Naloxone for Outpatient Use: Data Required to Support an NDA

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Regulatory Approach

Two regulatory pathways: 505(b)(1) or 505(b)(2)

- 505(b)(2)
  - An application submitted …for a drug for which the investigations … relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted

Regulatory Approach

Two regulatory pathways: 505(b)(1) or 505(b)(2)

- A 505(b)(2) application may rely upon the Agency's previous finding of safety and effectiveness of a drug product approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act (i.e., NDAs).
- To rely on the Agency's previous findings, must establish a "bridge" (e.g., via comparative bioavailability, or relative BA data) between proposed product and each reference drug to demonstrate that such reliance is scientifically justified.

Naloxone Hydrochloride

- Indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids

- Also indicated for the diagnosis of suspected acute opioid overdosage.

Naloxone Hydrochloride

- After a satisfactory response, patient should be kept under continued surveillance and repeated doses of naloxone should be administered, as necessary, since the duration of action of some narcotics may exceed that of naloxone.
- Naloxone is not effective against respiratory depression due to non-opioid drugs. Reversal of buprenorphine-induced respiratory depression may be incomplete.

Naloxone Hydrochloride

- Abrupt reversal of narcotic depression may result:
  - nausea, vomiting
  - tremulousness, sweating
  - tachycardia, increased blood pressure
  - seizures and cardiac arrest
  - Reported in postoperative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema

Naloxone Hydrochloride

- 0.4 mg/mL
  - 1 mL single dose disposable prefilled syringes, with and without needles, 1 mL and 10 mL vials
- 1 mg/mL
  - 2 mL single dose disposable prefilled syringes with and without needles

Naloxone Hydrochloride

- Naloxone hydrochloride injection may be administered intravenously, intramuscularly, or subcutaneously.
- An initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously, repeat at 2 to 3 minute intervals.
- Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Key Questions

- What is the relative bioavailability of the new product compared to an approved product?
  - If the relative BA is low, will there be adequate efficacy?
  - If the relative BA is high, are there implications for the safety profile?
- Can the product be used by the intended population?
  - Administration by someone other than the patient

Preparing for Clinical Studies

- CMC
  - Standard requirements for product manufacturing and quality apply

Preparing for Clinical Studies

- Use of Devices – Intranasal
  - Describe the modification(s) of an approved device, if any, in the NDA.
  - Provide spray characterization data, e.g., spray pattern, droplet size distribution, and pump delivery.
  - Provide a three-point droplet size distribution, including the percentage of droplets ≤ 10μ
  - Novel devices will need review by CDRH

Preparing for Clinical Studies

- Use of Devices – Intramuscular
  - Full description of device
  - Will require review by CDRH

Preparing for Clinical Studies

- Nonclinical
  - In general, local tolerance studies in two species of adequate duration

Or

- Clinical monitoring of local tissues during the trial an acceptable alternative in this setting (if no novel excipients)
  - Likely single-dose use
  - Clinical experience exists with naloxone
  - Supportive human data

FDA Advice

1. Evaluate the relative bioavailability of at least two different doses compared to parenteral injection of naloxone (IM, IV or SC)
   a. Target plasma naloxone levels detectable in all subjects for a meaningful duration comparable to approved product
   b. Dose selection will be based on assumptions of different levels of absolute bioavailability of intranasal naloxone.

FDA Advice

2. Based on the results of the first study, a second pivotal relative bioavailability study may be needed
   a. Compare a parenteral dose of naloxone of at least 0.4 mg to dose(s) of the new product that would be expected to result in similar or greater drug exposure.

FDA Advice

3. If not bioequivalent, efficacy studies will be needed
    - Very challenging
    - Patient population – community, first responders, emergency department, peri-operative patients, other
    - Informed consent
    - If the systemic BA is low, trials may not be ethical

FDA Advice

4. How much safety data will depend on how much the pharmacokinetic profile differs from the reference product
5. Additional data about usability of the product may be requested
6. Novel excipients or container closures may require additional studies