Contains Nonbinding Recommendations

Draft Guidance on Uridine Triacetate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Granules; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-way crossover in-vivo
   Strength: 6GM (6GM measured from 10GM package; or three 2GM packages)
   Subjects: Healthy males and females (non-pregnant)
   Additional Comments: 10GM administration of uridine triacetate oral granules has not been demonstrated to be safe for use in healthy subjects; while 6GM has demonstrated to be well tolerated in healthy subjects. The applicant may consider using 2GM (one 2GM package) as the testing strength if planning to only submit an abbreviated new drug application (ANDA) referencing XURIDEN.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-way crossover in-vivo
   Strength: 6GM (6GM measured from 10GM package; or three 2GM packages)
   Subjects: Healthy males and females (non-pregnant)
   Additional Comments: see comments above

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

Since the active metabolite uridine is an endogenous substance, the serum concentrations of uridine should be corrected for baseline endogenous levels. Please refer to the Draft Guidance on Ergocalciferol Capsule for additional information regarding endogenous compounds.

Bioequivalence based on (90% CI): Uridine

Waiver request of in-vivo testing: Please note that XURIDEN® 2GM/PACKAGE and VISTOGARD® 10GM/PACKAGE are the subject of two separate reference-listed drug products (RLD). Two separate applications must be submitted comparing to the appropriate reference products. An applicant may request a waiver of in vivo bioequivalence testing for the 2GM/PACKAGE using XURIDEN® Oral Granules as the RLD, based on (i) acceptable bioequivalence studies at the recommended 6GM dose, (ii) acceptable dissolution testing

between both strengths, and (iii) proportional similarity in the formulations between both strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of both strengths of the test and reference products. Specifications will be determined upon review of the ANDA.

In Vitro Comparative Feeding Tube Studies: These studies only apply if applicant is planning to submit ANDA referencing VISTOGARD ® (10GM/PACKAGE).

The approved labeling for the reference product states that the product may be administered through a nasogastric tube (NG tube) or gastrostomy tube (G Tube) when necessary (e.g, severe mucositis or coma). Conduct the following in vitro comparative testing to compare the performance of the test product (T) to that of the reference product (R) to support feeding tube administration. Both NG tube (8 Fr) and G tube (12 Fr) need to be evaluated.

Feeding tube preparation procedure: Prepare the feeding tube studies using 12 units each of the test and the reference products at the 10 gram for 0 and 15 minutes by the following procedure:

1) Prepare approximately 4 fluid ounces of a food starch-based thickening product in water and stir briskly until the thickener has dissolved. Crush the contents of one full 10 gram packet of drug granules to a fine powder. Add the crushed drug granules to 4 ounces of the reconstituted food starch-based thickening product.

2) Connect an oral syringe to the feeding tube, transfer the drug granule suspension into the oral syringe, and pass the suspension through the feeding tube into a collection container. After administration of the suspension using feeding tube, flush the feeding tube with additional amount of water.

3) Repeat the testing procedure described above with a fresh set of 12 units. However, after suspending the tablet content in step (a), wait 15 minutes prior to injecting the contents into the feeding tube.

1. Comparative recovery testing: conduct comparative recovery studies to determine what percentage of the initial dose passes through a combination of oral syringe and feeding tube. Follow the feeding tube preparation procedure outlined above. Determine the percentage of uridine triacetate recovered at the tube exit relative to the initial dose for both the test and the reference products using a validated analytical method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. If high variability is observed, the applicant may increase the number of units used for this test. Visually examine the tube and the syringe for any aggregation, adherence, clogging, etc.

   In addition, as the labeling indicates that the product may be administered up to four times per day, the worst case scenario determination should include repeated administration conditions (e.g. the same tube should be used for four sequential administrations of the drug product)

2. Risk assessment of administration conditions: Feeding tubes (NG/G) may be made with different materials (e.g., PVC, silicone, and polyurethane) which can impact the inner tube diameter. Feeding tubes are also available with different designs (e.g. number of ports and/or eyes; retention balloons; open or closed distal end) which can impact the flow of material through the tube. The applicant should consider the design of the various feeding tubes that may be used for product administration, and test a representative selection (a minimum of 3 for both NG and G tubes) of tube designs to ensure complete delivery of the drug product. Note that for G tubes, at least one tube should be tested with an inflated balloon configuration. Evaluation of testing conditions may be made on the basis of recovery study (testing procedure as above) and visual analysis and documented with photographs and videos.

3. Standard operating procedure submission: Submit standard operating procedures for the above in vitro feeding tube testing. Include details about the type of water, the pH of water, brand and type of thickening product, flush volume used in the studies, the tube and syringe used (e.g. material, brand, size, with or without balloon, etc.), holding position of the tube, shaking method, analytical site and testing dates, etc. for each of the studies. Submit individual data, mean values, standard deviations, and coefficients of variation (CV %) in all the testing in an Excel file. Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all observations and supply supporting photographs. For recovery studies, videos may be provided to document the testing process and associated observations. Provide the pre-study and within-study assay validation report. Conduct all the above testing on unexpired test and reference batches.