

### Draft Guidance on Azathioprine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Azathioprine

**Form/Route:** Tablet /Oral

**Recommended studies:** 1 study

Type of study: Fasting

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

Strength: 50 mg

Subjects: Patients who are on a regimen of oral azathioprine tablets.

Additional Comments: Specific recommendations are provided below.

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**Analytes to measure (in appropriate biological fluid):** Azathioprine and its active metabolite, 6-mercaptopurine in plasma

**Bioequivalence based on (90% CI):** Azathioprine

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C<sub>max</sub>.

**Waiver request of *in-vivo* testing:** 25mg, 75 mg and 100 mg based on (i) acceptable bioequivalence studies on the 50 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths.

**Dissolution test method and sampling times:**

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units of the test and reference products. Specifications will be determined upon review of the application.

**Additional comments regarding the PK bioequivalence study**

1. Submission of an Investigational New Drug Application (IND) is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as Azathioprine (See 21 C.F.R § 320.31).

2. These studies should be conducted in patients who are already receiving azathioprine at a fixed dose of 50 mg/day or 100 mg/day. If you choose to enroll patients who are on a regimen of 100 mg/day, then each patient should receive two tablets of 50 mg strength.
3. The bioequivalence study should be conducted on 2 consecutive days of a standard treatment cycle, with each of these days representing a study period. No additional washout is necessary.
4. The study should be designed around each patient's existing azathioprine regimen.
5. No changes in dose or regimen should be made for the purpose of the bioequivalence study.
6. In a crossover study, the dose that each patient receives should be the same between the two study periods. If a change in dose is needed, that patient should be dropped from the study.
7. Any concomitant medications taken by each patient should be the same for the two study periods. If a change in concomitant medications is necessary, that patient should be dropped from the study.
8. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study.
9. Patients with inherited deficiency of methyltransferase activity must be excluded from these studies.
10. The protocol may exclude concomitant chemotherapy and should exclude prior exposure to doxorubicin.
11. The informed consent should include a description of the known genotoxicity of 6-mercaptopurine in human cells and animal models.