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Division of Dockets Management  
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## CITIZEN PETITION

The undersigned submits this petition under 21 C.F.R. §§ 10.25(a), 10.30, and 314.161(a)(3) to request the Commissioner of Food and Drugs to make a determination as to whether a listed drug that has been voluntarily withdrawn from sale in the United States was withdrawn for safety or effectiveness reasons.

### *A. Action Requested*

According to publicly-available reports, Novartis Pharmaceutical Corporation voluntarily withdrew its drug Syntocinon® (oxytocin) Nasal Spray from sale. The undersigned is seeking a determination by the Commissioner that Novartis's voluntary withdrawal of Syntocinon® from sale was for reasons other than safety or effectiveness.

### *B. Statement of Grounds*

On August 7, 1997, FDA announced withdrawal of approval of 28 new drug applications, including NDA 12-285, for Syntocinon® (oxytocin nasal solution) Nasal Spray. According to the Federal Register notice, the holder of the NDA, Novartis Pharmaceutical Corporation, had notified FDA in writing that the product was no longer marketed. 62 Fed. Reg. 42575 (Aug. 7, 1997). The Federal Register notice does not explain the reason why the product was no longer marketed. Attachment A.

Syntocinon® is now listed in the "Discontinued Section" of the electronic Orange Book on FDA's web site. According to section 1.11 of the Preface to the Orange Book, a drug product in the Discontinued Section as to which a determination has already been made that withdrawal was not for safety and effectiveness reasons will have the following statement after its product strength: "Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons." There is no such annotation next to the product strength for Syntocinon®. Attachment B.

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Information from the Syntocinon® NDA file, available through a commercial vendor (FOI Services), does not suggest the product was discontinued for reasons of safety or effectiveness. Sandoz Pharmaceuticals submitted an NDA in January 1960, and FDA permitted that NDA to become effective in August 1960. (Sandoz U.S. is now a member of the Novartis Group of Companies.) The agency provided various handwritten notes related to review of the original NDA, which are difficult to decipher, but none of which suggests the product – once permitted to be marketed – would be discontinued for safety reasons. Attachment C. The version of section 505 of the Federal Food, Drug, and Cosmetic Act effective in 1960 required a new drug applicant to submit clinical trials showing only that the new drug was "safe" (i.e., not also that it was "effective") for use under the conditions described in the labeling. The initial labeling (in the 1962 Physician's Desk Reference) provided that Syntocinon® was indicated to prevent or relieve complications associated with lactation, and in particular to relieve the pressure of milk present in the breast. Use during pregnancy was "not recommended." Attachment D.

"Syntocinon nasal spray (oxytocin solution equivalent to 40 U.S.P. posterior pituitary units per millileter)" was reviewed in the Drug Efficacy Study Implementation (DESI) program. FDA concurred in the conclusion of the National Academy of Sciences/National Research Council that Syntocinon® was "effective only for the indication 'initial milk letdown.'" 33 Fed. Reg. 9037 (June 19, 1968). Attachment C.

In its 1980 labeling, also provided by FDA to FOI Services, Syntocinon® was indicated for initial milk let-down and contraindicated in pregnancy and cases of hypersensitivity. Attachment C. The labeling printed in the last Physician's Desk Reference prior to market withdrawal listed contraindications in cases of "pregnancy" and "hypersensitivity." The "adverse reaction" section listed lack of efficacy, nasal irritation and/or rhinorrhea, uterine bleeding, uterine contraction, and lacrimation. It added "[o]ne case each of seizure and 'psychotic state' are the most severe reactions reported. No other reactions have been described." Attachment E.

FDA's MedWatch website captures safety-related labeling changes, drug and biologic safety alerts, Class I recalls, market withdrawals, and public health advisories from 1995 to the present. The Adverse Event Reporting System (AERS) collects information about adverse events, medication errors, and product problems that occur after the administration of an approved drug product. Neither database contains entries for Syntocinon®.

No other publicly-available information suggests that Syntocinon® was withdrawn for safety or effectiveness reasons. Neither "Syntocinon" nor "oxytocin" has ever been mentioned in an SEC filing by Sandoz or Novartis. Trade press and newspaper searches on Lexis-Nexis revealed no additional information suggesting the product was withdrawn for safety or effectiveness reasons. A PubMed search turned up one article in the *Journal of Reproductive Medicine* about an isolated case of "severe water intoxication, hyponatremic encephalopathy, and convulsions" associated with "excessive self-administration of an oxytocin nasal spray." Attachment F. The abstracts of the remaining three articles do not suggest issues relating to the product's safety or effectiveness for its approved indication.

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Attachment F. There are no published state or federal court decisions relating to product liability arising out of the use of Syntocinon®. I conducted searches on the Internet using common search engines (Google and Yahoo). The reference site <www.drugs.com> contains an entry on Syntocinon® nasal spray that dates to 1994. It lists as "rare" side effects of the nasal spray the following: "nasal irritation; runny nose; tearing of the eyes." The NIH website lists as additional "rare" side effects "convulsions (seizures); mental disturbances; [and] unexpected bleeding or contractions of the uterus." A University of Michigan website suggests that the product is still available from compounding pharmacies. Attachment G. I found no information on the Internet suggesting the product was withdrawn for safety or effectiveness reasons.

I conclude, on the basis of the research outlined above, that discontinuation of Syntocinon® was undertaken voluntarily and for reasons of business and market strategy. I request that, if the Commissioner confirms my conclusion, the agency annotate the listing for Syntocinon® in the Orange Book to indicate that it was not withdrawn for reasons of safety or effectiveness. If instead the Commissioner determines that Syntocinon® was withdrawn from sale for safety or effectiveness reasons, I request that the agency publish a notice of this determination in the *Federal Register*.

The petitioner respectfully requests that the Commissioner take the requested action as soon as possible.

### *C. Environmental Impact Statement*

A claim for categorical exclusion from the requirement of submission of an environmental assessment is made pursuant to 21 C.F.R. § 23.31.

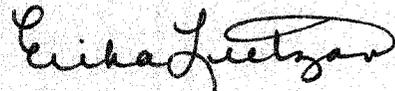
### *D. Economic Impact*

Information on the economic impact of this request will be provided on request.

*E. Certification*

The undersigned certifies that, to the best of her knowledge and belief, 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.

Respectfully Submitted,



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Attachments