



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

San Juan District  
Compliance Branch  
466 Fernández Juncos  
San Juan, Puerto Rico 00901-3223

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February 4, 2004

**WARNING LETTER**  
**SJN-04-03**

**Certified Mail**  
**Return Receipt Request**

Mr. Jaime González Castrodad  
President  
Domel Laboratories  
P. O. Box 1228  
Saint Just, Puerto Rico 00978

Dear Mr. González Castrodad:

This letter is in reference to the inspection of your facility located at Calle De Diego 488 Altos, Río Piedras, Puerto Rico 00924 on June 24 – 26, and July 1 – 2, 9 and 23, 2003 by an Investigator from the U.S. Food and Drug Administration.

During our inspection, the Investigator collected labeling and promotional material for several products identified below that are marketed and distributed by your firm. Our review of these materials revealed serious violations of the U. S. Food, Drug and Cosmetic Act (the Act) and Title 21, Code of Federal Regulations (21 CFR). Products for which objectionable claims are being made include, but are not limited to the following:

**Dometuss-DM, Dometuss Cough/Cold Formula Softgels and Garylin Throat Spray**

Dometuss-DM contains guaifenesin and dextromethorphan hydrobromide and is offered as an antitussive and expectorant. The Dometuss Cough/Cold Formula Softgels product contains pseudoephedrine hydrochloride, acetaminophen, and dextromethorphan hydrobromide and is offered as a cough suppressant, nasal decongestant, analgesic, and antipyretic. The Garylin Throat Spray contains benzocaine, cetylpyridinium chloride, pyrilamine maleate, and ethanol and is offered as an anesthetic, antiseptic, and antihistaminic.

The labels for the above products each bear the statement “Rx Only”. All of the products are either subject to final regulations under the OTC (over-the-counter) Drug Review or will be subject to such regulations when pending proposals are finalized. Final regulations covering

OTC antitussive and nasal decongestant are currently in effect at Title 21 Code of Federal Regulations (21 CFR) part 341. There are proposed regulations covering internal analgesics and oral health care preparations. All of the active ingredients and claims for the three products are covered under the OTC Drug Review. None of the products are entitled to bear the "Rx only" legend since they can be marketed as OTC drugs. Therefore, all three products are misbranded [Section 503(b)(4)(B) of the Act].

The Dometuss Cough/Cold Formula is further misbranded under section 502(f)(2) of the Act because it fails to bear the following required warnings, or the specific required wording for the warnings:

- Alcohol Warning for internal analgesics (acetaminophen) — 21 CFR 201.322(a)(1)
- Antitussive warning regarding persistent cough — 21 CFR 341.74(c)(1) & (c)(2)
- Drug Interaction warning regarding MAOI inhibitors — 21 CFR 341.74(c)(4)(v) and 21 CFR 341.80 (c)(1)(i)(D)
- "Do not exceed recommended dosage if nervousness..." warning for pseudoephedrine — 21 CFR 341.80(c)(1)(i)(A)
- Pregnancy warning — 21 CFR 201.63
- "Keep out of reach of children" and accidental ingestion warnings — 21 CFR 330.1(g)

The Dometuss Cough/Cold Formula is further misbranded under section 502(f)(1) of the Act because it fails to bear the following required information regarding adequate directions for use:

- The labeled dosage for dextromethorphan hydrobromide (20 mg every 6 to 8 hours) does not conform to the required dosage of 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours — 21 CFR 341.74(d)(1)(iii)
- The labeled dosage for pseudoephedrine hydrochloride (60 mg every 6 to 8 hours) does not conform to the required dosage of 60 mg every 4 to 6 hours. Further, the statement "not to exceed 12 softgels in 24 hours" would allow for an excessive total daily dose of pseudoephedrine, even though the directions do not specify that maximum dose — 21 CFR 341.80(d)(1)(ii)

The Dometuss Cough/Cold Formula is also misbranded under section 502(a) of the Act for the following reasons:

- The "Indications" heading fails to bear the required information regarding the antitussive indication — 21 CFR 341.74(b)

- The label bears warning statements that are not included in the warnings required by final regulations for antitussives and nasal decongestants. These include “may cause drowsiness” and “avoid driving a motor vehicle or operating machinery”.

Because the Dometuss Cough/Cold Formula Softgels fails to comply with the final monographs as noted above, the product is an unapproved “new drug” which may not be marketed in this country unless it is subject of an approved New Drug Application (NDA) under Section 505(a) of the Act.

The Garylin Throat Spray is a “new drug” [Section 201(p) of the Act] because it contains an active ingredient, pyrillamine maleate, which has been found to be not generally recognized as safe and effective for use in an oral health care product [21 CFR 310.545(a)(14)]. Therefore, it may not be marketed in this country unless it is subject of an approved New Drug Application (NDA) under Section 505 of the Act.

The Dometuss-DM is misbranded under Section 502(f)(1) of the Act because the directions for use of one teaspoon (200 mg guaifenesin and 20 mg dextromethorphan hydrobromide) every 6 to 8 hours do not conform to the required directions of once every 4 hours for the 10 to 20 mg or every 6 to 8 hours for the 30 mg dosage of dextromethorphan hydrobromide [21 CFR 341.74(d)(1)(iii)] and 200 mg to 400 mg every 4 hours for guaifenesin [21 CFR 341.78(d)]. We also note the label bears the statement “For full product information, see package outsert”. We have not been provided with the “outsert” for review, so we are unable to comment on the complete labeling for this product. However, it is your responsibility to assure that the labeling conforms to all applicable requirements of 21 CFR 341 covering antitussive and expectorant drug products, in addition to any other applicable labeling requirements.

Drug Facts Format labeling regulations found at 21 CFR 201.66 will ultimately apply to all OTC drug products. Currently, products that are subject to final OTC monographs are required to be labeled in accordance with these regulations. Because both active ingredients in the Dometuss-DM product are subject to final regulations (antitussives and expectorants), it was required to comply as of May 16, 2002. Thus, the Dometuss-DM product is misbranded under section 502(c) of the Act for failure to comply with the Drug Facts Format labeling requirements. Additionally, products with active ingredients that are not yet subject to final monographs will have to comply with 21 CFR 201.66 in accordance with the implementation schedule set forth in the attached copy of page 38193 of the June 20, 2000, Federal Register (65 FR 38193).

The inspection disclosed that you have failed to submit a drug listing for all drug products distributed under your Domel Laboratories own label. Owners that distribute drug products under their own label or trade name manufactured by a registered establishment should follow the procedures described in 21 CFR 207.20(b). The above violations concern certain new labeling requirements, and are not meant to be an all-inclusive list of deficiencies on your labels. Other label violations can subject the dietary supplement to legal action. It is your responsibility to assure that all of your products are labeled in compliance with all applicable status and regulations enforced by FDA.

In addition, we have concerns with products that make disease claims. Products for which objectionable claims are being made include the following:

**“Lipex 10 mg”, “Stonex”, “Daflonex 600 mg” and “Btrex”**

The labeling and promotional material for these products contains statements that represent or imply that these products are intended to be utilized in the cure, mitigation, treatment or prevention of diseases. Such claims cause the products to be drugs under section 201(g)(1)(B) of the Act.

**Lipex 10 mg tablets**

Disease claims in the product’s insert include:

“Lipex is indicated as an adjunct to dietary and lifestyle recommendation to reduce elevated LDL-C and total cholesterol levels. Its primary application is in type 2 hypercholesterolemia including 2a subtype (characterized by elevated total serum cholesterol and LDC-C levels) and 2b subtype (mixed hypercholesterolemia characterized by elevated total serum cholesterol, LDL-C and triglycerided levels). Lipex can be used as an alternative to aspirin as an anti-platelet agent.”

“Lipex not only effectively decreases serum cholesterol levels, but also reduces the cholesterol content in differing tissues such as liver, heart and fatty tissue.”

“Lipex prevents and reverses atherosclerotic lesion and thrombosis”

“Lipex prevents intimal [*sic*] thickening and smooth muscle cell.”

“Lipex produces a dose-dependent and significant reduction of serum total cholesterol and LDL-c and levels HDL-c values were also increased in a dose-dependant manner.”

“Lipex lowers total and LDL-C....”

“The cholesterol lowering effects of Lipex are persistent and it does not lose its effect overtime.”

“Lipex is a new cholesterol lowering agent....”

**Stonex softgels**

Disease claims made in the product’s label and insert include:

“Stonex is indicated for prophylaxis and treatment of urolithiasis, Nephrolithiasis, Renal Colic, Dysuria, Oliguria, Urinary tract infections, pre and postoperative

treatment of urological disorders. Improvement of renal functions. Generally, prophylaxis and treatment of any renal and urinary disorders.”

“Effective painless expulsion of ureteric calculi if the site and size permit. Prevents nephrocalcinosis. Protects against [*sic*] urothiasis without diet restriction. Equally effective in subacute and chronic urinary tract infections.”

### **Btrex tablets**

Disease claims made in the product’s label include:

“Btrex tablets are indicated ... with particular emphasis for individuals with or at risk for cardiovascular disease, cerebrovascular disease, arteriosclerotic vascular disease, neurological disorders, Alzheimer [*sic*] disease, and renal disease.”

In addition, the use of the vignette depicting an electrocardiogram tracing in the product's label constitutes an implied disease claim because it suggests that the product is useful in the prevention, mitigation, treatment or cure of cardiovascular disease.

Furthermore, the use of the term “Rx Only” on the Lipix, Stonex and Btrex labels implies that these products belong to a class of products that are intended to diagnose, mitigate, treat, cure, or prevent disease, i.e. prescription drugs (see 21 CFR 101.93(g)(2)(v)). In conjunction with the products' inserts that contain disease claims, this agency considers the utilization of “Rx Only” on the labels to be an implied disease claim.

Because we are unaware of any evidence that these products are generally recognized as safe and effective when used as indicated in the labeling, they are new drugs as defined under Section 201(p) of the Act. Therefore, these products may not be legally marketed in the United States without an approved New Drug Application (NDA), in accordance with section 505(a) of the Act.

The labeling of your product Btrex indicates that you intend to market this product as a dietary supplement. If you intended to market any of your products as dietary supplements, they must meet the definition of a dietary supplement in accordance with Section 201(ff) of the Act, and must also comply with the applicable food labeling regulations in 21 CFR Part 101. Even if these products met the legal definition of a dietary supplement, they may be subject to regulation as a drug based on disease claims in the labeling. Section 403(r)(6) of the Act provides that structure/function claims may be made on the product’s labeling for dietary supplements in certain limited circumstances. The Act specifically prohibits express or implicit claims that a dietary supplement has an effect on a specific disease or class of diseases unless FDA has authorized subject claims in accordance with applicable health claim regulations under 21 CFR 101.14 and 101.70, listed under in the new drug approval process in 21 CFR 314 or through the issuance of an OTC monograph, as stated in 21 CFR 330.

Be advised that if you correct the above mentioned deficiencies in your labeling and provide only allowable structure/function claims for these products, as dietary supplements these would still be misbranded in that:

- The products fail to include the term “dietary supplement” as part of the statement of identity, as required by sections 403(i)(1) and 403(s)(2)(B) of the Act and 21 CFR 101.3(g). The word “dietary” may be replaced by the name of the dietary ingredients in the product or an appropriately descriptive term, e.g., “calcium supplement” or “herbal supplement with vitamins”.
- The products fail to present nutrition information required by section 403(q)(5)(F) of the Act as a Supplement Facts panel in the format required under 21 CFR 101.36.

We acknowledge receipt of your letter dated August 11, 2003 responding to the Current Good Manufacturing Practices (CGMP) objectionable conditions in the areas of holding and distribution (21 CFR 211.142 and 211.150), equipment calibration (21 CFR 211.68(a), records and reports (21 CFR 211.180), distribution records (21 CFR 211.196) and sanitation procedures [21 CFR 211.56(a) and (b)] cited in the FD-483 issued on July 23, 2003. The voluntary corrections implemented during the course of the investigation in conjunction with the corrective actions that you have outlined in your letter, once fully implemented, appear to adequately address the CGMP deficiencies reported. However, your response did not include any reference concerning labeling deviations noticed in your products that were discussed with you during the course of the inspection and at the discussion with management meeting.

We strongly suggest that you review all your labeling for all of the products you are marketing, taking particular note of the types of claims that may cause your products to be unapproved and misbranded under the Act. You should take prompt measures to correct these deviations. Failure to promptly correct the deviations noted may result in regulatory action without further notice. Such action includes seizure and/ or injunction.

Please notify this office in writing, within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct these violations including an explanation of each step taken to prevent their reoccurrence. You may wish to include in your response documentation such as revised labels or other useful information that would assist us in evaluating your corrections. If corrective action cannot be completed within 15 working days, state the reasons for the delay and the time frame within the corrections will be completed.

Mr. González Castrodad/Domel Laboratories  
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Your written reply to these concerns should be directed to the Food and Drug Administration, attention: Rafael Nevárez, Compliance Officer, at 466 Fernández Juncos Avenue, San Juan, Puerto Rico 00901-3223. If you have any questions regarding any issue in this letter, please contact Mr. Nevárez at (787) 474-9545. You can also find this Act and the food and dietary/supplement labeling regulations through links in FDA's Internet homepage at <http://www.fda.gov>.

Sincerely,



*for* Donald J. Voeller  
District Director  
San Juan District

Enclosure:

65 FR 38193 dated June 20, 2000 (Drug Facts Format Implementation)