN route

Nonclinical

- Potential safety concerns related to talc and high molecular weight polyethylene oxide when product is manipulated
- If AR19 is manipulated in a manner that results in syringeable HMW PEO administration, we cannot rule out the possibility of TMA.
- Talc exposure via injecting or snorting manipulated AR19 capsules likely poses a concern similar to other non-ADF oral formulations that contain talc.

Public Health Implications

- Would ADF stimulants provide meaningful public health benefit (i.e., reduce harms in patients and others)?
  - Could reduce use by riskier, but less common, non-oral routes, but do not address the most common route of non-medical use (oral)
    - Similar limitation for ADF opioid analgesics
  - Potential for differential impacts in different populations
    - Which patients might benefit from ADF stimulants?
      - Most obtain prescription stimulants for non-medical use through diversion
    - Would an ADF stimulant reduce *initiation* of non-oral routes or development of addiction?
    - Could some (e.g., those with advanced SUD, polysubstance use) substitute more dangerous illicit stimulants?
  - Excipient harms if injected?

Points for Discussion

- Considering the patterns of prescription stimulant nonmedical use in the United States, please discuss the potential public health impact of prescription stimulants formulated to be abuse-deterrent.
- Based on the information provided, including the intranasal study comparing this product to amphetamine sulfate, has the Applicant provided adequate evidence that the formulation of AR19 would deter IN use?
- Based on the information provided, including the syringeability study, has the Applicant provided adequate evidence that the formulation of AR19 would deter IV use?

Points for Discussion

- Based on the information provided, has the Applicant adequately characterized the safety of AR19?
- Discuss whether the benefits of AR19 outweigh the risks for the proposed indication.
- What, if any, additional data are needed to address outstanding issues?


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