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Draft Guidance on Uridine Triacetate

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In July 2017, FDA issued a draft product-specific guidance for industry on generic uridine triacetate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Uridine triacetate

Dosage Form; Route: Granule; oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 6 g (6 g measured from one packet of uridine triacetate granules, 10 g/packet)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: For applicants planning to only submit an ANDA referencing the reference product of uridine triacetate granules 2 g/packet, in vivo bioequivalence study may be conducted using up to three packets of the 2 g/packet product taking into consideration the baseline uridine concentrations.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 6 g (6 g measured from one packet of uridine triacetate granules, 10 g/packet)
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analyte to measure: Uridine in plasma

Because the active metabolite uridine is an endogenous substance, the plasma concentrations of uridine should be corrected for baseline endogenous concentrations. Refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*[a]

Bioequivalence based on (90% CI): Baseline-corrected uridine

Waiver request of in vivo testing: Note that uridine triacetate granules 2 g/packet and uridine triacetate granules 10 g/packet are the subject of two separate reference products. If applicants plan to pursue both products, two separate applications must be submitted comparing to the appropriate reference products. In this case, applicants may request a waiver of in vivo bioequivalence testing for the uridine triacetate granules 2 g/packet, based on the following: (i) acceptable bioequivalence studies on the 6 g dose (6 g measured from one packet of 10 g/packet), (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon review of the ANDA.

Product-specific testing conditions for in vitro feeding tube studies: These studies apply only if applicant is planning to submit an ANDA referencing the reference product of uridine triacetate granules, 10 g/packet.

The approved labeling for the reference product states that the product may be administered via a nasogastric (NG) tube or gastrostomy (G) tube when necessary (e.g., severe mucositis or coma). Conduct the in vitro feeding tube studies including comparative recovery testing with four repeated administrations, and sedimentation volume and redispersibility testing. For general procedures of in vitro feeding tube studies, refer to the most recent version of the FDA guidance for industry on *Oral Drug Products Administered Via Enteral Feeding Tube: In Vitro Testing and Labeling Recommendations*.[a]

Testing tubes: NG tube (8 French) and G tube (12 French)

Testing strength: 10 g

Dispersion medium: Disperse the crushed drug granules in 4 fluid ounces (about 120 mL) of the reconstituted food starch-based thickening product. After administration of the mixture using a NG tube or G tube, flush the tube with water.

Incubation times: 0 and 15 minutes

Revision History: Recommended July 2017; Revised May 2022

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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.