NOVARTIS

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Via Hand Delivery

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

The undersigned, on behalf of Novartis Pharmaceuticals Corporation ("Novartis"), submits this Petition pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq. (the "Act"), and in accordance with the procedural requirements specified in 21 C.F.R. § 10.30, to request that the Commissioner of Food and Drugs ("the Commissioner") not approve any ANDA seeking approval of a zoledronic acid injectable IV (infusion) product based on omitting protected information in Reclast labeling.

As discussed more fully below, generic zoledronic acid injectable IV (infusion) ("zoledronic acid") labeling that omits protected information in Reclast labeling will result in a "carve out" of most safety-related information from the Prescribing Information, including safety information relevant to treatment of *all* patients. Consequently, physicians will not be informed of all precautions and warnings that need to be clinically considered when prescribing zoledronic acid to Paget's disease patients. Pharmacists will not be informed of all drug-drug interactions and adverse reactions that need to be taken into account when dispensing zoledronic acid for these patients. Nurses and other health-care professionals administering zoledronic acid will not be informed of all important safety information associated with infusing Paget's disease patients.

This is a Reclast-specific situation resulting from the unique nature of the Reclast labeling, which consists predominantly of prescribing information relating to its use in the treatment of four osteoporosis indications. Novartis believes approximately 350,000 patients are currently being treated with Reclast. Of these 350,000 patients, only about 1,000 patients (or 0.28%) are being treated for Paget's disease. Two patents cover all of the Reclast osteoporosis labeling, which is directed at the overwhelming use of the product, but which also is applicable to its unprotected use. The approval of any generic zoledronic acid product cannot be allowed to proceed based upon the carve-out of the patent-protected osteoporosis labeling, because the Prescribing Information that would be left would omit important safety information relevant to the product's use in Paget's disease and thereby preclude safe use of the carve-out-labeled product in this remaining indication.

In short, any such product would be less safe than Reclast for the treatment of Paget's disease, because physicians and other health-care providers would not have access to safety information necessary to the product's safe use in the approximately 1,000 patients being treated for Paget's disease.

A. ACTION REQUESTED

Petitioner requests that the Commissioner not approve any abbreviated new drug application (ANDA), which seeks approval of a zoledronic acid injectable IV (infusion) product based on omitting protected information in Reclast labeling. Petitioner further requests that the Commissioner only approve an ANDA for a zoledronic acid product whose labeling includes adequate safety information, including all protected information in Reclast labeling.

B. STATEMENT OF GROUNDS

I. The Reclast Labeling Uniquely Consists Of Efficacy And Safety Data Relating Primarily To Its Predominant Use In Its Approved Osteoporosis Populations, But Which Also Is Relevant To Its Safe Use In Paget's Disease, With Limited Unprotected Safety Information Related To Its Unprotected Use In Paget's Disease

Reclast was first approved by FDA in 2007. It is approved for the treatment of two diseases: (1) osteoporosis, a condition in which bones become weakened; and (2) Paget's disease, a clinically-rare genetic condition that disrupts the normal cycle of bone cell turnover and causes enlarged and misshapen bones. Reclast is administered intravenously as a 5 mg dose diluted in standard buffer media. Reclast is sold only in a liquid form that is fully diluted and ready to be administered.

The Reclast labeling contains extensive data and information resulting from clinical trials evaluating its use in its four approved osteoporosis populations. This information is essential to the safe and effective use of Reclast in all patients. Only a narrow, rare-disease population (Paget's disease) is not covered by the protected labeling. Even for those Paget's disease patients, however, some of the protected labeling information is essential to their safe treatment, and its inclusion is necessary to raise the awareness of physicians and other health-care professionals of the risks of treating Paget's disease patients with zoledronic acid. As detailed in section II, below, the protected Reclast labeling contains critical prescribing information pertaining to administration of zoledronic acid that any physician should receive to appropriately determine treatment for all indications with zoledronic acid.

All osteoporosis-related information in the Reclast labeling is protected information. Reclast and its methods of use are covered by two *Orange Book*-listed patents: U.S Patent No. 7,932,241 (the "'241 Patent"), entitled *Pharmaceutical products comprising bisphosphonates*, and issued on April 26, 2011; and U.S. Patent No. 8,052,987 (the "'987 Patent"), entitled *Method of administering bisphosphonates* and issued on November 8, 2011. The '241 Patent

covers to use of a plastic-coated vial able to hold zoledronic acid for extended periods. The '987 patent is directed to the discovery that Reclast could be effective when administered once per year, or even less frequently.

Recognizing that an ANDA sponsor is not required to notify an NDA holder that its ANDA includes a Section viii statement, it is Novartis' belief that some eight ANDA sponsors seeking approval to market generic versions of Reclast apparently have submitted Section viii statements along with proposed carve-outs of what the ANDA sponsors consider to be the protected information. Novartis anticipates that such Section viii statements indicate that the ANDA sponsors are not seeking approval to manufacture or sell a generic version of Reclast for the treatment of osteoporosis, but are only seeking approval for the treatment of Paget's disease.[1]

As a regulatory matter, even if these sponsors correctly represent that their proposed ANDA products will not be sold for the treatment of osteoporosis (which Novartis believes is knowingly incorrect), the pivotal regulatory issue is whether the post-carve-out labeling of such generic products will permit their safe use for the remaining, unprotected Paget's disease indication.

The Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]" and "information . . . to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug. . . ." 21 U.S.C. §§ 355(j)(2)(A)(i), (v). The Act provides the following two exceptions for when ANDA labeling may differ from that of the listed drug: (1) because changes reflect differences approved pursuant to an ANDA suitability petition; or (2) because the drugs are produced or distributed by different manufacturers. 21 U.S.C. § 355(j)(2)(A)(v). FDA regulations implementing the statutory exceptions to the same labeling requirement state that "differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include . . . omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act". 21 CFR § 314.94(a)(8)(iv). The regulations further provide, however, that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, FDA must find that "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7).

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[1] Novartis does not know what specific protected information any Section viii ANDA sponsor proposes to carve out from its labeling. Consequently, Novartis is not in a position to evaluate the scope of any such omissions or to comment on their appropriateness.

II. Carving Out The Protected Osteoporosis Information From Reclast Labeling Would Result In The Omission Of Most Information Relating To The Safe Use Of The Product, Including Information Directly Relevant To The Product's Safe Use In Treating Paget's Disease, Thereby Depriving Any Physician Of Information They Should Receive To Appropriately Determine Treatment With A Zoledronic Acid Product For All Approved Indications

In connection with Reclast, ANDA applicants presumably are seeking to omit protected information regarding its four approved osteoporosis indications (*i.e.*, prevention and treatment of osteoporosis in postmenopausal women, treatment of men with osteoporosis, and treatment and prevention of glucocorticoid-induced osteoporosis in men and women). In order to carve out all of the protected information covered by Novartis' patents, the ANDA applicants must delete all references in the labeling that suggest the use of zoledronic acid for the protected indications, including references to osteoporosis, post-menopausal women, use of corticosteroids, concomitant use of glucocorticoids, and the specific dosing regimens for the osteoporosis indications (*i.e.*, once-a-year or once-every-two-years dosing). In carving out this protected information, the ANDA applicants effectively will be required to delete data or information that is necessary for the safe and effective use of their product for the treatment of Paget's disease. This would render such products less safe than Reclast when such products are used to treat Paget's disease. Accordingly, FDA should not permit the carve out and should condition the approval of any ANDA on the inclusion of all protected information in the Reclast labeling .

To carve out the protected osteoporosis information, several critically-important, safety-related sections of the Reclast labeling must be deleted in part or in their entirety.[2] As reflected in the attached mock-up of the carve outs that would be required to omit protected information, this would necessitate the following safety-related labeling omissions:

- A Section viii statement ANDA sponsor must address the **ADVERSE REACTIONS** sections that specifically discuss the protected information from the osteoporosis clinical trials. Section 6.1 of the labeling discusses adverse events observed in the clinical trials of Reclast and is split into subsections that discuss the clinical trials supporting each approved osteoporosis indication for

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[2] As discussed in the main text below, this is not a routine carve-out situation that simply involves omitting protected information in the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES sections (1.1, 1.2, 1.3, 1.4, 1.6, 2.1, 2.2, 2.3, 2.4, 14.1, 14.2, 14.3, and 14.4) describing the use of zoledronic acid to treat or prevent osteoporosis. All of that protected information, of course, would need to be removed in its entirety. (In the Clinical Studies section, it is not possible to modify descriptions to delete references to the specific indication studied, because of the detailed discussion regarding patients (*e.g.*, postmenopausal women), dosing regimens (*e.g.*, once per year), and efficacy endpoints (BMD, fractures), and thus the descriptions of the osteoporosis clinical trials must be deleted in their entirety.) In addition, references to osteoporosis would need to be omitted from the Pediatric Use, Geriatric Use, Pharmacokinetics, and PATIENT COUNSELING INFORMATION sections (8.4, 8.5, 12.3, and 17), and the Medication Guide.

Reclast. An ANDA sponsor would need to omit the entirety of the subsections discussing protected indications (*e.g.*, osteoporosis, post-menopausal women, corticosteroids, dosing regimens applicable to the osteoporosis indications). Simply omitting the specifics of the trials that suggest use of the drug for the protected indication is inappropriate here, because the discussions of the clinical trials in the **ADVERSE REACTIONS** sections are replete with references to osteoporosis, postmenopausal women, yearly or extended dosing, and corticosteroid therapy.[3] That information, however, is essential to the safe use of zoledronic acid for treatment of Paget's disease. For example, the discussions of the osteoporosis trials in the **ADVERSE REACTIONS** section mention rates of atrial fibrillation and injection site reactions, neither of which is discussed in the Paget's disease subsection. It is critically important for physicians to know about these adverse reactions when treating Paget's disease patients. Carving out this protected information from the labeling of a proposed product would render a proposed product less safe than Reclast for treatment of Paget's disease.

- Similarly, the **WARNINGS AND PRECAUTIONS** subsection (5.5) relating to Atypical Subtrochanteric and Diaphyseal Femoral Fractures must be omitted at least in part if not in its entirety. For example, the protected labeling statement, "A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture," must be deleted to avoid suggesting use of zoledronic acid for the protected indication of glucocorticoid-induced osteoporosis. The omission of this information would make the resulting product less safe than Reclast in the treatment of Paget's disease, the highest frequency of which occurs in geriatric populations with a slight predominance among men[4] (who generally are more likely to be taking glucocorticoids), because it would put those patients at greater risk of fracture. Specifically, this deletion would mean that physicians administering zoledronic acid to treat their patients with Paget's disease would be unaware of the fracture risk among those patients taking concomitant glucocorticoids, which historically have been used in Paget's disease patients to relieve symptoms and control progression of Paget's disease.[5]

- In addition, the Pharmacodynamics section (12.2) describing the pharmacodynamics of Reclast based upon the osteoporosis treatment trial and

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[3] *Cf.* FDA Docket No. FDA-2010-P-0545, PDN (Feb. 24, 2011).

[4] R.D. Altman, D.A. Bloch, M.C. Hochberg, &W.A. Murphy, *Prevalence of Pelvic Paget's Disease of Bone in the United States*, JOURNAL OF BONE AND MINERAL RESEARCH, 2000;15:461-465 (attached).

[5] Although not recommended to treat Paget's disease, "glucocorticoids can relieve the symptoms of the disease" and can "suppress the progression of Paget's disease". BIOREGENERATIVE ENGINEERING: PRINCIPLES AND APPLICATIONS, Shu Q. Liu, at page 929 (attached).

> based on bone turnover markers compared to the "pre-menopausal range" would need to be deleted in its entirety to avoid suggesting use of zoledronic acid to treat osteoporosis. Its carve out is significant, because it contains important information for a physician treating all patients, including those with Paget's disease, because this section contains the only labeled pharmacodynamics information available on Reclast. It is important for physicians treating Paget's disease to have that information in order to see the pharmacodynamic bases upon which the dosage for Paget's disease is based.[6]

Under these circumstances, an ANDA should not be approved with the protected information omitted from its labeling. The safe use of any zoledronic acid product depends on inclusion of the protected information in its labeling. Without such information, a zoledronic acid injectable IV would be less safe than Reclast for the remaining Paget's disease indication.

III. Agency Precedent Reinforces The Conclusion That Omission Of Any Protected Information From Reclast Labeling Must Not Be Permitted

When the Agency has confronted comparable labeling circumstances in the past, FDA appropriately has determined that it cannot approve ANDAs that omit the protected information.

In a unique situation much like this one, FDA determined that ANDA approvals omitting the protected information was inappropriate "because this labeling is necessary to enable physicians to adequately assess the risks and benefits" of the product for the entire labeled population, including those patients not discussed in the protected labeling.[7] In another situation, where an NDA holder's protected information provided quantitative details "about the extent of changes in exposure that can occur with co-administration of certain drugs," FDA concluded that any generic version approved through an ANDA "needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity."[8]

The labeling and clinical situation with Reclast does not differ in any material respect from these Agency precedents. Like these two prior situations, the Reclast labeling is unique in containing primarily protected information directed at the product's use in the overwhelming majority of its indicated populations. However, like these earlier precedents, the Reclast protected information also is relevant to the prescribing and administration of the product for all approved populations, including the one, remaining, rare-disease population addressed in the unprotected labeling. The end result here should be no different than it was in those prior two

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[6] It is well established that "analysis of the pharmacological properties of bisphosphonates and design of appropriate therapeutic regimens for bone diseases depend to a large extent on the interpretation of pharmacodynamic information." OSTEOPOROSIS, edited by Robert Marcus, David Feldman, & Jennifer Kelsey, at page 632 (attached).

[7] FDA Docket No. 2003P-0518/CP1, PAV1 (Sep. 20, 2004), at page 4.

[8] FDA Docket No. FDA-2010-P-0614, PPAD (May 25, 2011), at pages 19, 20.

cases.

This situation stands in contrast to those in which FDA has allowed carve-outs based simply on the deletion of one or more indications for use[9] or the omission of discrete portions of segregated safety information.[10] Instead, as indicated at the outset, this unique situation necessitates the omission of data and information in the labeling directed at over 99% of the indicated treatment population, and, most importantly, those data and information are relevant to the prescribing and administration of the product in the remainder of the indicated treatment population. Accordingly, FDA must not approve ANDAs that omit the protected information from Reclast labeling. The Agency instead must ensure that any zoledronic acid injectable IV (infusion) product approved pursuant to an ANDA contains all of the protected information in Reclast labeling.

C. ENVIRONMENTAL IMPACT

An environmental assessment report on the action requested in this Petition is not required, as Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31(a).

D. ECONOMIC IMPACT

A statement of the economic impact of the requested action will be provided if required by the Commissioner following review of this Petition, in accordance with 21 C.F.R. § 10.30.

E. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: November 8, 2011. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am making these representations on the behalf of Novartis Pharmaceuticals Corporation as a part of my responsibilities as an employee; I am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

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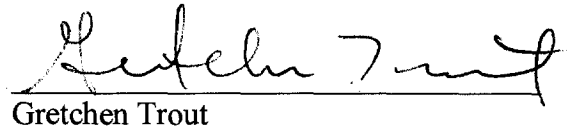
9 *Cf.* FDA Docket No. FDA-2010P-0087 (July 30, 2010).

10 *Cf.* FDA Docket Nos. FDA 2011-P0662 & FDA-2011-P-0663 (Mar. 27, 2012).

Respectfully submitted,



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Attachments (4)

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NOVARTIS

Memorandum

To **Division of Dockets Management**
US FDA
5630 Fishers Lane, Room 1061
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Date **4 March 2013**

Concerning **Novartis Pharmaceuticals Corporation Citizen Petition: Zoledronic Acid**

The attached Citizen Petition for zoledronic acid was submitted to Mr. David Joy, FDA Regulatory Counsel, on Friday 1 March 2013 by fax and by e-mail. Mr. Joy confirmed receipt via telephone conversation on the same day.

Regards,

Gretchen Trout