

Medication Delivery

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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Suitability Petition 2004P-0085/CP 1

On February 24, 2004, Bedford Laboratories (Bedford) filed a Suitability Petition (Bedford Petition) with the Food and Drug Administration (FDA). The petition requested FDA to allow Bedford to file an Abbreviated New Drug Application (ANDA) for esmolol hydrochloride (esmolol) in a new, lyophilized vial formulation with the listed drug being Brevibloc® Concentrate Ampules for Injection. The Bedford product is both a change in dosage form from a liquid ampule for the listed drug product to a lyophilized vial and a change in strength as the lyophilized product when initially diluted will have a concentration of 100 mg/mL esmolol compared to a concentration of 250 mg/mL for Brevibloc Concentrate (both further diluted to a final concentration of 10 mg/mL).

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In the Bedford Petition the grounds for the application are:

1. The stability of the product is enhanced in the lyophilized form versus the aqueous form.
2. The new dosage form may help to prevent fatal medication errors.
3. The new dosage form allows the availability of a cheaper equivalent form of the drug product.

For the reasons set forth below, the Bedford Petition should be denied:

- I. The claim that stability of the product is enhanced in the lyophilized form versus the aqueous form:

Esmolol hydrochloride (esmolol) is a very rapidly cleared selective beta₁-adrenergic receptor-blocking agent whose rapid clearance is due to hydrolysis by erythrocyte cytosol esterases. As it can be unstable in an aqueous solution, any formulation changes must be viewed critically. Under non-enzymatic conditions, esmolol decomposes through hydrolysis of a methyl ester linkage to form ASL-8123 (an acid derivative of esmolol) and methanol. The chemical decomposition is dependent on several factors within the microenvironment of the molecule such as moisture content, pH, type and concentration of buffers, temperature and the concentration of esmolol itself.

Esmolol hydrochloride crystalline powder is extremely stable as compared to an aqueous and/or a co-solvent form. However, lyophilized esmolol powder may contain bulking or stabilizing agents which might be amorphous and/or partially crystalline material which could significantly affect the stability and levels of degradation products in both the shorter and longer terms.

If the 0.16% impurity profile referenced in the Bedford Petition refers to the major degradant, ASL-8123, then, upon reconstitution of the lyophilized esmolol, the concentration of ASL-8123 will act as a thermodynamic sink, accelerating the degradation of the esmolol solution (pKa of ASL-8123 is 4.2). In the absence of detailed stability information on the lyophilized formulation, the assumption of comparability cannot be made.

II. The claim that a new dosage form may help to prevent fatal medication errors:

Reducing medication errors have long been a focus in health care. The recently released 2003 Institute of Medicine report *To Err is Human: Building a Safer Health System* estimates that 70,000 patients in the United States die per year from medication errors and that 1 in every 854 inpatient deaths are caused by medication errors.¹ The 2002 USP MEDMARX anonymous error-reporting database of 192,477 records demonstrates that such errors can occur in any portion of the process of getting a drug product to a patient: prescribing (21% of errors), documenting (23%), dispensing (22%), administering (33%)

and monitoring (1%).² These errors were the result of improper dosage/quantity in 25% of cases and the wrong dosage form in 2% of cases. Two percent of the errors may have contributed to or resulted in harm to a patient. Of note, while only 2.2% of all errors were calculation errors, these errors resulted in 6.4% of harmful errors.

The consequences of a medication error to the patient depend in part on the drug involved. Some drugs such as antibiotics have a wide therapeutic index and require massive overdosage to put patient safety at risk. Others, like esmolol, have a smaller therapeutic index. In 2003, the Institute for Safe Medication Practices created a list of High-Alert Medications that included 30 drugs and drug categories.³ Adrenergic antagonists are listed as a drug category but esmolol is not listed as a specific high-risk drug. The omission of esmolol as a high-risk drug is remarkable considering the potential for life-threatening toxicity of an overdose. This may be related to the comprehensive risk management program instituted by Baxter since esmolol was launched in 1986.

When Brevibloc was approved and launched in the United States in 1986, two presentations were available, a ready to use vial with a concentration of 10 mg/mL and a concentrated ampule with a concentration of 250 mg/mL for use in preparing continuous IV infusions. After launch, both Baxter and the FDA received reports of the concentrated form being infused directly, sometimes with fatal outcomes. In 1995, several labeling and packaging changes were made to the concentrated ampule. A red warning flag stating "MUST BE DILUTED" was applied to the upper part of the ampule

bulb. In 2000, this warning flag was expanded to cover both the upper and lower portions of the ampule, making it virtually impossible to open the ampule without noting the warning flag. As well, a "Dear Hospital Pharmacist and Health Care Professional" letter was issued in July 1995 warning the medical community of the potential for error that could result in fatal consequences. The FDA also publicized the potential problem.⁴ Baxter sales representatives held in-service training programs for hospital pharmacists and nurses who might be called on to use the concentrated ampule to admix the IV solution.

From 1994-1999, the majority of overdosage reports resulted from confusion of the ready to use vial with the concentrated ampule. The incidence of overdosage during that period was 0.158 per 10,000 estimated patients. From 2000-2003, with institution of the risk management program, the majority of overdose reports were due to dilution errors and the incidence of overdosage dropped to 0.0363 per 10,000 estimated patients.⁵

Introducing a new, lyophilized dosage form with a different strength (100 mg/mL versus 250 mg/mL for Brevibloc ampule) when initially reconstituted runs the risk of increasing misdosing during admixing of IV esmolol infusions. This strength does not match any currently marketed strength of esmolol drug product leading to potential confusion and error. Pharmacists and nurses who have been trained and are familiar with dilution of Brevibloc Concentrate could make dilution errors with the new product. Errors in drug computations are relatively common with one study demonstrating computations by registered nurses are only 86% correct, which would have resulted in 1 in 12 doses

having a drug concentration either 10 times higher or lower than the dose ordered.⁶ This is particularly important as esmolol concentrate is stocked in both the central hospital pharmacy and in satellite pharmacies in the ICU, CCU and OR and is frequently used in emergency situations where a nurse is preparing the admixture. Another study determined that the mean error rate for admixtures by hospital pharmacists was 9% (145 errors in 1,670 doses) with wrong dose errors being the most common (9%).⁷

Additionally, the need to first reconstitute the lyophilized formulation may place patients at additional unnecessary risk for harm. The Bedford lyophilized formulation requires the further dilution of the intermediate concentrate in an IV bag, which adds an second dilution step and an extra opportunity for dilution error to the preparation process when compared to the listed drug. Of greater concern is that the formulation referenced in the Bedford Petition has a different volume (25 mL) and concentration (100 mg/mL) upon reconstitution when compared to the all currently marketed presentations of esmolol. This invites additional opportunity for error unless hospital staff are fully educated and trained in the new formulation and concentration prior to its availability. Hospital staff will have to be trained and made aware of the particular product that is stocked in their hospital. Potentially, a hospital could stock Baxter's product and a generic lyophilized dosage form for the same indications requiring different preparation instructions. Since stocking of both products is a possibility, this results in an increased risk of incorrect dosage being given to patients. Hospitals will need to establish and validate procedures for the proper segregation and isolation of different dosage forms of esmolol. This will

be especially difficult for a drug used in emergent circumstances in patients who are critically ill.

21 CFR 314.93 states that a petition will not be approved if “any of the proposed changes from the listed drug would jeopardize the safe and effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem.” A lyophilized concentrated esmolol vial would need to have an appropriate and prominent warning label on the product and warnings in the package insert concerning Dosage and Administration. The sponsor should also have an appropriate risk management plan in place. Hospital pharmacists and nurses who might use the new product would need to be educated in the differences in concentration from the listed drug and the proper dilution of the new formulation. Those performing admixture of the new product would need to be fully familiar with the differences from the listed product prior to encountering it in the hospital.

With such a “High-Alert” drug, changes in product presentation and concentration that could lead to misdosing are a patient safety concern. The Joint Commission of Accreditation of Healthcare Organizations lists as Safety Goal 3: “Improve the safety of using medications” and as Goal 3b “Standardize and limit the number of drug concentrations available in the organization.”⁸ A consensus conference on the safety of IV drug delivery systems recommended “Simplification and standardization to minimize variability of available IV systems and drug concentrations” for safe delivery of IV medication.⁹ As such, it would seem that for a generic drug in this category to be

considered interchangeable with the listed drug, the formulation and concentration should be identical, not merely similar.

An additional consideration for any parenteral product is bacterial contamination as it is one of the most frequent risks accompanying the admixture of drugs into sterile infusions.¹⁰ An in-use study of IV solutions in flexible plastic containers found that 4.9% (18 of 365) of containers and 5.5% (20 of 365) of administration sets were positive for bacterial growth.¹¹ The additional reconstitution step for the lyophilized esmolol concentrate allows an additional opportunity for such contamination when compared to Brevibloc Concentrate.

Potential misdosing extends beyond the labeling of the product. It cannot be assumed that admixed IV solutions or reconstituted lyophilized products are homogeneous mixtures. When admixed potassium chloride was studied, incomplete mixing was found, especially in flexible polyvinyl bags.¹² Incomplete mixing upon reconstitution of the lyophilized vial could lead to variability in the administered dose of esmolol when compared to Brevibloc Concentrate and resultant under- or overdosing.

- III. The claim that a new dosage form allows the availability of a cheaper equivalent form of the drug product that does not infringe the rights of the innovator:

Clinical and regulatory decisions cannot be based solely on economical considerations but must consider the safety of the patient. Introducing a different and unfamiliar presentation of esmolol with more complex dilution requirements could likely increase the potential for error as delineated in Section II. As these errors would result in risk to patients, this statement is irrelevant. Any potential savings would be greatly offset by any injury to a patient. The Institute of Medicine report noted, "almost two percent of admissions experience a preventable adverse drug event, resulting in an average increased length of stay of 4.6 days and an average increase in hospital costs of nearly \$4,700 per admission."¹

In its Petition, and without any analysis, Bedford summarily concludes that its proposed drug product does not infringe any of Baxter's patent rights. We disagree with this unsupported conclusion (and, indeed, is improper in Bedford's Petition). As FDA knows, the listed drug product on which Bedford relies is subject to the protection of certain patents listed in Approved Drug Products with Therapeutic Equivalence Evaluations (a/k/a the "Orange Book"). The listed patents are United States Patent Nos. 4,593,119; 5,017,609; 6,310,094 and 6,528,540. These patents will require Bedford's certification as to each patent upon its submission, if permitted, of an ANDA and may also affect the approval date of any such ANDA. We respectfully request that FDA's response remind Bedford in this regard.

For all the aforementioned reasons, the undersigned respectfully requests that the FDA deny the Bedford Petition.

Sincerely,



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