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VIA ELECTRONIC SUBMISSION (WWW.REGULATIONS.GOV)
Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Buchanan Ingersoll & Rooney PC ("Buchanan") hereby submits this Citizen Petition to the U.S. Food and Drug Administration ("FDA" or "the Agency") regarding TABLOID® (thioguanine) 40 mg tablets, New Drug Application ("NDA") 012429, ("TABLOID") under 21 C.F.R. § 10.30 requesting that the Commissioner of Food and Drugs: (1) maintain and strictly apply the requirements of the current product specific guidance ("PSG") to any Abbreviated New Drug Application ("ANDA") for thioguanine tablets[1], particularly 40 mg tablets, to ensure such ANDAs contain the results of an in vivo study demonstrating bioequivalence to the referenced listed drug ("RLD") TABLOID, prior to approval; and (2) pursuant to FDA's biopharmaceutics classification system, refrain from granting a waiver as to performing in vivo bioequivalence testing for any generic formulation of thioguanine.

TABLOID is a cytotoxic orally administered chemotherapeutic drug indicated for remission induction and remission consolidation treatment of acute nonlymphocytic leukemias.[2] As with other cancer drugs, thioguanine poses the risk of causing myelosuppression, a side effect where cell production by bone marrow is inhibited.[3] This condition can be life-threatening and may demand modification or cessation of the dosage. Information regarding the risk of

[1] FDA, Draft Guidance on Thioguanine (Sept. 19, 2012) (hereinafter "PSG for Thioguanine") *available at* https://www.accessdata.fda.gov/drugsatfda_docs/psg/Thioguanine_Tabs_012429_RC09-12.pdf. All PSG can be found on FDA's "Product-Specific Guidances for Generic Drug Development" database *available at* https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

[2] *See* Current Approved Label for TABLOID (NDA 012429) (last accessed Jan. 29, 2025).

[3] *Id.*

myelosuppression is contained in several sections of the package insert ("PI") for TABLOID including the CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTONS and OVERDOSE sections.[4]

Although the most notable adverse event and primary toxicity of thioguanine is myelosuppression, other adverse event and toxicities have also occasionally been observed, particularly when thioguanine is used in combination with other cancer chemotherapeutic agents.[5] For example, thioguanine poses a high risk of liver toxicity, with current labeling for TABLOID containing the following, prominently displayed warning:

> **Hepatoxicity and Bone Marrow Suppression**
>
> SINCE DRUGS USED IN CANCER CHEMOTHERAPY ARE POTENTIALLY HAZARDOUS, IT IS RECOMMENDED THAT ONLY PHYSICIANS EXPERIENCED WITH THE RISKS OF THIOGUANINE AND KNOWLEDGEABLE IN THE NATURAL HISTORY OF ACUTE NONLYMPHOCYTIC LEUKEMIAS ADMINISTER THIS DRUG.
>
> THIOGUANINE IS NOT RECOMMENDED FOR MAINTENANCE THERAPY OR SIMILAR LONG-TERM CONTINUOUS TREATMENTS DUE TO THE HIGH RISK OF LIVER TOXICITY ASSOCIATED WITH VASCULAR ENDOTHELIAL DAMAGE (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).[6]

Due to the potential for liver toxicity, medical providers and patients are instructed to promptly discontinue treatment if any evidence of liver toxicity, including clinical jaundice, is present.[7] These serious side effects also require that patients be closely and frequently monitored via clinical and hematological evaluation during treatment with TABLOID.[8] This includes "liver function tests (serum transaminases, alkaline phosphatase, bilirubin) at weekly intervals when first beginning therapy and at monthly intervals thereafter."[9] More frequent performance of these liver function tests is recommended for patients with known pre-existing liver disease or in patients who

[4] *Id.* at 3–8.

[5] *See* Current Approved Label for TABLOID (NDA 012429) (last accessed Jan. 29, 2025).

[6] *Id.* at 3.

[7] *Id.* at 4–5 and 7.

[8] *Id.* at 2, 4, and 5.

[9] *Id.* at 5.

are receiving thioguanine and other hepatotoxic drugs.[10] Additionally, for patients with repeated severe myelosuppression, evaluation for be thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency is also required.[11]

Using a method of determining bioequivalence that is not suitably accurate nor considered a sensitive method would result in therapeutic inequivalence and also pose significant safety risks or otherwise endanger the lives of patients. The request herein is not only consistent with current bioequivalence guidance established within the PSG for Thioguanine but will also make certain that the scientific standards and criteria set forth in such guidance to ensure safety and effectiveness remain in effect and are equitably applied to all ANDAs before they may be approved.

Accordingly, FDA should grant this Petition in its entirety.

A. ACTION REQUESTED

The petitioner requests that the Commissioner take the following actions:

1. Maintain and strictly apply the requirements of the current PSG for Thioguanine, which represents scientifically appropriate standards for this class of drugs (oral chemotherapeutic dosage forms), to all pending, newly submitted, and future ANDAs for thioguanine tablets.

2. Pursuant to FDA's biopharmaceutics classification system, refrain from granting a waiver of the requirement to perform in vivo bioequivalence testing (a "biowaiver") for any generic formulation of thioguanine.

B. STATEMENT OF GROUNDS

I. BRIEF OVERVIEW OF THE STATUTORY AND REGULATORY BACKGROUND

The Federal Food, Drug, and Cosmetic Act ("FFDCA") requires new drugs to undergo rigorous clinical and non-clinical testing to demonstrate that they are safe and effective prior to approval as an NDA.[12] Such drugs are commonly referred to as "innovator" or "brand" drugs. Comparatively, a company that is developing a generic version of an approved new drug would

[10] *Id.*

[11] *Id.* at 4.

[12] FFDCA § 505; 21 U.S.C. § 355.

normally seek approval of the generic drug via an ANDA.[13] This abbreviated approval pathway was established in the Drug Price Competition and Patent Term Restoration Act of 1984 (also commonly referred to as the Hatch-Waxman Act).[14]

A main reason for the creation of the ANDA pathway was to increase generic competition and decrease production costs by allowing generic drugs to enter the market without having to gather all the same scientific data as the innovator drug. Specifically, while ANDAs must include data and information that demonstrate the generic drug's quality in reference to the RLD, they do not generally require extensive preclinical (animal) and certain clinical (human) data to establish safety and effectiveness before being approved. Instead, companies that develop generic drugs may rely on FDA's prior findings of safety and efficacy established for the originally approved NDA that becomes the RLD for the ANDA.

In order to ensure that a generic drug could perform in the same manner as the brand product, the ANDA pathway requires that a generic drug product be determined to be therapeutically equivalent to the RLD. To establish therapeutic equivalence for ANDA approval, generics must ensure they are both a pharmaceutical equivalent and bioequivalent to the RLD.

To be considered a pharmaceutical equivalent, a generic must have the same active ingredient, dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted, as the RLD.[15] The generic must also meet compendial or other applicable standards of strength, quality, purity, and identity.[16]

As to bioequivalence, FDA has defined this to mean "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[17] In other words, bioequivalence means that the generic drug must have the same or similar pharmacokinetic and pharmacodynamic properties as the brand drug, ensuring similar efficacy and safety profiles.

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[13] FFDCA § 505(j); 21 U.S.C. § 355(j).

[14] The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[15] 21 C.F.R. § 314.92(a)(1); 21 C.F.R. §§ 314.94(a)(4)–(6).The ANDA must also generally have the same labeling as the RLD, with limited exceptions. 21 C.F.R. § 314.94(a)(8).

[16] 21 C.F.R. §§ 314.94(a)(4).

[17] 21 C.F.R. § 314.3(b).

FDA requires an ANDA applicant to use "the most accurate, sensitive, and reproducible approach" to demonstrate bioequivalence.[18] For drugs that are systemically absorbed, bioequivalence is typically demonstrated via the conduct of a comparative in vivo bioavailability study between the generic drug and the RLD itself. This type of study measures the rate and extent to which the generic drug is absorbed in the systemic circulatory system in subjects to ensure it is the same as that for the RLD.

II. FDA SHOULD MAINTAIN AND STRICTLY APPLY THE REQUIREMENTS OF THE CURRENT PSG FOR THIOGUANINE TO ALL PENDING, NEWLY SUBMITTED, AND FUTURE ANDAS FOR THIOGUANINE TABLETS

PSGs help streamline generic drug product development by describing the Agency's current thinking on the evidence needed to demonstrate that a certain generic drug product is therapeutically equivalent to the corresponding RLD product.[19] PSGs also include key scientific science and research results and assist with identifying the most appropriate methodology/approach to generating the evidence needed to support ANDA approval.[20] FDA has stated that "[t]his includes in vivo and/or in vitro bioequivalence studies, dissolution testing methods, and various waiver options such as Biopharmaceutics Classification System or BCS-based waiver."[21] Overall, FDA has made clear that PSG are a "value-added proposition" that provide a practical pathway for generic drug approval.[22]

As stated above, TABLOID poses the risk of myelosuppression, a condition which can be serious and life-threatening and may demand modification or cessation of the dosage.[23] TABLOID also poses the risk of other adverse event and toxicities, such a liver toxicity.[24] As such, careful and frequent monitoring via clinical and hematological evaluation during treatment with TABLOID is required or otherwise recommended.

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[18] 21 C.F.R. § 320.24(a).

[19] FDA, "The ABCs of Product Specific Guidances" webpage (last accessed Dec. 24, 2024) *available at* https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/abcs-product-specific-guidances#:~:text=Product%2Dspecific%20guidances%20(or%20PSGs,listed%20drug%20(RLD)%20product; *see also* FDA, "Product-Specific Guidances for Generic Drug Development" webpage (last accessed Dec. 24, 2024) *available at* https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

[20] *Id.*

[21] *Id.*

[22] *Id.*

[23] *See* Current Approved Label for TABLOID (NDA 012429) (last accessed Jan. 29, 2025).

[24] *Id.*

Using a method of determining bioequivalence that is not suitably accurate nor considered a sensitive method would result in therapeutic inequivalence and also endanger the lives of patients. Due to this, FDA established the PSG for Thioguanine which represents scientifically appropriate standards for this class of drugs (oral chemotherapeutic dosage forms).

The request herein is not asking for a change to the current PSG for Thioguanine but instead requesting it be maintained and strictly applied to all pending, newly submitted, and future ANDAs for thioguanine tablets. This includes strict adherence to FDA's determination that waiver requests of in vivo testing are "not applicable."[25] Maintaining and strictly applying the scientific standards and criteria set forth in the current PSG for Thioguanine will ensure safety and effectiveness of all ANDAs themselves and, in turn, ensure patient safety.

Accordingly, FDA should grant this Petition. In the event that FDA determines the current PSG for Thioguanine should be modified, we request FDA: (1) require all pending and recently submitted ANDAs to follow the current PSG for Thioguanine; (2) announce any changes to the PSG for Thioguanine in the Federal Register; and (3) allow for a period of time by which those that disagree with any proposed changes may petition FDA and provide contrary evidence to dispute FDA's proposed changes and assertions (i.e., an appropriate notice and comment period in accordance with the Administrative Procedures Act).

III. FDA SHOULD DENY ALL BCS-BASED BIOWAIVERS OF THE REQUIREMENT TO DEMONSTRATE IN VIVO BIOAVAILABILITY

Under some circumstances FDA will waive in vivo testing requirements (also referred to as a "biowaiver") and allow bioequivalence to be determined via in vitro dissolution testing.[26] Eligibility to use this approach is based on the solubility and permeability of a drug.[27] In order to determine whether a drug is eligible for a waiver, FDA employs the biopharmaceutics classification system ("BCS") which encompasses four classes of active pharmaceutical ingredients used in drug products.[28] These classifications[29] are as follows:

[25] PSG for Thioguanine.

[26] FDA Final Guidance, "M9 Biopharmaceutics Classification System-Based Biowaivers," at 1 (May 2021) (hereinafter referred to as the "M9 Guidance") *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m9-biopharmaceutics-classification-system-based-biowaivers.

[27] *Id.*

[28] M9 Guidance at 1–2.

[29] *Id.*

1. Class I: High Solubility – High Permeability
2. Class II: Low Solubility – High Permeability
3. Class III: High Solubility – Low Permeability
4. Class IV: Low Solubility – Low Permeability

These classifications, and in turn the BCS-based biowaiver, apply only to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation.[30] For example, a waiver may be justified for BCS Class I (highly soluble and highly permeable drug substances) and BCS Class III (highly soluble-poorly permeable) drug substances that exhibit rapid in vitro dissolution and meet numerically specified dissolution criteria.[31] Additionally, a drug product is eligible for a BCS-based biowaiver provided that it satisfies "the criteria regarding solubility and permeability (BCS Class I and III), the drug product is an immediate-release oral dosage form with systemic action, and the drug product is the same dosage form and strength as the reference product."[32]

a. BCS for TABLOID (thioguanine)

Relative to solubility**,** a drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 milliliters (mL) or less of aqueous media over the pH range of 1.2–6.8 at 37±1°C.[33] Thioguanine is recognized as being poorly soluble in water and thus has "low solubility" in accordance with the BCS solubility criteria.[34]

Relative to permeability, assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies (e.g., absolute bioavailability or mass balance) and further states that high permeability can be concluded when the absolute

[30] *Id.*

[31] M9 Guidance at 2–8.

[32] M9 Guidance at 4.

[33] M9 Guidance 2–3.

[34] Bayoumy, A.B., Crouwel, F., Chanda, N. et al., "Advances in Thiopurine Drug Delivery: The Current State-of-the-Art," Eur. J. Drug Metab. Pharmacokinet. 46, 743–758 (Sept. 6, 2021) (Attachment A) *available at* https://link.springer.com/article/10.1007/s13318-021-00716-x (Thiopurines, due to their chemical properties, are known for low solubility in water and varying rates of bioavailability) referencing Friedman, A.B., Sparrow, M.P., Gibson, P.R., "Thiopurines: Azathioprine, Mercaptopurine, and Thioguanine," Compendium of Inflammatory Diseases, Springer, Basel. p. 1–12.

bioavailability is ≥85%.[35] High permeability can also be concluded if ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites.[36]

The PI for TABLOID[37] states that the absorption of an oral dose of thioguanine in humans is incomplete and variable, averaging approximately 30% of the administered dose (range: 14% to 46%). The PI for TABLOID also states that oral administration of radiolabeled thioguanine revealed only trace quantities of parent drug in the urine.[38] Therefore, thioguanine has low permeability in accordance with BCS permeability criteria.

Based upon the BCS, the low solubility and low permeability of thioguanine place this drug substance in BCS Class IV. In turn, it must be concluded that thioguanine is ineligible for a BCS-based biowaiver.

b. NTI Characteristics of Thioguanine Warrant the Denial of any Biowaiver Requests

In addition to its inability to meet the BSC Class I or Class III solubility and permeability waiver criteria, thioguanine should be excluded from consideration for a biowaiver because it bears characteristics of a Narrow Therapeutic Index ("NTI") drug which are ineligible for BCS-based biowaivers.[39]

NTI drugs are defined as being "drugs where small differences in dose or blood concentration may lead to therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity."[40] Because of this, NTI

[35] M9 Guidance at 3.

[36] *Id.*

[37] *See* Current Approved Label for TABLOID (NDA 012429) at 1 (last accessed Jan. 29, 2025).

[38] *Id.*

[39] M9 Guidance at 2.

[40] FDA, "FY2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs" webpage (last accessed Dec. 24, 2024) *available at* https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-narrow-therapeutic-index-drugs#:~:text=Narrow%20therapeutic%20index%20drugs%20are,or%20significant%20disability%20or%20incapacity.

drugs require careful dosing and patient monitoring.[41] FDA also recommends tighter quality and bioequivalence standards to ensure the safety and efficacy of generic NTI drugs.[42]

As stated above, TABLOID poses the risk of myelosuppression, a condition which can be serious and life-threatening and may demand modification or cessation of the dosage.[43] TABLOID also poses the risk of other adverse event and toxicities, such a liver toxicity.[44] As such, careful and frequent monitoring via clinical and hematological evaluation during treatment with TABLOID is required or otherwise recommended to avoid serious and life-threatening adverse events and to ensure adequate patient response. Other sections of the PI contain corresponding instructions for the healthcare provider, including the following:

- **WARNINGS:** Patients must be carefully monitored (see PRECAUTIONS, Laboratory Tests). Early indications of liver toxicity are signs associated with portal hypertension such as thrombocytopenia out of proportion with neutropenia and splenomegaly. Elevations of liver enzymes have also been reported in association with liver toxicity but do not always occur.[45]

- **PRECAUTIONS:** Deterioration in liver function studies during thioguanine therapy should prompt discontinuation of treatment and a search for an explanation of the hepatotoxicity.[46]

- **Laboratory Tests:** Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression. (see WARNINGS). It is advisable to monitor liver function tests (serum transaminases, alkaline phosphatase, bilirubin) at weekly intervals when first beginning therapy and at monthly intervals thereafter. It may be advisable to perform liver function tests more frequently in patients with known pre-existing liver disease or in patients who are receiving thioguanine and other

[41] FDA, "Setting and Implementing Standards for Narrow Therapeutic Index Drugs" webpage (last accessed Dec. 24, 2024) *available at* https://www.fda.gov/drugs/cder-conversations/setting-and-implementing-standards-narrow-therapeutic-index-drugs.

[42] FDA, "FY2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs" webpage (last accessed Dec. 24, 2024) *available at* https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-narrow-therapeutic-index-drugs#:~:text=Narrow%20therapeutic%20index%20drugs%20are,or%20significant%20disability%20or%20incapacity.

[43] *See* Current Approved Label for TABLOID (NDA 012429) (last accessed Jan. 29, 2025).

[44] *Id.*

[45] *Id.* at 4.

[46] *Id.* at 5.

> hepatotoxic drugs. Patients should be instructed to discontinue thioguanine immediately if clinical jaundice is detected (see WARNINGS).[47]

The NTI characteristics of oral chemotherapeutic drugs have also been recognized in a 2014 publication in the Journal of Oncology Practice[48] which stated the following:

> Oral Chemotherapeutic Drugs are rapidly becoming a popular dosage form for cancer treatment. These medications have a narrow therapeutic index, and their metabolism can be easily affected by food and/or drug interactions. These interactions can significantly reduce the effectiveness of oral chemotherapy, which could possibly result in harm to patients.[49]

The article also cites thioguanine as one of these oral chemotherapeutic treatments.[50] Additionally, the article acknowledges the absence of studies evaluating warfarin effects and QTc prolongation.[51]

Overall, these factors underscore the need to determine bioequivalence of any generic formulation of thioguanine using a highly accurate and sensitive methodology in order to mitigate the risk of therapeutic failures and potentially life-threatening adverse events. Accordingly, FDA should grant this Petition and deny all biowaivers related to performing in vivo bioequivalence testing for any generic formulation of thioguanine.

IV. CONCLUSION

Based upon current scientific standards and criteria set forth in the current PSG for Thioguanine, it is clear that the maintenance and strict appliance of the current PSG for Thioguanine to all generics of thioguanine will ensure not only safety and effectiveness of all ANDAs but will also ensure patient safety. Moreover, it is clear that, based upon its classification as BCS Class IV, coupled with the NTI characteristics of thioguanine itself, no generic formulation of thioguanine tablets would be eligible for a biowaiver.

Accordingly, we request that the Commissioner grant this Petition and take the following actions: (1) maintain and strictly apply the requirements of the current PSG for Thioguanine, which

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[47] *Id.*

[48] Eve M Segal et al., "Oral Chemotherapy Food and Drug Interactions: A Comprehensive Review of the Literature," 10 J. Oncol Pract. e255–68 (Jul. 2014) (emphasis added) (Attachment B).

[49] *Id.* at e255 (emphasis added).

[50] *Id.* at e255–e259.

[51] *Id.* at e268.

represent scientifically appropriate standards for this class of drugs (oral chemotherapeutic dosage forms), to all pending, newly submitted, and future ANDAs for thioguanine tablets; and (2) pursuant to FDA's biopharmaceutics classification system, refrain from granting a waiver of the requirement to perform in vivo bioequivalence testing for any generic formulation of thioguanine.

C. ENVIRONMENTAL IMPACT

A categorical exclusion is claimed in accordance with 21 C.F.R. §§ 25.30, 25.31. Therefore, an environmental impact analysis is not required.

D. ECONOMIC IMPACT

In accordance with 21 C.F.R. § 10.30(b), information on economic impact will be submitted upon request.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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