Contains Nonbinding Recommendations

Draft Guidance on Verteporfin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Verteporfin

Form/Route: Liposome injection/Intravenous

Recommended studies: 2 options: In Vitro or In Vivo Studies

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1. In Vitro Option

When the test and reference liposome products

- have the same drug product composition (qualitatively (Q1) and quantitatively (Q2) the same) and
- have equivalent liposome characteristics including liposome size, composition, morphology, number of lamellae, electrical surface potential, and in vitro drug leakage under physiologically relevant conditions.

In vivo bioequivalence study can be waived. In vitro characterization should be conducted with at least three lots of both test and reference products.

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2. In Vivo Option (One Study)

If a test product is Q1 and Q2 the same as the RLD but has different in vitro liposome characteristics from the RLD, BE should be established by conducting an in vivo study in healthy subjects. We recommend that any sponsor choosing this option submit their protocol to the OGD Division of Bioequivalence for review and concurrence prior to initiating the study.

Type of study: Fasting*
Design: Single-dose, two-way crossover in vivo
Strength: 15 mg/vial
Dose: 6 mg/m^2
Subjects: Healthy volunteers

Additional Comments: 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 in order 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. Females should not be pregnant or lactating.

Analytes to measure (in appropriate biological fluid): Verteporfin in plasma

Bioequivalence based on (90% CI): Plasma AUC and C_{max} for total verteporfin. Note: the pivotal bioequivalence study should be conducted using test product produced by the proposed commercial scale manufacturing process.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Scientific Rationale for Waiver of In Vivo Bioequivalence Studies

1. Verteporfin liposomes are administered intravenously. Both in vitro and in vivo studies revealed immediate and complete transfer of verteporfin from liposomes to plasma proteins, indicating no drug retention in liposomes after intravenous administration. The liposome vesicles only serve as a verteporfin solubilizer.

    - Due to leaky nature of the lipid layer in the Visudyne formulation, there is an immediate and complete verteporfin release in 5% v/v fetal bovine serum at 37°C.

    - A preclinical tissue distribution study showed that the liposome formulation did not cause accumulation of verteporfin in mouse liver, lung and spleen compared with DMSO solubilized verteporfin, indicating negligible reticulo-endothelial system (RES) uptake of verteporfin after i.v. administration of Visudyne.

    - A clinical pharmacokinetic study showed a relatively large volume of distribution of liposomal verteporfin (0.6 L/kg) and a high plasma protein binding (90%), indicating an extensive extravascular distribution of released verteporfin.

    All above evidence suggests that there is no retention of verteporfin in liposomes after i.v administration of Visudyne and Visudye can be regarded as a parenteral “pseudo” solution. According to FDA guidance, BE is accepted as "self-evident" if a drug product contains the same active and inactive ingredients in the same concentration as the reference listed drug (RLD) and when the drug product is a parenteral solution intended solely for administration by injection. Hence, if a test product formulation is Q1 and Q2 the same as the reference product and demonstrates immediate and complete release of verteporfin, in vivo BE study of generic verteporfin can be waived. Additional in vitro

characterization is required to demonstrate product equivalence between generic and RLD (see below).

Additional information:

Same drug product composition

To waive in vivo BE study, a sponsor of a generic verteporfin liposome injection must demonstrate qualitative and quantitative sameness between the test and reference products, except differences in buffers, preservatives and antioxidants provided that the sponsor identifies and characterizes these differences and demonstrates that the differences do not impact the safety/efficacy profile of the drug products. Currently, FDA has no recommendations for the type of studies that would be needed to demonstrate that differences in buffers, preservatives and antioxidants do not impact the safety/efficacy profile of the drug product.

Lipid excipients are critical in the liposome formulation. ANDA sponsors 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 at the same level of detail expected for a drug substance as suggested in the liposome drug products draft guidance[1]. ANDA sponsors should have specification on lipid excipients that are similar to those 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

In vitro liposome characterization should be conducted on at least three batches of the ANDA and RLD products (at least one ANDA batch should be produced by a commercial scale process). Attributes that should be included in the characterization of ANDAs claiming equivalence to Visudyne™ are:

- 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

Due to the leaky nature of lipid layer, there is immediate and complete verteporfin release in blood circulation. Thus liposome size of Visudyne does not appear to be critical with regard to release and disposition of verteporfin. However, the liposome size may affect the drug administration and product shelf-life. For example, large liposomes can block the infusion

[1] Draft guidance for industry: Liposome drug products chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation, FDA (2002) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf

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 RLD.

- 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 and shelf-life of liposome verteporfin. Liposome surface charge should be 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 raw lipid excipients and freeze dried liposomes should be comparable to those of RLD.

- In vitro release under physiologically relevant conditions

The waiver of in vivo BE study for verteporfin liposome products is based on the immediate and complete release of verteporfin in blood circulation following intravenous administration. Hence, the ANDA applicants are expected to demonstrate immediate and complete release of verteporfin under physiologically relevant conditions.

Equivalent in vivo plasma pharmacokinetics of total drug

We recommend a single dose, two-way crossover, and fasting bioequivalence study in healthy subjects at 6 mg/m^2 dose. 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 ANDA and RLD products.