



HIKMA FARMACÊUTICA (PORTUGAL), S.A.

February 5, 2007

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

**Citizen Petition**

**Re: Determination that Brethine® (Terbutaline Sulfate Injection, USP) Reference Listed Drug has been voluntarily withdrawn from sale in the United States.**

Dear Sir or Madam:

The undersigned submits this petition pursuant to 505(7) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.25, 10.30 and 314.161 requesting that the commissioner of the Food and Drug Administration (FDA) make a prompt determination that the discontinuation of the Reference Listed Drug (RLD), Brethine®, was not for safety or effectiveness reasons. With this determination, the undersigned asks that FDA declare that it is appropriate to submit an Abbreviated New Drug Application (ANDA) for Terbutaline Sulfate Injection, USP that relies on an RLD that is no longer marketed.

**A. Actions Requested**

The RLD upon which this petition is based is Brethine® (Terbutaline Sulfate Injection, USP) marketed by aaiPharma. AaiPharma is the NDA holder of this product, NDA 18-571, which was approved by FDA prior to January 1, 1982. A copy of the internet Orange Book listing for Brethine® is provided in Attachment 1. This information confirms Brethine® as discontinued.

The Petitioner requests that FDA make a determination that the withdrawal of the above referenced RLD was for reasons other than safety or efficacy and thus permit the filing of ANDAs referencing Brethine®.

The RLD had one marketed package presentation:

<u>NDC #</u>	<u>Concentration</u>	<u>Fill volume</u>
66591-435-11	1mg/mL	1mL in 2mL amber vial

**B. Statement of Grounds**

In the Petitioner's opinion and to the best of the Petitioner's knowledge, the withdrawal of the RLD was voluntary, was solely for marketing reasons and was not for safety or effectiveness reasons. The Petitioner notes that there may be business grounds to support the

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discontinuance of the drug product. AaiPharma filed for bankruptcy in May 2005 and sold substantially all assets of the pharmaceutical division to Xanodyne Pharmaceuticals, Inc. See Attachment 2 for the press release.

AaiPharma received FDA approval of a glass vial form of the injectable Brethine® product, as opposed to the glass ampoule presentation, on April 19, 2004. The vial presentation improved the safety and convenience of administering this drug and replaced the ampoule presentation. An FDA Patient Safety News Report is included in attachment 3. It was launched into the U.S. market on November 1, 2004.

The glass vial presentation was reformulated to contain contain 0.055% disodium edetate (see Physicians insert) whereas the ampoule formulation did not contain disodium edetate. The formulation rationale for this ingredient would be based on the fact that terbutaline sulfate is very susceptible to oxidative reactions catalyzed by metal ions. The presence of metal ions, even in trace quantities, accelerates the degradation of terbutaline sulfate.

Brethine® injectable, in the original ampoule presentation, was formulated without the addition of disodium edetate. The generic products were modelled after this formulation since all were approved in early 2004. The new vial formulation of Brethine® was launched in November 2004. This formulation included 0.055% disodium edetate. Since the Brethine® has been discontinued, the earliest approved generic was chosen as the replacement RLD. However, this replacement RLD represents the older ampoule formulation of Brethine® and not the reformulated vial presentation. See electronic orange book information for the generics included in Attachment 4. The Brethine® Physician Insert is provided in Attachment 5.

### C. Environmental Impact

A categorical exclusion is claimed as the granting of the Petition will result in an ANDA for a drug product that is consistent with the parameters for exclusion under 21CFR 25.31 (a).

### D. Economic Impact

Information under this section will be submitted if requested by the Commissioner following review of this petition.



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#### E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views upon which the Petition relies and that it includes representative information known to the Petitioner which are unfavorable to the Petition

- Attachment 1: Copy of the internet Orange Book listing for Brethine®
- Attachment 2: Press release citing the bankruptcy of aaiPharma and sale of Pharmaceutical Division
- Attachment 3: FDA Patient Safety News
- Attachment 4: Copy of internet Orange Book for generic presentations.
- Attachment 5: Brethine® Physician Insert (2004)

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