Contains Nonbinding Recommendations

Draft Guidance on Bupivacaine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Bupivacaine

Dosage Form; Route: Injectable, liposomal; injection

Recommended Studies: One study

When the test and reference multivesicular liposome products:

- Have the same drug product composition and
- Have equivalent liposome characteristics including liposome composition, amount of free and encapsulated drug, internal environment of liposome, liposomal particle structure and morphology, liposome size distribution, electrical surface potential or charge, and in vitro release rates.

The following clinical study is recommended to demonstrate bioequivalence:

Pharmacokinetic (PK) bioequivalence study:

Type of study: Fasting*

Design: Single-dose, two-way crossover in-vivo

Strength: 266 mg/20 mL

Subjects: Healthy males and nonpregnant females, general population

Additional Comments: Delivered via local subcutaneous infiltration in the flank area. A moving needle technique should be used for administration. Study treatment in Period 2 should be administered at least 20 days after the Period 1 treatment.

*Alternatively, the sponsor can provide a non-high-fat diet during the proposed study or the treatment can be initiated 2 hours after a standard (non-high-fat) breakfast.

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

Bioequivalence based on (90% CI): Bupivacaine

Waiver request of in-vivo testing: Not Applicable

Note: the pivotal bioequivalence study should be conducted using test product produced by the proposed commercial scale manufacturing process.

Additional Information for the Sponsor:

Same drug product composition

Being a parenteral drug product, a generic bupivacaine liposomal injection must be qualitatively and quantitatively the same as the RLD, except differences in buffers, preservatives and antioxidants provided that the 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 demonstrate that differences in buffers, preservatives and antioxidants do not impact the safety/efficacy profile of the drug product.

Lipid excipients are critical in multivesicular liposomes. ANDA sponsors should obtain lipids from the same category of synthesis route (natural or synthetic) as found in the RLD formulation. 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].

Equivalent liposome characteristics

As with other locally acting products with complex bioequivalence requirements (such as nasal sprays and inhalation products), in vitro liposome characterization should be conducted on at least three batches of the ANDA and RLD product (at least one ANDA batch should be produced by the commercial scale process and used in the in vivo bioequivalence study). Attributes that should be included in comparative characterizations between the ANDA and RLD products are the following:

- Liposome composition: lipid content, free and encapsulated drug.
- Internal aqueous environment of liposome.
- Liposomal particle structure and morphology: Unlike traditional liposomes, multivesicular liposome consists of a non-lamellar honeycomb structure. This unique structure and morphology is important for the sustained-release property. The structure and morphology of the test and reference products should be comparable including the internal honeycomb structure.
- In vitro drug release rates: The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

[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

Dissolution test method and sampling times: Not applicable