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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

We submit this petition pursuant to section 10.30 of title 21, Code of Federal Regulations, and under sections 301(d) and 505(a) of the Federal Food, Drug, and Cosmetic Act (the Act) on behalf of our client, Éclat Pharmaceuticals, LLC (Éclat). This petition requests that the Commissioner of Food and Drugs take immediate enforcement action against unapproved drug products being illegally marketed as an alternative to an existing FDA-approved drug product, and to secure the removal of these products from the market.

A. Action Requested

According to the FDA's National Drug Code Directory, the following companies are marketing unapproved neostigmine methylsulfate injectable drug products in direct violation of sections 301(d) and 505(a) of the Federal Food, Drug, and Cosmetic Act:

Cardinal Health (1 mg/mL)
West-Ward Pharmaceuticals Corp. (0.5 mg/mL and 1 mg/mL)
Fresenius Kabi USA, LLC (0.5 mg/mL and 1 mg/mL)
American Regent, Inc. (0.5 mg/mL and 1 mg/mL)
General Injectables & Vaccines, Inc. (1 mg/mL)

Éclat respectfully requests that the Commissioner of Food and Drugs initiate expedited enforcement action requiring that these manufacturers immediately remove the unapproved injectable neostigmine methylsulfate products from the market because they are competing with an FDA-approved drug product (NDA 204078, Bloxiverz® neostigmine methylsulfate injection), thus, posing a direct challenge to the integrity of the new drug approval system. Additionally, they are marketed with incomplete labeling that may raise potential safety risks, and, as demonstrated by FDA Warning Letters identifying failures to comply with quality control requirements, they may be produced in violation of the Act in other ways.

FDA-2013-P-1000

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B. Statement of Grounds

The Marketed Unapproved Drugs Compliance Policy Guide (CPG) indicates that drug products that are marketed without an FDA approval or compliance with an OTC monograph cannot be assured of being safe and effective for their intended uses.[1] FDA has stated that it has "an interest in taking steps to either encourage the manufactures of [marketed unapproved] products to obtain the required evidence and comply with the approval provisions of [the Act] or remove the products from the market."[2] When a company takes the initiative to obtain approval for a marketed unapproved drug, the CPG indicates that FDA generally anticipates providing a grace period of roughly one year between approval and the initiation of enforcement action against the unapproved versions of that drug that remain on the market. The CPG, however, also indicates that certain circumstances may prompt more rapid enforcement action. With regard to injectable neostigmine methylsulfate products, Éclat believes that expedited enforcement and prompt removal of the unapproved versions is warranted (1) in order to protect the integrity of FDA's new drug approval framework, (2) because the labeling of unapproved neostigmine methylsulfate products presents unique safety risks, and (3) it is likely that several unapproved neostigmine methylsulfate drugs are violative of the Act in other ways.

1. Challenge to the New Drug Approval Framework

When unapproved products are allowed to be marketed in direct competition with approved drug products they challenge the integrity of the drug supply and the FDA drug approval system. The FDA has indicated that when a firm voluntarily obtains approval of an NDA for a product that other companies are marketing without approval, the removal of the unapproved versions becomes a priority.

2. Unique Safety Risks Presented by Unapproved Neostigmine Product Labels

Because of significant differences between the labeling for Bloxiverz and the currently marketed versions of the drug, a safety risk may exist if Bloxiverz and the unapproved versions of neostigmine methylsulfate are allowed to be marketed simultaneously. The FDA-approved labeling for Bloxiverz differs from the labeling of the marketed unapproved products in the following significant ways:

> Dosage and Administration – The dosage recommendations present on the Bloxiverz label are based on clinical evidence of efficacy of the labeled doses for recovery from

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[1] FDA, *Compliance Policy Guide § 440.100: Marketed New Drugs Without NDAs or ANDAs* (Sept. 19, 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070290.pdf.

[2] *Id.*

neuromuscular blockade to a train-of-four (TOF) ratio of 0.9. This level of recovery is the current gold standard benchmark for documenting complete neuromuscular blockade reversal. A TOF ratio of less than 0.9 may indicate impaired pharyngeal function with the risk of aspiration in the case of regurgitation, and a TOF ratio of less than 0.7 indicates subjects might additionally have an impaired hypoxic ventilatory response. The unapproved products do not provide recommendations for assessing residual blockade using peripheral nerve stimulation nor do the directions for use specify a desired TOF level of recovery. In the absence of these specific recommendations, it is very possible that many patients could be significantly under-dosed, resulting in residual neuromuscular blockade and the potential for respiratory depression and other complications of incomplete reversal in the recovery room.

Differences also exist in the dosing instructions. The studies that support the label dose recommendations for Bloxiverz evaluated dosing according to the milligrams of neostigmine administered per kilogram of body weight of the patient. Bloxiverz dosing recommendations are likewise expressed as milligrams per kilogram body weight. As such they provide guidance to the anesthesiologist for patients across the spectrum of possible body weights. By contrast, labeling for all of the marketed, but unapproved neostigmine methylsulfate injection products recommend a range of doses (i.e., 0.5 to 2 mg) to be repeated as required without guidance as to how dosing should be adjusted according to patient body weight. These differences may cause confusion and could potentially lead to inappropriate dosing.

Special Populations – Specific dosage recommendations are present on Bloxiverz labeling for pediatric patients, geriatric patients, and patients with renal or hepatic impairment. These directions are absent from the labels of marketed unapproved neostigmine methylsulfate injection products. The absence of this information on the unapproved labeling creates a disadvantage for anesthesiologists seeking guidance for appropriate dosing for these populations.

3. Currently Marketed Neostigmine Products May Violate the Act's Quality Control Requirements

It appears that FDA has recently identified quality control problems at the manufacturing facilities of some of the manufacturers of the unapproved neostigmine methylsulfate. Two of the manufacturers identified above, APP Pharmaceuticals (a division of Fresenius Kabi USA, LLC) and American Regent/Luitpold, received warning letters in the last two years regarding manufacturing issues with their parenteral products. Luitpold temporarily suspended distribution of drug products manufactured at their Shirley, New York facility to allow remediation.

The February 22, 2012 warning letter addressed to APP Pharmaceuticals noted that in addition to other cGMP violations the firm was marketing a number of unapproved products and affirmed the FDA's expectation that "products marketed without required FDA approval be removed from the market." At the time of the warning letter, there were no FDA-approved applications on file for these drugs and APP Pharmaceuticals was advised to contact the FDA unapproved drugs coordinator to discuss the application process for these drugs.

Now that an FDA-approved, cGMP-compliant alternative exists for the neostigmine methylsulfate marketed by APP Pharmaceuticals and other manufacturers, FDA should move quickly to require the immediate removal of non-compliant neostigmine methylsulfate products from the market.

Further, perhaps due to quality problems like those discussed above or because of business priorities, the manufacturers of unapproved versions of neostigmine methylsulfate are currently having difficulty meeting market demand. A review of the FDA webpage for drug shortages (a portion of which is copied below) indicates that several manufacturers are experiencing supply issues:

Neostigmine Methylsulfate Injection, USP (Initial Posting - 1/14/2012)

Company	Product	Availability and Estimated Shortage Duration	Related Information	Shortage Reason (per New Legislation-FDASIA)*	Date Updated
APP Customer Service 1-888-386-1300	0.5 mg/mL, 5 mg/10 mL MDV (NDC # 63323-382-10)	Available. Check wholesaler for inventory.		Increase in demand.	Reverified 7/17/2013
	1 mg/mL, 10 mg/10 mL MDV (NDC # 63323-383-10)	Available. Check wholesaler for inventory.			
American Regent/Luitpold 1-800-645-1706	1 mg/mL, 10 mL vial, package of 25 (NDC 00517-0033-25)	Available	American Regent is currently releasing Neostigmine Methylsulfate Injection 1 mg/mL	Other	Reverified 7/15/2013
	0.5 mg/mL, 10 mL vial, package of 25 (NDC 00517-0034-25)	Unavailable	American Regent is currently not releasing Neostigmine Methylsulfate Injection 0.5 mg/mL		
West-Ward Pharmaceuticals Customer Service: 1-800-631-2174	0.5 mg/mL, 10 mL vial (NDC 0641-6076-10) 1 mg/mL, 10 mL vial (NDC 0641-6077-10)	West-Ward currently has limited quantities available of both presentations West-Ward has accelerated production on this product.	West-Ward is anticipating having product available by the end of July 2013. Product will be made available as it is released.	Demand increase for the drug.	Reverified 7/26/2013

Consequently, although FDA has indicated that discretion will be applied in removing competing unapproved versions of a product if concerns exist about the ability of the holder of the approved application to meet patient needs and the impact of removing the unapproved product from the market, the current manufacturers' poor performance in supplying the market makes such a concern less relevant in this case.

Additionally, Éclat is able to assure the Agency that it has the capability of adequately supplying the market demand for neostigmine methylsulfate injection, and there is no concern that FDA's removal of unapproved neostigmine products from the market would result in a drug shortage of neostigmine methylsulfate.

C. Environmental Impact Statement

A claim for categorical exclusion of the requirement for submission of an environmental assessment is made pursuant to title 21 CFR §25.31.

D. Economic Impact

This information will be submitted only if requested by the Commissioner following review of the petition.

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

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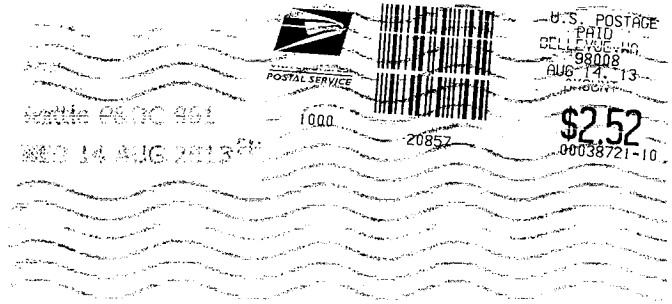

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