Contains Nonbinding Recommendations

Draft Guidance on Difluprednate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Difluprednate

Dosage Form; Route: Emulsion; ophthalmic

Strength: 0.05%

Recommended Study: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product, the following criteria should be met.

i. The test and Reference Listed Drug (RLD) formulations are qualitatively[1] and quantitatively[2] the same (Q1/Q2)

ii. Acceptable comparative physicochemical characterization of the test and RLD formulations. The comparative study should be performed on at least three exhibit lots of both test and reference products.[3]

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality, and surface tension. Sponsors should also submit information on the drug distribution in different phases within the formulation.

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) based on D_{50} and SPAN (alternatively harmonic intensity-weighted average particle diameter and polydispersity index derived from cumulant analysis of the intensity size distribution) for the globule size distribution only (the other parameters do not require PBE analysis). The applicants should provide no less than 10 datasets from 3 batches each of the Test and Reference products to be used in the PBE analysis. Sponsors should compare the size parameter upon serial dilution (if applicable) of the Test and Reference products, and provide histograms of size distribution data of each diluted sample.

iii. Acceptable comparative in vitro drug release rate tests of difluprednate from the test and Reference formulations. The methodology used for in vitro drug release testing

[1] Q_1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.
[3] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

should be able to discriminate the effect of process variability in the production of the test formulation.

II. In vivo option:

Recommended studies: One study

Type of study: Bioequivalence study with pharmacokinetic (PK) endpoint
Design: Single-dose, parallel design, in vivo in aqueous humor
Strength: 0.05%
Subjects: Patients undergoing indicated cataract surgery
Additional comments: Please refer to the Draft Guidance on Loteprednol Etabonate ophthalmic suspension/drops[4] for additional comments regarding the In Vivo pharmacokinetic study in aqueous humor.

Analytes to measure (in appropriate biological fluid): Difluprednate and its active metabolite, 6α, 9-difluoroprednisolone 17-butyrate (DFB), in aqueous humor

Bioequivalence based on (90% CI): Difluprednate

Please submit DFB metabolite data as supportive evidence of therapeutic outcome. However, the DFB metabolite data will be subject to the CI approach for BE demonstration if you demonstrate that the difluprednate parent drug levels are too low to allow reliable analytical measurement.

Dissolution test method and sampling times: Not applicable

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM249244.pdf