

**TRANSMITTED BY FACSIMILE**

G.Pohl-Boskamp GmbH & Co. KG
c/o Arbor Pharmaceuticals, Inc.
Allison Lowry, Director, Quality and Regulatory Affairs
980 Hammond Drive, Bldg 2, Suite 1250
Atlanta, GA 30328

RE: NDA #018705
Nitrolingual[®] Pumpspray (nitroglycerin lingual spray)
MACMIS #19582

Dear Ms. Lowry:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (NLPS.11.09.074.04) (sales aid), direct-to-consumer (DTC) patient brochure (brochure) (NLPS.12.09.78A.01), and patient brochure holder (brochure holder) (NLPS 12.09.78B.00) for Nitrolingual[®] Pumpspray (nitroglycerin lingual spray) (Nitrolingual Pumpspray) submitted under cover of Form FDA-2253¹ by Sciele Pharma, Inc., a Shionogi company, and by copy, Arbor Pharmaceuticals, Inc. The sales aid and brochure are false or misleading because they present unsubstantiated claims, including unsubstantiated superiority claims, and minimize and omit serious risks associated with the drug. The brochure holder is false or misleading because it minimizes and omits serious risks associated with the use of the drug. Thus, these promotional materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), & (ii); (e)(7)(i) & (viii).

Background

The INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Nitrolingual Pumpspray states the following:

Nitrolingual[®] Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

The PI for Nitrolingual Pumpspray includes contraindications regarding its use in patients who are allergic to it as well as in patients taking certain drugs for erectile dysfunction (phosphodiesterase inhibitors), as their concomitant use can cause severe hypotension. The PI also contains warnings regarding severe hypotension due to concomitant use of Nitrolingual Pumpspray and phosphodiesterase inhibitors and that the use of any form of

¹The above promotional pieces were submitted under cover of Form FDA-2253 by Sciele Pharma, Inc. On January 11, 2010, Sciele Pharma, Inc. changed its name to Shionogi Pharma, Inc. (Shionogi). On October 4, 2010, Shionogi informed DDMAC about the transfer of US Agent responsibilities for promotional and advertising activities for Nitrolingual Pumpspray to Arbor Pharmaceuticals, Inc.

nitroglycerin during the early days of acute myocardial infarction requires particular attention to hemodynamic monitoring and clinical status.

The PI contains precautions regarding severe hypotension, particularly with upright posture, and even with small doses of nitroglycerin which may also be accompanied by paradoxical bradycardia and increased angina pectoris. Therefore, Nitrolingual Pumpspray should be used with caution in patients with low systolic blood pressure (e.g., below 90 mm Hg) or those who may have volume depletion from diuretic therapy. In addition, the PI states that nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy and that tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur.

The most common adverse reaction for Nitrolingual Pumpspray is headache, which may be severe and persistent, with an incidence on the order of about 50% in some studies. Adverse events occurring at a frequency greater than 2% were headache, dizziness, and paresthesia.

Unsubstantiated Superiority Claims/Unsubstantiated Claims

Promotional materials are misleading if they contain representations or suggestions 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 and brochure includes claims and presentations such as the following (emphasis in original):

Sales Aid

- A bar graph entitled, “Relief Within 60 seconds in One Study”² below the bolded claim, **“NITROLINGUAL® PUMPSPRAY OFFERS MORE RAPID RELIEF THAN TABLETS”**² presenting the results of an 8-week randomized study which depicts a higher percentage of patients reporting relief of angina within one minute following nitroglycerin lingual spray administration compared to patients using nitroglycerin tablets. The following claims are included below this presentation:
 - “Relief within 60 seconds in 69% of patients receiving Nitrolingual Pumpspray vs 38% of patients receiving tablets ($P<0.001$)”²
 - “Speed to relief is a critical advantage for patients in the midst of an attack”

Brochure

- **“Nitrolingual® Pumpspray (nitroglycerin lingual spray) can provide relief within 60 seconds.”**²
 - “In one study, results showed that 69% of patients reported relief within 60 seconds vs 38% of patients who used tablets”²
- Graphic image under the claim, **“Fast Pain Relief”** showing the results of an 8-week, randomized study depicting that more patients using nitroglycerin lingual spray experienced relief of angina within one minute when compared to patients using nitroglycerin tablets, in conjunction with the following claims:

²Vandenburch MJ, Wright LG, Griffiths GK, et al. Sublingual nitroglycerin or spray in the treatment of angina. *Br J Clin Pract.* 1986;40:524-527.

- **“Nitroglycerin lingual spray—Roughly 7 out of 10 patients (69%) experienced relief within 1 minute”**
- **“Nitroglycerin tablets—Less than 4 out of 10 patients (38%) experienced relief within 1 minute”**

In addition, the sales aid and brochure include the following claims and presentations (emphasis in original):

Sales Aid

- “Patients prescribed nitroglycerin tablets frequently carry a potentially subpotent medication”³
 - “In one study, more than one-third of CHD patients who used tablets carried medication that was older than 6 months”³
- A graph entitled, “Nitrolingual Pumpspray Demonstrated Statistically Significant Brachial Artery Vasodilatory Response vs Tablets at 2, 4, and 15 Minutes”⁴
- “Rapidly, magnitude, and duration of vasodilatory action is greater with spray than with tablets, as assessed by brachial artery ultrasound in healthy volunteers”⁴
- “Lower incidence of headache with spray than with tablets”²
 - “In one 8-week, randomized study of patients with a history of angina, 58% of patients using nitroglycerin lingual spray reported no headache vs 39% of patients using nitroglycerin tablets (n=352; p<.001)”

Brochure

- **“In one study, more patients reported no headache”**
- “Headaches are a common side effect of nitroglycerin medication. However, it has been shown that patients with a history of angina pectoris using nitroglycerin lingual spray did not experience headaches as often as tablet users.”
 - “58% of patients using nitroglycerin lingual spray reported no headache vs 39% of patients who used tablets (n=352; P<0.001)”²

Claims and presentations such as those noted above are misleading because they imply that Nitrolingual Pumpspray is more potent and provides faster pain relief from acute angina pectoris with fewer or no headaches compared to the nitroglycerin tablet formulation, and is therefore clinically superior, when such is not supported by substantial evidence or substantial clinical experience. In addition, claims presented in the sales aid regarding rethinking angina treatment (i.e., “RE THINK Angina Treatment,” “RE THINK The Need for Stability,” “RE THINK The Need for Speed”) further contribute to the misleading implication that Nitroglycerin Pumpspray is superior to nitroglycerin tablets.

Generally, claims of superiority must be supported by two adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of a drug and a

³ Zimmerman FH, Fass AE, Katz DR, et al. Nitroglycerin prescription and potency in patients participating in exercise-based cardiac rehabilitation. *J Cardiopulm Rehabil Prev.* 2009;29:376-379.

⁴Ducharme A, Dupuis J, McNicoll S, et al. Comparison of nitroglycerin lingual spray and sublingual tablet on time of onset and duration of brachial artery vasodilation in normal subjects. *Am J Cardiol*;1999;84(8):952-4.

comparator drug. The sales aid and brochure cite a study conducted by Vandenburg, et al.² to support these claims and the sales aid also cites a study conducted by Ducharme A, et al.⁴ However, the study conducted by Vandenburg, et al.² does not constitute substantial evidence or substantial clinical experience to support claims of clinical superiority for Nitrolingual Pumpspray over the nitroglycerin tablet formulation because it used subjective questionnaires to assess the efficacy and safety of nitroglycerin lingual spray and nitroglycerin tablets. The study conducted by Ducharme A, et al.⁴ was an open-label trial in 20 healthy volunteers that compared the vasodilatory effects (measured by brachial artery echography) of the nitroglycerin lingual spray and the nitroglycerin sublingual tablet. This trial also does not constitute substantial evidence or substantial clinical experience to support superiority claims such as those noted above because it was not adequately powered, used an open-label study design, and evaluated an endpoint that has unknown clinical relevance.

Furthermore, claims in the sales aid implying that Nitrolingual Pumpspray is clinically superior to nitroglycerin tablets because patients prescribed nitroglycerin tablets frequently carry nitroglycerin tablets which are subpotent are misleading because they are not supported by substantial evidence or substantial clinical experience. Specifically, the sales aid cites a survey conducted by Zimmerman FH, et al.³ in which patients were asked to self-report on the type of product they used (spray or tablet), whether they routinely carried the product, and how often they used the medicine. Patients who used nitroglycerin tablets were asked to indicate their most recent purchase of the drug. Patients who used nitroglycerin lingual spray were asked whether their prescription was within two years. No information was provided confirming that the nitroglycerin tablets were, in fact, post-expiration or subpotent. Therefore, this reference does not support the claim that patients prescribed nitroglycerin tablets frequently carry tablets which are subpotent, nor does it constitute substantial evidence to support the implication that Nitrolingual Pumpspray is clinically superior to nitroglycerin tablets.

The sales aid and brochure also contains the following claims (emphasis in original):

Sales Aid

- **“NITROLINGUAL[®] PUMPSPRAY IS A PATIENT-FRIENDLY CHOICE”**^{5,6}
- **“A delivery system that provides reliable relief”**^{2,7}
 - “Eliminates hard-to-open prescription bottles and the need to fumble with small tablets”⁸
 - “Convenient and easy-to-use”^{5,6}
 - “Not affected by dry mouth or diminished salivary secretions”

⁵ Wight LJ, Vandenburg MJ, Potter CE, et al. A large scale comparative study in general practice with nitroglycerin spray and tablet formulations in elderly patients with angina pectoris. *Eur J Clin Pharmacol.* 1992;42:341-342.

⁶ Wight, LJ, Potter CE, Vandenburg MJ, et al. Experience with Nitrolingual spray in general practice. *Br J Clin Pract.* 1990;44:55-57.

⁷ Kimchi A, Lee G, Amsterdam E, et al. Increased exercise tolerance after nitroglycerin oral spray: a new and effective therapeutic modality in angina pectoris. *Circulation.* 1983;67:124-127.

⁸ Glyceryl trinitrate for angina: tablet or spray? *Drug Ther Bull.* 1992;30:93-95.

Brochure

- **“Simple and easy to use”**

The totality of the above claims in the sales aid misleadingly implies that Nitrolingual Pumpspray is “patient-friendly” and that overall treatment is “convenient” when compared to nitroglycerin tablets, when this is not the case. The references cited to support these claims are not adequate and well-controlled clinical studies that specifically assess the “patient-friendliness” and overall “convenience” of Nitrolingual Pumpspray treatment. “Patient-friendly” and “convenience” are broad terms that include many factors (e.g., dosing and administration, efficacy, risks and adverse events, and cost) measured from the patient’s perspective. Additionally, the PI describes multiple considerations for use and detailed instructions on how the drug is to be administered (see Background section). In addition, the claim in the brochure that Nitrolingual Pumpspray is “[s]imple and easy to use” is also misleading for the aforementioned considerations described in the PI. Therefore, claims presented in the sales aid and brochure implying that that Nitrolingual Pumpspray is simple, convenient, and/or easy to use are not self-evident and are not supported by adequate evidence.

Furthermore, FDA is not aware of substantial evidence or substantial clinical experience to support the claim that Nitrolingual Pumpspray is, “Not affected by dry mouth or diminished salivary secretions.” If you have data to support this claim, please submit them to FDA for review.

The brochure presents the claim, “Don’t let chest pain from angina pectoris slow you down” (emphasis added). This claim misleadingly implies that patients who use Nitrolingual Pumpspray to prevent or treat chest pain will not be “slow[ed]. . .down” at all by their angina pectoris. While we acknowledge that Nitrolingual Pumpspray has been shown to increase exercise tolerance in patients with exertional angina pectoris, we are not aware of substantial evidence or substantial clinical experience supporting the suggestion that patients who use Nitrolingual Pumpspray to prevent or treat chest pain will not be “slow[ed]. . .down” at all by their angina pectoris. If you have data to support this implication, please submit them to FDA for review.

Omission and Minimization of Risk Information

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.

The sales aid, brochure, and the brochure holder state that, “Nitrolingual Pumpspray should be used with caution if patients. . .show hypersensitivity to this and other nitrates or nitrites.” However, according to the PI, “Nitroglycerin is contraindicated in patients who are allergic to it.” Thus, the direction to use Nitrolingual Pumpspray “with caution” in patients who show hypersensitivity to it, minimizes the contraindication of Nitrolingual Pumpspray in patients who are allergic to it.

The sales aid, brochure, and brochure holder claim that, “Nitrolingual Pumpspray should be used with caution if patients have low systolic blood pressure. . . .” This claim minimizes the risk of severe hypotension in patients with low systolic blood pressure because it omits the material facts that, “[S]evere hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin. The drug, therefore, should be used with caution in subjects who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure. . . . Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.”

The sales aid completely omits the warning regarding the use of Nitrolingual Pumpspray after an acute myocardial infarction and the precautions regarding hypertrophic cardiomyopathy and tolerance associated with the use of Nitrolingual Pumpspray, thereby suggesting that the drug is safer than has been demonstrated (see Background section). Similarly, the brochure and brochure holder completely omit important information such as the precaution regarding tolerance associated with the use of Nitrolingual Pumpspray.

Promotional materials are also misleading if they fail to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug, taking into account all techniques apt to achieve emphasis. Specifically, the brochure and brochure holder are misleading because they prominently present efficacy claims in large bolded font size and in colorful text and graphics surrounded by significant amount of white space. However, the risk information in the brochure and brochure holder is relegated to the bottom of the back cover and is presented in paragraph format. Furthermore, while the brochure and brochure holder present efficacy claims for Nitrolingual Pumpspray in language that is easily understandable to consumers, they present the risk information using complex medical terminology that is not likely to be comprehended by the same audience (e.g., “phosphodiesterase inhibitors,” “low systolic blood pressure,” “diuretic therapy”). The overall effect of this presentation undermines the communication of important risk information, thereby minimizing the risks associated with Nitrolingual Pumpspray and misleadingly suggesting that it is safer than has been demonstrated.

Conclusion and Requested Action

For the reasons discussed above, the sales aid, brochure, and the brochure holder misbrand Nitrolingual Pumpspray in violation of the Act, 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), & (ii); (e)(7)(i) & (viii).

DDMAC requests that Arbor Pharmaceuticals, Inc. immediately cease the dissemination of violative promotional materials for Nitrolingual Pumpspray, such as those described above. Please submit a written response to this letter on or before May 10, 2011, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Nitrolingual Pumpspray that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. If you have any questions or comments, please contact me by facsimile at (301) 847-8444, or write to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705. In all future correspondence regarding this matter, please refer to MACMIS ID #

19582 in addition to the NDA number. We remind 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 Nitrolingual Pumpspray comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Zarna Patel, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communication

Emily Baker, Pharm.D.
Regulatory Review Officer
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZARNA PATEL
04/26/2011

EMILY K BAKER
04/26/2011