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Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
Rm. 1-23  
12420 Parklawn Dr.  
Rockville, MD 20857

**RE: DOCKET NUMBER 02P-0469/CP 1 CITIZEN PETITION FILED ON BEHALF OF ALLERGAN, INC.**

The undersigned hereby submits this response to the citizen petition filed with the Food and Drug Administration (FDA) on behalf of Allergan Inc. (Allergan), dated October 25, 2002 and assigned the Docket Number 02P-0469/CP1. This response to Allergan's petition is submitted under 21 CFR 10.25(a) and 10.30, and pursuant to 21 CFR 314.161 to respectfully request that the Commissioner of Food and Drugs make a prompt determination as to whether a listed drug that has been voluntarily withdrawn from sale in the United States was withdrawn for reasons other than safety or effectiveness.

**A. ACTION REQUESTED**

The undersigned continues to seek an expeditious determination by the Commissioner of the Food and Drug Administration (FDA) that Allergan's voluntary withdrawal from sale of ALPHAGAN® 0.2% was for reasons other than safety or effectiveness, and that ALPHAGAN® 0.2% may therefore continue to be relied upon as a reference listed drug in abbreviated new drug applications (ANDAs).

02P.0469

~~02P.0490~~

C1

~~CP1~~

## **B. STATEMENT OF GROUNDS**

Allergan recently filed a Citizen Petition with FDA dated October 25, 2002, (Docket Number 02P-0469/CP 1). The threshold basis for Allergan's position is its contention that ALPHAGAN® was withdrawn from the market for safety and efficacy reasons as contemplated by 21 CFR 314.161, and that FDA should refuse approval of any ANDAs for generic brimonidine tartrate ophthalmic solution 0.2% as required under 21 CFR 314.127(a)(11) to ensure patients are not prescribed a "less safe" formulation of the drug.

Allergan's Citizen Petition lacks merit in that the statutes and regulations cited by Allergan do not support a conclusion that ALPHAGAN® was withdrawn from the market due to safety or efficacy reasons nor does it support that FDA should refuse to approve any Abbreviated New Drug Application (ANDA) referencing ALPHAGAN®. The decision by Allergan to remove ALPHAGAN® from the market "to ensure patients are not prescribed a less safe formulation of this drug" was a business/marketing decision made by Allergan. The Citizen Petition (02P-0469/CP 1) filed by Allergan is clearly an attempted flagrant abuse of the system. While Allergan maintains it has withdrawn ALPHAGAN® from the United States market for "safety and efficacy reasons," they continue to market ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% in the European region, Canada and many other countries in the world.

Allergan states in Docket Number 02P-0469/CP 1, "First, Allergan has voluntarily withdrawn ALPHAGAN® BTOS 0.2% in lieu of its FDA approved ALPHAGAN P® BTOS 0.15% because ALPHAGAN® P BTOS 0.15% has a better safety profile with lower incidence of allergy than ALPHAGAN® BTOS 0.2%." This Allergan position was clearly not supported by the Division of Analgesic, Anti-Inflammatory and Ophthalmic Drug Products in its review of NDA 21-262. In the Summary Basis of Approval for NDA 21-262, FDA found "Brimonidine-Purite 0.15% has an IOP lowering ability which is equivalent to ALPHAGAN®" and "Brimonidine-Purite 0.15%, 0.2% and ALPHAGAN® have similar adverse event profiles". Furthermore, FDA found that more patients were discontinued from therapy due to lack of efficacy in the Brimonidine-Purite 0.15% treatment groups compared

with that in the ALPHAGAN® 0.2% treatment group, and such differences were approaching statistical significance at level 0.05 in the two studies (See Appendix 1).

Allergan states in Docket Number 02P-0469/CP 1, “To be clear, Allergan did not withdraw ALPHAGAN® BTOS 0.2% because it is unsafe”, which further demonstrates this was business/marketing decision.

Allergan states in Docket Number 02P-0469/CP 1, “After a year of marketing, in which clinical practice confirmed that ALPHAGAN ® P was safer and resulted in improved patient compliance and Allergan determined that it could supply sufficient quantities of ALPHAGAN P® to cover ALPHAGAN® prescriptions, ALPHAGAN® was withdrawn from the market. Currently, there is no BTOS 0.2% product being supplied to the market; rather, the safer BTOS 0.15% is readily available and is being prescribed to glaucoma patients.” Alcon is not aware of any additional adequate head-to-head studies comparing ALPHAGAN® to ALPHAGAN® P that would support the claim of “safer” or “improves patient compliance.” Additionally, on October 24, 2002 during Allergan’s 3<sup>rd</sup> Quarter 2002 public conference call, the President of Allergan, David E. I. Pyott, made the statement “ALPHAGAN® is 93% out of distribution; total elimination from the market is projected within 2 - 3 weeks,” indicating that Allergan did not recall the ALPHAGAN® product at any time after concluding that ALPHAGAN® should be withdrawn for safety and effectiveness reasons. Furthermore, Allergan continues to manufacture and distribute ALPHAGAN® 0.2% in at least the following countries: Germany, France, Spain, United Kingdom, Canada, Italy, Brazil, Mexico, Greece, Australia, Puerto Rico, Turkey, Korea, Switzerland, Portugal, Austria, Egypt, Argentina, Belgium, Colombia, Philippines, Dominican Republic, Chile, Czech Republic, South Africa, Venezuela, China, Peru, Ecuador, Hong Kong, Thailand, Uruguay, Poland, Hungary, and Taiwan.

Allergan states in Docket Number 02P-0469/CP 1, “FDA should refuse approval of ANDAs for BTOS 0.2% because FDA no longer has a means of ensuring the safety of this formulation in the pediatric population.” Interestingly, Allergan markets ALPHAGAN® outside the United States with the associated Physician/Patient Information stating “The safety and effectiveness of ALPHAGAN® in children has not been established.” Additionally, we are

not aware of any efforts by Allergan to revise its labeling in the countries where Alphagan is marketed to incorporate the labeling statements that it expresses so much concern about in its petition. Apparently, Allergan has different criteria for what ensures pediatric safety in the labeling for different regions/countries of the world.

Allergan states in Docket Number 02P-0469/CP 1, “Without a complete label for reference, a generic BTOS 0.2% formulation is demonstrably unsafe for use in children regardless of BPCA’s labeling alternative. For example, even if the FDA allowed generic BTOS 0.2% manufacturers to add a warning of potential coma in children under the age of two to their label (per Section 11 of the BPCA), without the ALPHAGAN® label’s detailed discussion of the significant occurrence of somnolence in older children, healthcare professionals run the risk of underestimating the drug’s possibility of causing severe central nervous system effects in a young child.” These statements from Allergan are yet a further demonstration of ‘gamesmanship’ on the part of Allergan in a desperate attempt to prevent or impede legitimate generic competition in the marketplace.

There has been clear precedent set by FDA regarding Section 11 of the BPCA. The Associate Commissioner for Regulatory Affairs, Dennis E. Baker ruled that “Section 11 of the BPCA permits approval of abbreviated new drug applications (ANDAs) for drugs when pediatric labeling for the innovator drug is protected by patent or exclusivity. Section 11 also describes labeling FDA may require for the generic drug. Under this provision, FDA will determine what labeling is appropriate for generic drugs when the innovator’s pediatric labeling has market protection. FDA will also specifically identify any pediatric contraindication, warning, or precautions that may be necessary” Also stated in this ruling, FDA has long stated that “NDA holders have no valid interest in precluding [risk] information for the labeling of other products (See Appendix 2).

The Summary of Product Characteristics (Package Insert) approved in the United Kingdom and Ireland simply states “The safety and effectiveness of ALPHAGAN® in children have not been established” (See Appendix 3). The Package Insert for ALPHAGAN® approved in Canada states “The use of ALPHAGAN® in paediatric patients is currently not recommended. Several serious adverse reactions have been reported in association with the

administration of ALPHAGAN® (brimonidine tartrate) Ophthalmic Solution 0.2% to infants in the age range of 28 days to 3 months. (see Adverse Reactions sections) Serious Reports of Adverse Reactions in Paediatric Patients: Several serious Adverse Reactions have been reported in association with the administration of ALPHAGAN® (brimonidine tartrate) Ophthalmic Solution 0.2% to infants in the age range of 28 days to 3 months. These reactions included: bradychardia, hypotension, hypothermia, hyptonia, apnea, dyspnoea, hypoventilation, cyanosis and lethargy resulting in hospitalization. Upon discontinuation of ALPHAGAN® the infants recovered without sequelae” (See Appendix 4).

All available evidence continues to indicate that the voluntary withdrawal from sale of ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% was strictly an economic/strategic decision by Allergan, totally unrelated to safety or efficacy, and that the product may still be referenced as a listed drug in ANDAs. Allergan states in its own citizen petition “To be clear, Allergan did not withdraw ALPHAGAN® BTOS 0.2% because it is unsafe.” FDA should make the determination that the voluntary withdrawal was not for safety and effectiveness reasons, and we request that ALPHAGAN® be listed in the discontinued section of the Orange Book and allow for reference to ALPHAGAN® as a listed drug.

Petitioner further requests that the Commissioner make this determination expeditiously, either on the agency’s own initiative or in response to our original petition (DOCKET NUMBER 02P-0404/CP 1, that was filed on August 27, 2002), pursuant to 21 CFR 314.161(a). Petitioner has a pending ANDA that was submitted prior to the voluntary withdrawal from sale of the listed drug ALPHAGAN®. For the reasons stated, Allergan’s citizen petition is fatally flawed procedurally, is without merit substantively, and is clearly an abuse of process to delay generic competition in contravention of the clear intent of Congress. The public interest and fundamental fairness support expeditious action in this case.

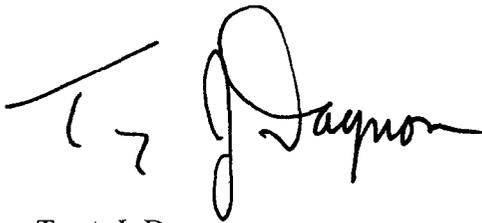
The petitioner respectfully continues to request that the Commissioner take the requested action as soon as possible.

**C. ENVIRONMENTAL IMPACT STATEMENT**

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

**D. CERTIFICATION**

The undersigned certifies that, to the best of his 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.

A handwritten signature in black ink, appearing to read "T. J. Dagnon". The signature is written in a cursive style with a large initial "T" and "J".

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