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Draft Guidance on Verteporfin

August 2024

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Active Ingredient:	Verteporfin
Dosage Form:	Injectable
Route:	Injection
Strength:	15 mg/vial
Recommended Studies:	Two options: (1) in vitro comparative characterization studies, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: In vitro comparative characterization studies

To demonstrate bioequivalence by this option, the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

Comparative physicochemical characterization of the test product and reference standard (RS) products. The comparative study should be performed on at least three batches of both the test product and RS products and should include:

a. Liposome size and size distribution
b. Liposome composition, including lipid and lactose contents, and free and encapsulated drug concentrations[3]
c. Liposome morphology and number of lamellae

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD.
[3] Verteporfin has two regioisomers, BPD-MA_C and BPD-MA_D. The molar ratio of BPD-MA_C and BPD-MA_D and the drug-to-lipid weight ratio should be comparable between test and RS products.

d. Liposome electrical surface potential
e. Lipid bilayer phase transition
f. Liposome in vitro drug leakage under physiologically relevant conditions

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

An in vivo pharmacokinetic bioequivalence study is requested for any generic verteporfin injection that has unacceptable data from in vitro comparative studies. Any prospective applicant choosing this option should discuss with the FDA their study plan via pre-abbreviated new drug application (pre-ANDA) product development meeting request prior to initiating the study.

1. Type of study: Fasting[4]
Design: Single-dose, two-way crossover in vivo
Strength: 15 mg/vial
Dose: 6 mg/m^2
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: A single dose, two-way crossover, and fasting bioequivalence study in healthy subjects at 6 mg/m^2 dose is recommended. Due to the immediate transfer of verteporfin from liposomes to lipoprotein in blood circulation, liposomal formulation does not cause specific accumulation of verteporfin in tissue and no liposome encapsulated verteporfin is present in circulation. Hence, total plasma verteporfin concentration can be measured to establish the bioequivalence between test and RS products.

Following injection with test or reference products, subjects should avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded to prevent the occurrence of a local burn which could be severe. Subjects who experience severe decrease of vision of 4 lines (ETDRS charts) or more within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels.

Analyte to measure: Verteporfin in plasma

Bioequivalence based on (90% CI): Verteporfin

Additional information:

Same drug product composition:
Being a parenteral drug product, a generic verteporfin injectable injection product must be Q1/Q2 the same as the RLD, except for differences in buffers, preservatives, and antioxidants; under the condition that the prospective applicant identifies and characterizes these differences and demonstrates that the differences do not impact the safety/efficacy profile of the drug product. Currently, FDA has no recommendations for the type of studies that would be needed to

[4] If the health conditions of patients prevent fasting, the sponsor can provide a non-high-fat diet during the proposed study. Alternatively, the treatment can be initiated 2 hours after a standard (non-high fat) breakfast.

demonstrate the impact of using different buffers, preservatives, or antioxidants on the safety/efficacy profile of the drug product.

Lipid excipients are critical in the liposome formulation. Prospective applicants should obtain lipids from the same category of synthesis route (natural or synthetic) as found in the RLD. Information concerning the chemistry, manufacturing and control of the lipid components should be provided as per the recommendations in the most recent version of the FDA guidance for industry on *Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation*.[a] Prospective applicants should have specification on lipid excipients that are like the lipid excipients used to produce the RLD. Additional comparative characterization (beyond meeting specifications) of lipid excipients, including the distribution of the molecular species should be provided.

Equivalent liposome characteristics:
Comparative physicochemical characterization studies should be performed on at least three batches of both the test and RS products, at least one test batch should be produced by the commercial scale process and be used in the in vitro comparative characterization studies or the in vivo bioequivalence study, and should include:

- Liposome composition: Liposome composition including lipid content, free and encapsulated drug, and lactose concentration should be measured. Verteporfin has two regioisomers, BPD-MA_C and BPD-MA_D. The molar ratio of BPD-MA_C and BPD-MA_D and the drug-to-lipid weight ratio should be comparable. The percentage of drug encapsulation can be calculated from liposome composition values.

- Liposome size and size distribution: Due to the leaky nature of its lipid bilayer, there is immediate and complete verteporfin release in blood circulation upon administration of verteporfin injection. Thus liposome size of the product is not critical regarding release and disposition of verteporfin. However, the liposome size may affect the drug administration. For example, large liposomes can block the infusion syringe filter. Furthermore, liposome size can be utilized to measure batch-to-batch variations. Hence, liposome mean particle size and distribution are recommended to be comparable to that of the RS.

- Liposome morphology and number of lamellae: Liposome morphology and lamellarity should be determined as the retention and release extent of verteporfin might be influenced by the degree of lamellarity.

- Electrical surface potential or charge: Surface charge on liposomes can affect the stability of liposome verteporfin. Liposome surface charge should be comparatively measured.

- Lipid bilayer phase transitions: Equivalence in lipid bilayer phase transitions will contribute to demonstrating equivalence in bilayer fluidity and uniformity. The phase transition profiles of the test product should be comparable to those of the RS product.

- In vitro verteporfin release under physiologically relevant conditions: The approach outlined under Option 1 of this guidance is based on the immediate and complete release of verteporfin in blood circulation expected to occur following intravenous administration. Hence, prospective applicants are expected to demonstrate immediate and complete release of verteporfin under physiologically relevant conditions.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.