



Dr. Gianfranco Fornasini
Senior Vice President, Scientific Affairs
Sigma-tau Pharmaceuticals, Inc.
9841 Washingtonian Blvd, Suite 500
Gaithersburg, MD 20878

RE: BLA #103411

Oncaspar[®] (pegaspargase) injection, for intramuscular or intravenous use
MA #47

Dear Dr. Fornasini:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP), of the U.S. Food and Drug Administration (FDA) has reviewed the "Oncaspar: Sustained Asparagine Depletion With Enhanced Patient Benefits" sales aid (08-ONC-125P) for Oncaspar[®] (pegaspargase) injection, for intramuscular or intravenous use (Oncaspar). The sales aid was obtained by an OPDP representative at a promotional exhibit booth in the commercial exhibit hall at the 52nd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy in San Francisco, California. This sales aid is false or misleading because it makes unsubstantiated superiority claims, minimizes important risk information, makes unsubstantiated claims for the drug product, and omits material facts. Thus, the sales aid misbrands Oncaspar in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (ii), (xviii); (e)(7)(i),(iii), (viii).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Oncaspar.¹ According to the FDA-approved product labeling (PI), Oncaspar is indicated as:

- A component of a multi-agent chemotherapeutic regimen for the first line treatment of patients with acute lymphoblastic leukemia (ALL).
- A component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL and hypersensitivity to native forms of L-asparaginase.

Oncaspar is contraindicated in patients with a:

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

- History of serious allergic reactions to Oncaspar
- History of serious thrombosis with prior L-asparaginase therapy
- History of pancreatitis with prior L-asparaginase therapy
- History of serious hemorrhagic events with prior L-asparaginase therapy

The PI for Oncaspar includes Warnings and Precautions for anaphylaxis and serious allergic reactions, thrombosis, pancreatitis, glucose intolerance, and coagulopathy. The most commonly reported adverse reactions with Oncaspar are allergic reactions (including anaphylaxis), hyperglycemia, pancreatitis, central nervous system (CNS) thrombosis, coagulopathy, hyperbilirubinemia, and elevated transaminases.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The sales aid is misleading because it presents numerous claims about Oncaspar relative to native L-asparaginase and Erwinia asparaginase that imply superiority of Oncaspar over these comparator products when this has not been demonstrated by substantial evidence or substantial clinical experience. The sales aid includes the following misleading claims and presentations (emphasis added):

- “Helping Patients Gain the **Full Benefits** of Asparaginase Therapy” (page one)
- “Oncaspar: Sustained Asparaginase Depletion with **Enhanced Patient Benefits**” (page one)
- “Oncaspar[®]: Fewer Doses and **Greater Flexibility**²”
...
• “Single-dose Oncaspar requires **fewer patient visits**³” (page six)
- “**Fewer patient visits**³” (page 10)

These statements misleadingly imply that patients will not experience the “full benefits” of asparaginase therapy, including all aspects of efficacy, safety, and convenience, when treated with formulations of asparaginase other than Oncaspar. The Children’s Cancer Group (CCG) 1962 study (Study 1 in the Oncaspar PI) supported the approval of Oncaspar in first-line treatment of ALL. This study was not designed to test superiority of Oncaspar, including enhanced efficacy, patient benefit, or greater dosing flexibility relative to native L-asparaginase or any other comparator drug. Thus, claims suggesting Oncaspar is superior to other asparaginase formulations are not supported by substantial evidence or substantial clinical experience.

These claims also misleadingly suggest that Oncaspar treatment requires fewer total patient visits relative to other forms of asparaginase treatment, and therefore provides more flexibility for patients, when this is not supported by substantial evidence. The reference

² Oncaspar [package insert]. Bridgewater, NJ: Enzon Pharmaceuticals, Inc; 2006.

³ Kurre HA, Ettinger AG, Veenstra DL, et al. A pharmacoeconomic analysis of pegaspargase versus native *Escherichia coli* L-asparaginase for the treatment of children with standard-risk, acute lymphoblastic leukemia: the Children’s Cancer Group study (CCG-1962). *J Pediatr Hematol Oncol.* 2002; 24(3): 175-181.

cited in support of these claims, the Kurre HA, et al. study, describes a pharmacoeconomic analysis in a subset of pediatric patients with newly diagnosed, standard-risk ALL enrolled in Study 1. The referenced study data were collected through voluntary, self-administered patient diaries, which did not capture any data related to day hospital visits and emergency room use. Furthermore, the data analysis assumed that clinic visit encounters for other medications, physical examinations, and laboratory tests were the same for pegaspargase and native L-asparaginase. The data analysis did not consider *all* of the relevant patient visit scenarios; therefore, there is not substantial evidence to support a claim of fewer total patient visits or greater flexibility for patients taking Oncaspar relative to its competitors.

The sales aid includes the following claims:

- “L-asparaginase depletes circulating asparagine, leading to the death of leukemic cells⁴” (page two)
- “**Oncaspar[®]: The Power of Pegylation**” (page three)
- “Pegylation significantly increases the half-life of asparaginase^{5,6,7}” (page three)
- “Pegylation protects L-asparaginase from enzyme degradation, allowing for sustained plasma concentrations⁸” (page three)
- “Oncaspar[®]: **Pegylation Enhances Patient Benefits**” (emphasis added) (page 10)

In addition, the statements on page three are accompanied by a chart entitled, “Half-life of 3 Asparaginase Preparations (hours)” which displays half-life data for Erwinia asparaginase, native L-asparaginase, and Oncaspar. The totality of the presentation on pegylation in this sales aid is misleading as it suggests that the longer half-life and “sustained plasma concentrations” of the Oncaspar preparation relative to Erwinia asparaginase and native L-asparaginase correlate with superior clinical efficacy when this is not the case.

The references cited to support these claims include an article by Harris JM, et al. which gives an overview of the pegylation process; the Oncaspar PI; the Avramis VI, et al. publication of results from Study 1 in the Oncaspar PI; and two small pharmacokinetic studies; none of which support claims related to superior efficacy of Oncaspar. The two small pharmacokinetic studies referenced in this presentation evaluated half-life data of the three asparaginase proteins as well as half-life of enzymatic activity in small pediatric populations. Study 1 from the Oncaspar PI compared the *immunogenicity*, *pharmacokinetics*, and *pharmacodynamics* of Oncaspar relative to native L-asparaginase. The endpoints in this study were incidence of high-titer anti-asparaginase antibody formation, duration of elevated serum asparaginase levels (>0.03 IU/mL), and duration of decreased serum asparagine concentration (< 1µM). Endpoints did NOT include the assessment of asparaginase **activity** or the ability to kill leukemic cells. Moreover, the study

⁴ Oncaspar [package insert]. Bridgewater, NJ: Enzon Pharmaceuticals, Inc; 2006.

⁵ Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamics relationships of asparaginase formulations: the past, the present and recommendations for the future. *Clin Pharmacokinet.* 2005; 44(4): 367-393.

⁶ Asselin BL, Whitin JC, Coppola DJ, Rupp IP, Sallan SE, Cohen HJ. Comparative pharmacokinetic studies of three asparaginase preparations. *J Clin Oncol.* 1993; 11(9): 1780-1786.

⁷ Asselin BL. The three asparaginases: comparative pharmacology and optimal use in childhood leukemia. In: Kaspers GJL, et al, eds. *Drug Resistance in Leukemia and Lymphoma III*. New York, NY: Kluwer Academic/Plenum Publishers; 1999: 621-629.

⁸ Harris JM, Martin NE, Modi M. Pegylation: a novel process for modifying pharmacokinetics. *Clin Pharmacokinet.* 2001; 40(7): 539-551.

showed that serum asparaginase level did *not* correlate with serum asparagine depletion. Therefore, it is misleading to suggest that pegylation of asparaginase confers superior clinical efficacy (i.e., an enhanced ability to kill leukemia cells) when this has not been demonstrated by substantial evidence or substantial clinical experience. Generally, adequate and well-controlled head-to-head comparative studies are necessary to support claims of superiority.

Minimization of Risk Information

Promotional materials are misleading if they contain claims indicating that a drug is safer than has been demonstrated by substantial evidence or substantial clinical experience and if they fail to present risks associated with a drug with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug.

The 10-page sales aid prominently presents efficacy claims with large bolded headlines and colorful graphics but fails to communicate any risk information until page eight. The most important risks, however, are not presented until page 10, the back cover of the piece, in a section titled "Important Safety Information." In contrast to the large type, ample white space, and colorful efficacy presentations contained in the first nine pages, this risk disclosure on the back page is presented in black font type and single-spaced bullets. As such, the piece fails to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. We note the statement, "Please see enclosed full Prescribing Information before prescribing Oncaspar" at the bottom of some of the pages in the sales aid; however, this statement does not mitigate the minimization of risk information throughout the piece.

Pages eight and nine of the sales aid include a table adapted from Table 1 in the Oncaspar PI showing incidence rates of selected Grade 3 and 4 adverse events, including clinical allergic reactions, as well as the following claims:

- "Differences exist between grade 2 dermatologic and grade 2 allergic reactions"
- "Local injection-site reactions can be mistaken for clinical allergic reactions"
- "Proper management of asparaginase-related adverse events may:
 - Improve patient safety
 - Allow patients to maintain the benefits of sustained asparagine depletion"

The totality of the presentation on these pages minimizes the serious risks of anaphylaxis and clinical allergic reactions to Oncaspar by suggesting that physicians may mistake injection-site reactions for allergic reactions and that the hypersensitivity reactions reported in the PI and displayed on page eight of the sales aid may have been inaccurately attributed to Oncaspar as a result of misclassified injection-site reactions. Furthermore, the presentation misleadingly implies that "proper management" of these serious allergic reactions may allow patients to remain on therapy, despite the fact that the WARNINGS AND PRECAUTIONS section of the PI clearly states, "Discontinue Oncaspar[®] in patients with serious allergic reactions."

In addition to the misleading presentation on pages eight and nine, page seven of the sales aid includes the claim: "No limit on duration of therapy." This claim further minimizes the

risks of immunogenicity and toxicity associated with Oncaspar. According to the PI, patients being treated with Oncaspar can develop serious allergic reactions, serious thrombotic events, and/or pancreatitis. As described in the Warnings and Precautions section of the Oncaspar PI, patients should immediately discontinue treatment if or when they develop any one of these severe conditions. Therefore, the duration of therapy *will* be limited in any patients that experience these adverse reactions. We note that the ISI on the back page of the sales aid includes the statement, “Oncaspar should be discontinued in the case of anaphylaxis or serious allergic reactions, thrombosis, or pancreatitis;” however, this does not mitigate the misleading impression conveyed by the statement on page seven.

Page eight of the sales aid includes the following claims:

- “Oncaspar: Low Rates of Hypersensitivity May Allow Patients to Remain on Therapy¹⁰”
- “[Low rates of hypersensitivity in patients allergic to native L-asparaginase”
- “68% of relapsed ALL patients with a history of hypersensitivity to native L-asparaginase did not experience a clinical allergic reaction to Oncaspar (n=62)”

These claims further minimize the risks of hypersensitivity reactions to Oncaspar by presenting the hypersensitivity data as a product benefit claim rather than a risk disclosure. The reference cited in support of these claims is the Oncaspar PI, which states, “The most common adverse reactions with Oncaspar[®] are allergic reactions (including anaphylaxis). . . .” Moreover, according to the PI, 32% of patients with a history of allergic reactions to native L-asparaginase experienced clinical allergic reactions to Oncaspar and 10% of patients with *no* prior hypersensitivity reactions to asparaginase experienced clinical allergic reactions to Oncaspar. By framing this important risk information as a potential benefit of treatment, these claims minimize the serious risks of hypersensitivity reactions.

Pages six and 10 of the sales aid include the following misleading claims:

- “When administered via IV, the pain caused by IM injections can be avoided⁹” (page six)
- “Avoidance of IM pain with option of IV administration⁹” (page 10)

The above claims are misleading because they suggest that IV administration of Oncaspar is not associated with any pain or negative consequences, when this is not the case. The reference cited to support these claims, the Avramis VI, et al. study, did not include assessments of different routes of administration. We acknowledge that IM injections may be painful; however, IV administration can also be painful and may lead to serious risks including infections, phlebitis, infiltration, and extravasation. These claims minimize these potential risks.

Unsubstantiated Claims

Promotional materials are false or misleading if they contain claims or presentations that are not supported by substantial clinical evidence or substantial clinical experience.

⁹ Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children’s Cancer Group study. *Blood*. 2002; 99(6): 1986-1994.

Page five of the sales aid includes the following claims:

- “Sustained asparagine depletion correlates with rapid blast clearance”
- “M1 achieved by majority of patients on days 7 and 14¹¹”
- “No evidence of M3 bone marrow on day 14¹¹”

These claims misleadingly imply that Oncaspar has demonstrated efficacy in terms of blast clearance rate and improved bone marrow blast score when this is not the case. The reference cited in support of these claims is a publication of the Study 1 trial results from the Oncaspar PI. Neither blast clearance nor bone marrow blast score were pre-specified endpoints in Study 1. The efficacy endpoints evaluated in the study were incidence of high-titer anti-asparaginase antibody formation, duration of elevated serum asparaginase levels (>0.03 IU/mL), and duration of decreased serum asparagine concentration (< 1µM). Evaluation of bone marrow blast scores was a post hoc analysis which is exploratory and does not constitute substantial evidence to support efficacy claims for Oncaspar.

Omission of Material Fact

Promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

Page one of the sales aid, the front cover, displays a picture of three people; two of the people are clearly children and one is an elderly female. In addition, page seven of the sales aid begins with the heading: “**Oncaspar[®]: No Age Restrictions**” (emphasis original). These presentations are misleading as they fail to reveal material facts about the use of Oncaspar in older patients. For example, in the Oncaspar PI, Study 1 and Study 2, which were used to determine the safety and effectiveness of Oncaspar for first line ALL treatment, included only pediatric patients ages one to nine and one to ten years old, respectively. Additionally, the PI states, “Clinical studies of Oncaspar[®] did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently than younger subjects.” We note that this disclaimer is included on the back cover of the sales aid; however, this does not mitigate the misleading impression made by the image and claim on pages one and seven, respectively.

Conclusion and Requested Action

For the reasons discussed above, the sales aid for Oncaspar misbrands the drug in violation of the FD&C Act, 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (ii), (xviii); (e)(7)(i), (iii), (viii).

OPDP requests that Sigma-tau Pharmaceuticals, Inc. immediately cease the dissemination of violative promotional materials for Oncaspar such as those described above. Please submit a written response to this letter on or before June 6, 2013, stating whether you intend to

¹¹ Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children’s Cancer Group study. *Blood*. 2002; 99(6): 1986-1994.

comply with this request, listing all promotional materials (with the 2253 submission date) for Oncaspar that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #47 in addition to the BLA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Oncaspar comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Kathleen Davis, RN
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Karen Rulli, Ph.D.
Team Leader
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN T DAVIS
05/22/2013

KAREN R RULLI
05/22/2013