CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208216Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 13, 2016
From	Anamitro Banerjee, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	208216
Type of Application	505(b)(2)
Applicant	Actavis LLC
Date of Receipt	June 30, 2015
PDUFA Goal Date	April 30, 2016
Proposed Proprietary Name	Azacitidine Injection
Dosage forms / Strength	Injection 100 mg/vial
Route of Administration	Subcutaneous and Intravenous
Proposed Indication(s)	Treatment of patients with the following FAB myelodysplastic syndrome (MDS) subtypes: Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL)
Recommended:	**Approval**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Product (Amit Mitra, Ph.D.); in Panorama, dated March 30, 2016
- Drug Substance (Haripada Sarker, Ph.D.); in Panorama, dated March 30, 2016
- Microbiology (Nutan Mytle, Ph.D.); in Panorama, dated March 30, 2016
- Manufacturing Facilities (Frank Wackes); in Panorama, dated March 30, 2016
- Manufacturing Process (David Anderson, Ph.D.); in Panorama, dated March 30, 2016
- Quality Biopharmaceutics (Banu Zolnik, Ph.D.); in Panorama, dated March 30, 2016
- Quality Method Validation (Laura Pogue, Ph.D.); in DARRTS, dated January 14, 2016
- Clinical (George Shashaty, M.D.); in DARRTS, dated April 04, 2016
- Pharmacology/Toxicology (Ramadevi Gudi, Ph.D.); in DARRTS, dated April 01, 2016

- DMEPA (Ebony Whaley, Pharm.D., BCPPS); in DARRTS, dated April 08, 2016

1. Introduction

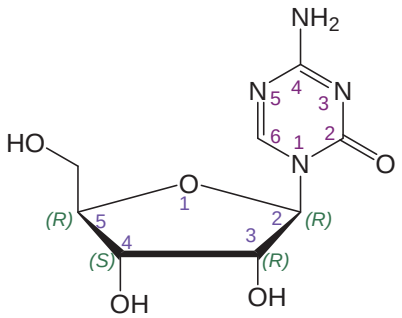
Actavis LLC has submitted NDA 208216 in support of a subcutaneous and intravenous formulation for azacitidine. The application is a 505(b)(2) application, referencing the lyophilized formulation VIDAZA (NDA 050794). VIDAZA is also available in 100 mg single dose vials. For subcutaneous administration, VIDAZA (lyophilized powder) is reconstituted with 4 mL sterile water for injection and shaken vigorously, resulting in a cloudy 4 mg/mL suspension. For intravenous administration, each vial of VIDAZA is reconstituted with 10 mL water for injection and shaken vigorously to obtain a clear solution. Depending on the desired dose, appropriate amount of the VIDAZA solution is injected into 50 – 100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection. Each sterile vial of VIDAZA contains 100 mg of azacitidine and 100 mg mannitol. The Actavis product does not contain mannitol. Sucrose (170 mg/vial) is added (b) (4) (b) (4) and phosphate (b) (4).

2. Background

Azacitidine is an analog of the pyrimidine nucleoside, cytidine and functions as a metabolic inhibitor indicated for treatment of patients with the following FAB myelodysplastic syndrome (MDS) subtypes: Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).
The current application relies on published literature and the Agency's determination of safety and efficacy for the azacitidine lyophilized powder for injection (VIDAZA), which have been previously approved for marketing under NDA 050794 on May 19, 2004.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for NDA 208216 is azacitidine, same as the listed drug VIDAZA.



4-amino-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,3,5-triazin-2(1*H*)-one
Chemical Formula: $C_8H_{12}N_4O_5$
Molecular Weight: 244 (b) (4)

Azacitidine is white to almost white powder that is insoluble or slightly soluble in most organic solvents. (b) (4) The applicant has listed the Log P of azacitidine as -2.3 and a pK_a of (b) (4). Based on the structure as well as solubility in different pH solutions, the listed pK_a of (b) (4) appears to be incorrect.

(b) (4)

(b) (4) The details of the manufacturing process and controls are provided in the DMF (b) (4). The DMF is currently adequate.

Actavis' proposed presentation is 100 mg/vial (b) (4) powder for subcutaneous (SC) and intravenous (IV) administration. In addition to the azacitidine drug substance, the formulation contains sucrose and phosphate (b) (4) (monosodium phosphate and disodium hydrogen phosphate). All the excipients are USP grade. (b) (4)

For administration via the SC route the powder is reconstituted as a suspension with 4 mL sterile water for injection resulting in a concentration of 25 mg/mL. For administration via the IV route the powder is reconstituted with 10 mL sterile water for injection resulting in a concentration of 10 mg/mL. Appropriate amount of this solution is withdrawn and delivered into a 50 to 100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

The drug product is supplied in a (b) (4) Type I clear glass vial closed with a (b) (4) stopper. The vial is capped (b) (4) The primary container is enclosed in a carton. The photostability data suggest that the azacitidine for injection is not photosensitive and a special primary packaging is not necessary for light protection.

(b) (4)

The related substances and residual solvent specification was consulted as to whether they are qualified at their proposed acceptance criteria. The Pharm-Tox reviewer reviewed the justification provided in the NDA and indicated that they are qualified at the proposed acceptance criteria. The analytical methods for the control of the drug product and the validation data were reviewed and found to be acceptable.

The applicant provided 12 months long term (25°C/60%RH) and 6 months accelerated stability data for 3 batches manufactured from one lot of drug substance. The batch size is approximately (b) (4) kg. The applicant has been (or proposing) testing the inverted samples at 3, 6, 9 12, 18, 24 and 48

months under long term conditions (25°C/60%RH) and at 30°C/75%RH. Accelerated (40°C/75%RH) stability studies are being conducted at 1, 3 and 6 months. The accelerated stability studies are being conducted under inverted conditions and at specific time points at 3 and 6 months both under inverted and upright conditions. Stability testing includes appearance, water content, assay of azacitidine, degradation products, bacterial endotoxin, sterility, reconstitution time for solution and resuspension time for suspension, dissolution time for solution, solution appearance after reconstitution, visible particles, subvisible particles, and pH of solution. Under long term storage conditions, the total impurities increased over time. A drop in assay and increased degradants were observed under accelerated conditions. The stability data is adequate for 24 months of expiry dating period. The applicant provided sufficient physical/chemical stability data to support storage of the reconstituted suspension (diluted with refrigerated water for injection) storage under refrigerated conditions for up to 30 hours with up to 30 minutes for equilibration to room temperature. The applicant also provided adequate physical and chemical stability data for holding the reconstituted solution for up to 2 hour at room temperature for immediate subcutaneous administration.

Facilities: (b) (4) is the drug substance manufacturing and analytical testing site (b) (4) This site is also responsible for packaging and labeling of drug substance, (b) (4) operations of drug substance, and stability testing of drug of the drug substance. Based upon the manufacturing and inspectional history, the firm is considered capable to manufacture azacitidine in accordance with DMF (b) (4). This site was found acceptable based on profile.
Manufacturing, processing, packaging, release testing and stability testing are performed at **Sindan- Pharma SRL (FEI 3005566806)**. No outside contract firms/facilities will be used in the manufacturing of Azacitidine for Injection for SC or IV use, 100 mg/vial. This firm has an acceptable inspectional history (NAI for the last 2 inspections completed (b) (4)). However, based on the risk associated with the manufacturing process, a PAI was recommended for this firm. A FDA-483 was issued to the firm for 2 general observations. Neither 483 observation is considered to have any significant impact upon the capability of the firm to manufacture the drug product Azacitidine. The field investigators classified the inspection as VAI and recommended approval of NDA 208216. An independent review of the EIR and the firm's response to the 483 observations was performed and this review concurred with an acceptable VAI classification and recommended the firm for approval. This firm is considered adequate and capable to manufacture Azacitidine for Injection for SC or IV use, 100 mg/vial based upon the pre-approval inspection findings.

4. Product Quality Microbiology

This product is (b) (4) lyophilized powder. (b) (4) (b) (4) (b) (4) The drug product specification includes bacterial endotoxins testing and sterility testing as per USP <85> and USP <71>, respectively. No pending microbiological concerns remain for the NDA.

5. Biopharmaceutics

The Division of Biopharmaceutics evaluated the overall information supporting the biowaiver request for the SC and IV routes. The applicant requested biowaiver based on the following:

- Comparison of injection site, and technique
- Effect of excipients on safety (sucrose vs. mannitol (b) (4))
- Comparison of physico-chemical characteristics and in vitro dissolution data
- Assessment of the impact of mannitol and sucrose on the PK and renal elimination of azacitidine
- Pharmacokinetic information and literature data for the listed drug product, VIDAZA® (azacitidine) following SC and IV administration

The overall information/data described provided in the submission was found to be acceptable for the subcutaneous and IV routes of administration.

Since the SC suspension dissolves very rapidly, (b) (4) (b) (4). The applicant was requested to The reconstitution test with an acceptance criterion of not more than (b) (4) seconds is one of the tests included in the specifications controlling the quality of the proposed drug product.

Overall CMC Recommendation: The Office of Pharmaceutical Quality recommends an **APPROVAL** action for NDA 208216. No CMC deficiencies were identified in the OPQ review.

6. Clinical Pharmacology

No review

7. Non-Clinical Pharmacology/Toxicology

No nonclinical study reports were submitted for this NDA. The applicant is relying on the FDA's previous findings of safety and effectiveness of the listed drug VIDAZA (NDA 050794) in addition to the published literature in addition to results from the applicant's study comparing this product and VIDAZA for bioequivalence, dissolution and other quality attributes. This application is approvable from the perspective of pharmacology/toxicology.

8. Clinical/Statistical-Efficacy

Approval for Azacitidine for Injection is being sought via the 505(b)(2) pathway based on the information available to the FDA for the reference listed drug VIDAZA (NDA 050794). VIDAZA is provided as a sterile lyophilized powder containing 100 mg azacitidine and 100 mg mannitol in a (b) (4) mL vial. The proposed product also contains 100 mg azacitidine sterile lyophilized powder, but in a (b) (4) mL vial. This product however contains 170 mg sucrose and phosphate (b) (4) instead of mannitol.

No clinical data were submitted with this application. The applicant has based its conclusion of effectiveness and safety of azacitidine for injection on the data available to FDA for the listed drug VIDAZA. The applicant requested a waiver from the need to perform bioequivalence (BE) and bioavailability (BA) studies as the drug will be administered intravenously or subcutaneously. The applicant claims that the data/information provided in this application assures "sameness" of the drug.
The initial dose of the drug is 75 mg/m^2 given intravenously or subcutaneously daily for 7 days. After a 3 week hiatus, similar cycles are administered every 28 days. The dose may be increased to 100 mg/m^2 if no response occurs by 2^{nd} to 4^{th} cycle. The dose is reduced for neutropenia, thrombocytopenia, or an unexplained decrease in serum bicarbonate to <20 meq/L.

9. Safety

No new information provided. DMEPA reviewer recommends a revision in the carton to inform the healthcare practitioners that Azacitidine should be diluted prior to intravenous infusion.

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

All the disciplines participated in the labeling review. The labeling is identical to that of VIDAZA except for the name, inactive ingredients, applicant, and product specific information. The applicant accepted all the editorial changes to the PI and the carton and container labels proposed by the FDA.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product is nearly identical to the listed product, VIDAZA. No new clinical or nonclinical data were provided with this submission, as no studies were conducted for this 505(b)(2) application. The cross disciplinary team lead recommendation is for an **APPROVAL**.

- **Risk Benefit Assessment**

Please refer to NDA 050794.

Anamitro Banerjee -S
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