

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Ketotifen fumarate

November 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Ketotifen fumarate

Dosage Form; Route: Solution/drops; ophthalmic

Recommended Study: Request for waiver of in vivo bioequivalence study requirements

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b)(1), a generic ketotifen fumarate ophthalmic solution/drops product must be qualitatively (Q1)¹ and quantitatively (Q2)² the same as the Reference Listed Drug (RLD).

An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.³

Ketotifen fumarate ophthalmic solution/drops products should have comparable physicochemical properties to the Reference Standard (RS) including but not limited to pH, specific gravity, osmolality, buffer capacity, and viscosity, if applicable. Comparative analysis should be performed on three batches, if available, of both test and RS products.

¹ Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.

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 product.

³ Refer to 21 CFR 314.94(a)(9)(iv) for product for ophthalmic use. In addition, for ophthalmic route of administration, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo bioequivalence study or studies. Refer to the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*.

Additional information:

Device:

The Reference Listed Drug (RLD) is presented in a bottle fitted with a dropper tip. The dropper tip is the device constituent.

User interface assessment:

An Abbreviated New Drug Application (ANDA) for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.^a

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^a For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.