HFA-305

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 21 2003

Terry G. Mahn, Esq.
Fish & Richardson PC
1425 K Street, NW
11th Floor
Washington, DC 20005

Re: Docket No. 02P-0469/CP1

Dear Mr. Mahn:

This letter responds to your citizen petition dated October 25, 2002, submitted on behalf of Allergan, Inc. (Allergan).[1] Your petition requests that the Food and Drug Administration (FDA) refuse to approve or suspend approval of any abbreviated new drug applications (ANDAs) that refer to Alphagan 0.2% (brimonidine tartrate ophthalmic solution) as the reference listed drug (RLD). Specifically, you believe that FDA should refuse to approve such ANDAs because (1) Alphagan 0.2% was withdrawn from marketing for safety and effectiveness reasons and (2) exclusivity attaching to Alphagan 0.2%'s pediatric labeling precludes FDA from ensuring that generic versions are used safely in the pediatric population. We note that prior to receiving your petition, we received petitions from IVAX Pharmaceuticals, Inc. (IVAX) and Alcon requesting that FDA determine that Alphagan 0.2% was not withdrawn from sale for reasons of safety or effectiveness. As discussed in more detail below, the granting of IVAX's and Alcon's petitions (and the denial of your petition) would permit ANDAs to be approved that rely on Alphagan 0.2% as an RLD. We plan to grant IVAX's and Alcon's petitions and publish our responses in the *Federal Register*. For the reasons stated below, your petition is denied.

I. BACKGROUND

A. Brief History of Alphagan 0.2% and Alphagan P 0.15%

On September 6, 1996, FDA approved Allergan's new drug application (NDA) for brimonidine tartrate ophthalmic solution 0.2% (NDA 20-613) for use in lowering the intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Allergan marketed the product under the brand name Alphagan 0.2%. Alphagan 0.2% qualified for 5 years of new chemical entity (NCE) marketing exclusivity, which originally was set to expire on September 6, 2001. In June 1999, FDA issued a written

[1] Alcon, Inc. (Alcon) and Bausch & Lomb, Inc. (Bausch & Lomb) submitted comments in opposition to your petition on November 13, 2002, and December 5, 2002, respectively. You responded to Bausch & Lomb's comments on January 23, 2003. Bausch & Lomb submitted additional comments on February 10, 2003. You responded to those comments on March 18, 2003.

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request to Allergan under section 505A of the Federal Food, Drug, and Cosmetic Act (the Act)(21 U.S.C. 355a) requesting that Allergan conduct pediatric studies for Alphagan 0.2%. Allergan submitted the requested studies on August 14, 2001. Upon completing and submitting the studies in accordance with the written request, Allergan received 6 months of pediatric exclusivity under the program described in 21 U.S.C. 355a. This exclusivity, in effect, extended Alphagan's NCE exclusivity until March 6, 2002, and attached to its existing patents listed in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book). In addition, on December 20, 2001, FDA approved new pediatric labeling for Alphagan 0.2%, incorporating the pediatric use information generated from the studies. As a result, in addition to pediatric exclusivity, these studies qualified Alphagan 0.2% for 3 years of new clinical studies exclusivity (new patient population) under section 505(c)(3)(D)(iv) and 505(j)(5)(D)(iii) of the Act (21 U.S.C. 355(c)(3)(D)(iv) and 355(j)(5)(D)(iii)), to which the 6-months of pediatric exclusivity also attached. This exclusivity is due to expire on June 20, 2005.

On March 16, 2001, Allergan received FDA approval for another brimonidine tartrate ophthalmic solution (NDA 21-262). The new product, marketed under the brand name Alphagan P 0.15%,[2] was approved for the same indication as Alphagan 0.2% (i.e., lowering the IOP in patients with open-angle glaucoma or ocular hypertension).[3] However, Alphagan P 0.15% differs slightly from its predecessor -- the new product contains (1) a lower concentration of brimonidine (i.e., 0.15% compared to 0.2%) and (2) a different preservative (i.e., purite in lieu of benzalkonium chloride). As a new product, the approval of which necessitated clinical studies that were conducted by the sponsor, Alphagan P 0.15% received 3 years of new clinical studies exclusivity, which was originally due to expire March 16, 2004. The pediatric exclusivity gained from the studies of Alphagan 0.2% discussed above attached to this 3-year exclusivity grant, extending its effective expiration date to September 16, 2004. The pediatric exclusivity also attached to several patents listed for Alphagan P 0.15% in the Orange Book.[4] Upon approval, Alphagan P 0.15% included the same pediatric labeling as Alphagan 0.2%, based on the pediatric clinical study done using Alphagan 0.2%.

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[2] At various places in the record (including in the reviews of clinical trials), Alphagan P 0.15 % was referred to as brimonidine tartrate ophthalmic solution 0.15% (or BTOS 0.15%) and Allergan 0.2% was referred to as brimondine tartrate ophthalmic solution 0.2% (or BTOS 0.2%). For ease of reference, these products will be referred to as Alphagan P 0.15% and Alphagan 0.2%, respectively, throughout the remainder of this petition response.

[3] Allergan is also the sponsor of approved NDA 20-490 for Alphagan 0.5%. However, Alphagan 0.5% was approved for a different indication than the 0.2% and 0.15% strengths. Alphagan 0.5% was approved for the prevention of post-operative IOP elevations in patients undergoing argon laser trabeculoplasty.

[4] In addition to certain use patents that were submitted for both Alphagan 0.2% and Alphagan P 0.15% that are currently the subject of litigation with generic applicants, see *Allergan, Inc. v. Alcon Labs, Inc.*, 200 F. Supp. 2d 1219 (C.D. Cal. 2002), *aff'd* 324 F.3d 1322 (Fed. Cir. 2003); *Alcon Labs v. Allergan Inc.*, No. SA CV 02-1192 (C.D. Cal. Mar. 20, 2003), Allergan also submitted patents for Alphagan P 0.15% that, according to Allergan's certification, relate to purite (i.e., the product's preservative). The claimed purite patents have not been the subject of litigation to date. If they are not challenged and defeated, they could protect Alphagan P 0.15% against generic competitors for up to 12 years (i.e., until the year 2015).

FDA has received several ANDAs requesting approval to market generic versions of Alphagan 0.2%. While review of these ANDAs was pending, on August 20, 2002, Allergan informed FDA that it intended to withdraw Alphagan 0.2% from the market. Specifically, Allergan explained that "[i]n light of FDA's approval of Allergan's Alphagan P 0.15% product, continued marketing of Alphagan [0.2%] is no longer warranted and Alphagan P provides an improved safety profile." In later correspondence, dated September 6, 2002, Allergan clarified that it did not intend to withdraw its approved NDA 20-613 for Alphagan 0.2%, nor did it intend to recall any product that was already on the market at the time the decision to discontinue Alphagan 0.2% was made. Rather, it would allow existing supplies of Alphagan 0.2% to be depleted as the market transitioned to the newly approved product, Alphagan P 0.15%. Thus, in your petition, on behalf of Allergan, you stated that Alphagan 0.2% was withdrawn from the market after "Allergan determined that it could supply sufficient quantities of [Alphagan P 0.15%] to cover [Alphagan 0.2%] prescriptions" (*see* Pet. at 4). Following Allergan's letters indicating that it had discontinued marketing, Alphagan 0.2% was moved from the *Prescription Drug Product List* section to the *Discontinued Drug Product List* section of the Orange Book.

B. Implications of Allergan's Discontinuation of Alphagan 0.2%

As you know, Allergan's discontinuation of Alphagan 0.2% has implications for manufacturers who are interested in marketing generic versions of the product. For a generic product to be approved, it must reference and, with certain exceptions, be the "same" as a drug that was previously approved under a new drug application (21 U.S.C. 355(j)). The previously approved drug is often called the generic product's *reference listed drug* (and it is identified as such in the Orange Book) or RLD.

When a drug is voluntarily discontinued from marketing, it is moved to the Discontinued Drug Product List section of the Orange Book. A drug on the Discontinued Drug Product List can serve as an RLD only if certain preconditions are met. Before an ANDA can be approved that references a drug on the Discontinued Drug Product List, the Agency must determine whether the proposed RLD was withdrawn from marketing for safety or effectiveness reasons ((21 U.S.C. 355(j)(6);(21 CFR 314.161)). A drug listed on the Discontinued Drug Product List may not serve as an RLD if FDA determines that the product was withdrawn from sale for reasons of safety or effectiveness. *Id.* Thus, if FDA determines that Alphagan 0.2% was withdrawn from sale for safety or effectiveness reasons, Alphagan 0.2% would be removed from the Orange Book, and ANDAs that reference Alphagan 0.2% could not be approved.

In enacting regulations to implement the requirement that FDA determine if a product was withdrawn for safety or effectiveness reasons, FDA recognized that it would not always be in a position to know the reasons that a product was withdrawn. The preamble to the final rule notes that an NDA holder's stated reasons for withdrawal would not be determinative because they could be biased (*see* 57 FR 17950 at 17971; April 28, 1992). As stated in the preamble to the proposed rule, because Congress did not give the Agency

"subpoena power to call as witnesses the persons who made the decision to withdraw a product from sale," Congress must have "expected the Agency to rely upon circumstantial and logical inference" to determine the reasons for the withdrawal (*see* 54 FR 28872 at 28907; July 10, 1989). The preamble to the proposed rule further notes that the Agency's inquiry will "focus on whether there were sufficient concerns about safety and effectiveness to make a withdrawal from sale likely and reasonable." *Id.*

The preamble to the proposed regulation further suggested that if a drug manufacturer withdraws a drug from the market and that drug accounted for significant sales before its withdrawal, and there is no evidence to the contrary, there will be a rebuttable presumption that withdrawal was for safety or effectiveness reasons. However, it noted that the Agency will consider factors other than sales of the drug, including increases in the number of adverse drug reactions as well as published and unpublished studies of the drug questioning its safety or effectiveness, in determining the reasons for withdrawal. *Id.*

II. ANALYSIS

Your petition suggests two reasons for FDA to deny approval of ANDAs submitted for brimonidine tartrate ophthalmic solution 0.2%: (1) Alphagan 0.2%, the RLD, was withdrawn from sale for safety and effectiveness reasons, and (2) the RLD has 3 years of exclusivity for pediatric labeling and ANDAs cannot be approved safely without the labeling for which the RLD has protection.

We address each of these objections to ANDA approval in turn.

A. Alphagan 0.2% Was Not Withdrawn From the Market for Safety or Effectiveness Reasons

In your petition, you state that Allergan withdrew Alphagan 0.2% from the market because Alphagan P 0.15% has a better safety profile. Specifically, you claim that the clinical studies conducted for Alphagan P 0.15% demonstrate that it is associated with a numerically lower incidence of allergy-related adverse events than Alphagan 0.2%. You further reason that if Alphagan 0.2% has a higher incidence of allergy, it would be expected to be associated with a higher rate of treatment discontinuation, making it less effective than Alphagan P 0.15%. Based on this line of reasoning, you conclude that Allergan withdrew Alphagan 0.2% from the market for "safety and efficacy" reasons. In addition, you claim that physicians prefer Alphagan P 0.15%, suggesting that it is safer or more effective than its predecessor. Finally, you contend that Alphagan 0.2%'s profitability prior to withdrawal creates a presumption that the product was withdrawn for reasons of safety and effectiveness.

Based on our review of the petitions, comments, our files, as well as relevant databases and literature, we disagree with your conclusion. Thus, we have determined that Alphagan 0.2% was not withdrawn for safety or effectiveness reasons. Both Alphagan

0.2% and Alphagan P 0.15% were approved for their labeled indications because they were both determined, based on adequate and well-controlled clinical trials, to be safe and effective for those indications. Alphagan P 0.15% was approved, in fact, because it was determined to be *comparably* safe and effective to Alphagan 0.2%. We have examined the numerical differences in the clinical trial results between patients taking Alphagan 0.2% and Alphagan P 0.15% that you discuss in your petition and comments (*see* Pet. at 1-5; January 23, 2003, comments at 2-3 and 6-9; March 18, 2003, comments at 3-4.) Moreover, we have concluded that the numerical differences are not clinically significant.[5] In looking at the overall safety profile of a particular product, we examine both the risks and benefits of the product. In this case, any numerical decrease in allergy-related adverse events associated with the use of Alphagan P 0.15% is offset by a numerical decrease in IOP lowering associated with that product. In neither case (adverse events or IOP lowering) is the difference clinically significant, and the risk-to-benefit ratio of Alphagan P 0.15% is essentially the same as that of Alphagan 0.2%.

Moreover, nothing in the postmarketing history of Alphagan 0.2% indicates that it was withdrawn for reasons of safety or effectiveness. We have not found serious unexpected adverse events reported in the literature or in the adverse event databases. In addition, none of the adverse events reported for Alphagan 0.2% would not also be expected to be associated with use of Alphagan P 0.15%. Finally, your assertions regarding physician preference and Alphagan 0.2%'s profitability do not support your conclusion that the product was withdrawn for reasons of safety or effectiveness.

1. Numerical Differences in Clinical Study Results Are Not Clinically Significant

Both Alphagan 0.2% and Alphagan P 0.15% were approved for their labeled indications because each was determined, based on adequate and well-controlled clinical trials, to be safe and effective for those indications. In fact, Alphagan P 0.15%'s approval was based in part on FDA's determination that it was *comparably* safe and effective to Alphagan 0.2% based on two clinical studies. Its risk-benefit ratio is essentially the same as that of Alphagan 0.2%.

The approval of Alphagan 0.15% was supported, in part, by two pivotal studies that compared its safety and effectiveness to that of Alphagan 0.2%. The studies, assigned protocol numbers 190342-007 (study 007) and 190342-008 (study 008), were both multicenter, double-blind, randomized, parallel-group, and active-controlled studies comparing the safety and effectiveness of three brimonidine tartrate solutions.

[5] While your petition and comments mention results from the clinical trials at both 3 and 12 months, our detailed discussion of the results will be of the 3 month data, which was used to support the approval of Alphagan P 0.15%. It was on the basis of the 3 month data that we determined that Alphagan P 0.15% was comparably safe and effective to Alphagan 0.2%. We note, however, that we have also reviewed the 12 month data. Based on that review, we concluded that any differences in the clinical study results were not clinically significant and that the 12 month study data confirmed our determination that the two products are comparably safe and effective.

Specifically, patients were randomized into groups taking either (1) a 0.2% strength solution preserved with benzalkonium chloride (Alphagan 0.2%, referred to in the study analysis as *Alphagan*), (2) a 0.15% strength solution preserved with purite (Alphagan P 0.15%, referred to in the study analysis as *brimonidine-purite 0.15%*), or (3) a 0.2% strength solution preserved with purite which was never commercially marketed (referred to in the study analysis as *brimonidine-purite 0.2%*).

There were 593 patients enrolled in study 007. One hundred ninety-nine were randomized to the Alphagan 0.2% group, 197 were randomized to the Alphagan P 0.15% group, and 197 were randomized to the brimonidine-purite 0.2% group. There were 554 patients enrolled in study 008. One hundred eighty-four patients were randomized to the Alphagan 0.2% group, 184 patients were randomized to the Alphagan P 0.15% group, and 186 patients were randomized to the brimonidine-purite 0.2% group.

In arguing that Alphagan 0.2% was withdrawn for "safety and effectiveness" reasons, your petition cites certain numerical differences in the results of these studies between the Alphagan 0.2% and the Alphagan P 0.15% groups. You believe that the differences support a conclusion that Alphagan P 0.15% has a better safety profile than Alphagan 0.2%. However, FDA has examined the differences and has determined that they are not clinically significant. For example, while it is true that subjects in the clinical trials taking Alphagan P 0.15% experienced a numerically lower incidence of allergic reactions than those taking Alphagan 0.2%, subjects in the Alphagan 0.2% groups experienced a numerically greater increase in lowering of IOP than those in the Alphagan P 0.15% group. Moreover, neither difference is clinically significant. In addition, the differences in rates of discontinuations among patients in both groups are not statistically significant, with patients on Alphagan 0.2% being slightly more likely to discontinue due to adverse events and patients on Alphagan P 0.15% being slightly more likely to discontinue use due to lack of effectiveness. Overall, based on our experience reviewing clinical trial results, we have determined that these differences are consistent with those seen routinely in clinical trials comparing products of similar safety and effectiveness. The clinical trials confirmed that the risk-to-benefit ratio of both products is essentially the same.

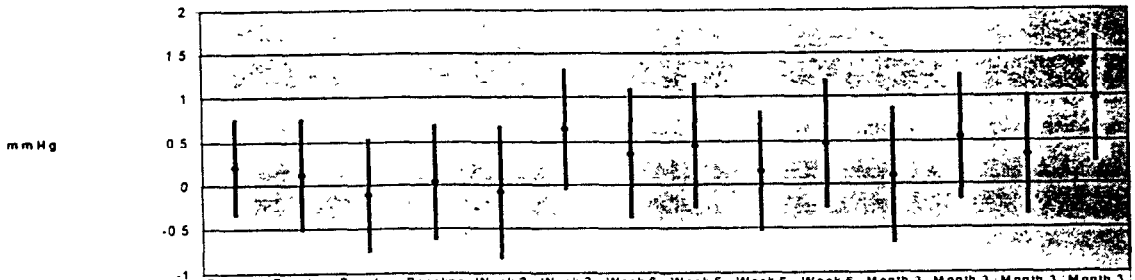
A more-detailed examination of the clinical trial results on which Allergan relies illustrates the basis for our conclusion that Alphagan P 0.15% is comparable to its predecessor and Alphagan 0.2% was not withdrawn for safety or effectiveness reasons.

a. Differences in IOP Lowering and Adverse Events in Studies 007 and 008 Were Not Clinically Significant

With regard to the differences in IOP lowering and adverse events, the clinical study results illustrate the *similarity* of the risk-to-benefit profiles of the two products, as opposed to suggesting that one product is superior to the other. With regard to IOP lowering, while the Alphagan 0.2% group routinely experienced a numerically greater reduction in lowering of IOP than the Alphagan P 0.15% group, this difference is not clinically significant and cannot form the basis of a superiority claim for Alphagan 0.2%.

The graphs below display the difference in IOP reduction between treatment groups in study 007, using the standard 1.5 mmHg 95% confidence interval.

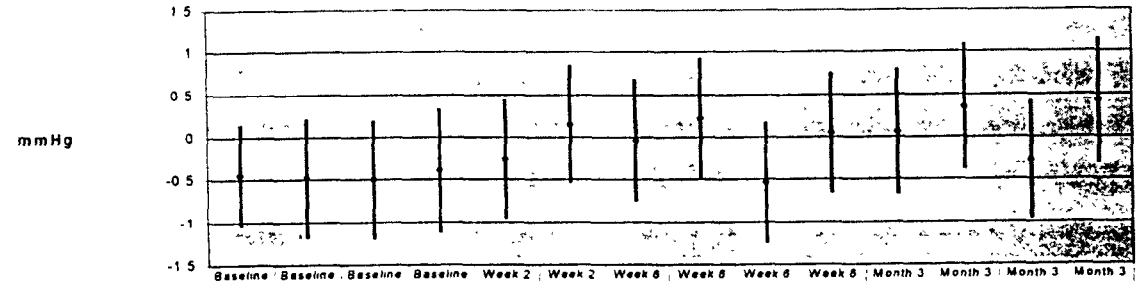
Mean Difference (Brimonidine Purite 0.15% - ALPHAGAN) with 95% Confidence Intervals - Study 007



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-0.33	-0.5	-0.74	-0.61	-0.62	-0.04	-0.37	-0.25	-0.52	-0.25	-0.65	-0.16	-0.34	0.28
Upper CI	0.75	0.75	0.52	0.68	0.66	1.31	1.08	1.14	0.82	1.18	0.86	1.24	1	1.66
Mean Difference	0.21	0.12	-0.11	0.04	-0.08	0.64	0.35	0.45	0.15	0.47	0.1	0.54	0.33	0.96

In study 007, the mean difference with 95% confidence limits in IOP lowering ability between the Alphagan P 0.15% group and the Alphagan 0.2% group is less than 1.5 mmHg for the majority of timepoints. The differences observed are not considered clinically significant.

Mean Difference (Brimonidine Purite 0.15% - ALPHAGAN) with 95% Confidence Intervals - Study 008



	Baseline (hr 0)	Baseline (hr 2)	Baseline (hr 7)	Baseline (hr 9)	Week 2 (hr 0)	Week 2 (hr 2)	Week 6 (hr 0)	Week 6 (hr 2)	Week 6 (hr 7)	Week 6 (hr 9)	Month 3 (hr 0)	Month 3 (hr 2)	Month 3 (hr 7)	Month 3 (hr 9)
Lower CI	-1.03	-1.17	-1.19	-1.11	-0.94	-0.52	-0.74	-0.48	-1.24	-0.64	-0.88	-0.37	-0.95	-0.29
Upper CI	0.13	0.2	0.18	0.32	0.43	0.83	0.67	0.91	0.16	0.74	0.78	1.07	0.41	1.13
Mean Difference	-0.45	-0.48	-0.5	-0.39	-0.25	0.15	-0.04	0.22	-0.54	0.05	0.08	0.35	-0.27	0.42

In study 008, the upper and lower limits of the 95% confidence intervals in lowering of IOP are less than 1.5 mmHg at all timepoints for the comparison between Alphagan P 0.15% and Alphagan 0.2% groups, and are within 1 mmHg for most timepoints. Again, the differences observed are not considered clinically significant.

Similarly, with regard to the differences in numbers of adverse events and serious adverse events, the differences between the groups treated with the two products were not clinically significant and cannot form the basis for a superiority claim for Alphagan P 0.15%. In study 007, adverse events were reported for 49.5% (97/196) of patients treated with Alphagan P 0.15%, 53.8% (106/197) of patients treated with brimonidine-purite 0.2%, and 56.8% (113/199) of patients treated with Alphagan 0.2%. The p value for these numerical differences was 0.344 and did not rise to the level of statistical significance. Overall, the most frequently reported adverse events (reported by > 5% of patients in any one treatment group) in descending order were conjunctival hyperemia, visual disturbance, oral dryness, eye pruritus, burning sensation in the eye, allergic conjunctivitis, infection, and eye dryness.

In study 007, serious adverse events were reported for 2.6% (5/196) of patients receiving Alphagan P 0.15%, 0.5% (1/197) of patients receiving brimonidine-purite 0.2%, and 1.0% (2/199) of patients receiving Alphagan 0.2%. Again, although there are numerical differences in serious adverse events (this time with Alphagan 0.2% having *fewer* serious adverse events than Alphagan P 0.15%), the p value associated with these differences was 0.188, and did not rise to the level of statistical significance.

In study 008, adverse events were reported for 54.9% (101/184) of patients treated with Alphagan P 0.15%, 55.4% (103/186) of patients treated with brimonidine-purite 0.2%, and 65.2% (120/184) of patients treated with Alphagan 0.2%. Once again, while there were numerical differences between treatment groups, the p value associated with these differences was 0.076 and did not rise to the level of statistical significance. The most common adverse events in descending order of overall incidence were conjunctival hyperemia, oral dryness, visual disturbance, burning sensation in the eye, eye pruritus, infection, allergic conjunctivitis, and conjunctival folliculosis. Serious adverse events were reported for 2.7% (5/184) of patients receiving Alphagan P 0.15%, 2.7% (5/186) of patients receiving brimonidine-purite 0.2%, and 3.3% (6/184) of patients receiving Alphagan 0.2%.

Based on the IOP lowering and adverse event results from studies 007 and 008, FDA determined that the differences between the Alphagan P 0.15% and Alphagan 0.2% treatment groups were not clinically significant.

b. Differences in Discontinuation Rates in Studies 007 and 008 Are Not Clinically Significant

Statistics regarding discontinuation rates of subjects in the Alphagan 0.2% and Alphagan P 0.15% groups in the clinical trials again emphasize the similar risk-to-benefit ratios of these two products. For example, there were 24 patients in Study 007 who discontinued from the Alphagan 0.2% group, while 25 patients discontinued from the Alphagan P 0.15% group. Of these subjects, more patients discontinued from the Alphagan 0.2% group than from the Alphagan P 0.15% group due to adverse events, while more patients discontinued from the Alphagan P 0.15% group than the Alphagan 0.2% group due to

lack of efficacy. The majority of the adverse events reported in the trial were allergic reactions that resolved upon discontinuation of the drug product.

There were 20 patients in study 008 who discontinued from the Alphagan 0.2% group, while 24 patients discontinued from the Alphagan P 0.15% group. Of these subjects, more patients discontinued from the Alphagan 0.2% group than from the Alphagan P 0.15% group due to adverse events, while more patients discontinued from the Alphagan P 0.15% group than the Alphagan 0.2% group due to lack of efficacy. The majority of the adverse events were allergic reactions that resolved upon discontinuation of the drug product. Although the reasons for discontinuation may be different, it is notable that approximately the same number of patients discontinued using each drug product in the submitted studies.

c. Conclusion: The Clinical Study Results Confirm Alphagan P 0.15% and Alphagan 0.2% Are Comparably Safe and Effective

Your assertion that Alphagan 0.2% was withdrawn for "safety and effectiveness" reasons because Alphagan P 0.15% is safer or more effective than its predecessor is not supported by the clinical studies that were submitted to support Alphagan P 0.15%'s approval. In fact, Alphagan P 0.15%'s approval was based on references to the safety and effectiveness of Alphagan 0.2% and FDA's determination that the two products had similar benefit-to-risk ratios as demonstrated in the head-to-head comparison studies. The numerical differences in the incidence of allergic reactions, mmHg of IOP lowering, and discontinuation seen in those studies are not clinically significant. They are consistent with the numerical differences that we expect to see and routinely do see in the vast majority of clinical trials and are not sufficient to support a superiority or inferiority claim. Therefore, we do not agree that the numerical differences suggest that Alphagan P 0.15% has a better safety profile or a significantly lower rate of discontinuation than Alphagan 0.2%. Based on the clinical studies performed for the two products, we find that Alphagan 0.2% and Alphagan P 0.15% are comparably safe and effective for their labeled indications. Furthermore, we note that since being approved, Alphagan P 0.15% has been treated as comparable to Alphagan 0.2%. For example, pediatric labeling was changed for both products based on a study done only with Alphagan 0.2%. In summary, all of the facts before us suggest that Alphagan P 0.15% is not safer and is not more effective than Alphagan 0.2%.

2. Nothing in Alphagan 0.2%'s Postmarketing History Undermines the Conclusion That Alphagan 0.2% and Alphagan P 0.15% Are Comparably Safe and Effective or Suggests That Alphagan 0.2% Was Withdrawn for Safety or Effectiveness Reasons

In evaluating your suggestion that Alphagan 0.2% was withdrawn for safety and effectiveness reasons, we have not limited our analysis to the clinical study results. We have also examined our files to determine if any information in Alphagan 0.2%'s marketing history would (1) undermine our conclusion that Alphagan 0.2% and Alphagan

P 0.15% are comparably safe and effective or (2) suggest that Alphagan 0.2% was withdrawn for safety or effectiveness reasons. In reviewing our files for Alphagan 0.2%, we have placed particular emphasis on the summary of adverse events contained in periodic adverse event reports and annual reports for the drug. We have also reviewed our files for oral and written communications regarding the withdrawal from sale of this drug product. Finally, we have reviewed the Center for Drug Evaluation and Research's Datamart database of reported adverse experiences and have performed a literature search using the National Library of Medicine's Pub Med to determine if any unanticipated safety signals regarding use of Alphagan 0.2% could be detected. In our review, we found no information that would suggest that the benefit-risk analysis on which Alphagan 0.2%'s approval was based had changed or that it was not comparably safe and effective to Alphagan P 0.15%.

3. Arguments Regarding Physician Preference and Alphagan 0.2%'s Profitability Do Not Support the Conclusion That Alphagan 0.2% Was Withdrawn for Safety or Effectiveness Reasons

The majority of information supporting our above analysis was derived from the NDA files of Alphagan 0.2% and Alphagan P 0.15%. However, we note that in your comments you suggest that "the commercial success of Alphagan P 0.15% as a replacement for Alphagan [0.2%] based on physician acceptance" is "more relevant" than the NDA materials for assessing the comparative effectiveness of the two products (*see* March 18, 2003, comments at 4). We find this reasoning unpersuasive. The fact that physicians have begun prescribing Alphagan P 0.15% now that Alphagan 0.2% has been withdrawn from the market does not support a conclusion that Alphagan P 0.15% is more effective than its predecessor. It probably reflects only the lack of available alternatives. You acknowledge that when physicians did have a choice, Alphagan 0.2% was overwhelmingly preferred to Alphagan P 0.15%. Specifically, you state in your January 23, 2003, comments that as of August 2002 when Allergan withdrew Alphagan 0.2%, its sales were four times higher than those for Alphagan P 0.15% (*see id.* at 3). Accordingly, physician preference does not support your contention that Alphagan 0.2% was withdrawn for safety and effectiveness reasons.

In contrast to your physician preference argument, in your January 23, 2003, comments, you highlight how profitable Alphagan 0.2% was before its withdrawal and suggest that its profitability entitles Allergan to the presumption that it withdrew Alphagan 0.2% for safety or effectiveness reasons. However, the presumption that safety and effectiveness concerns motivated the market withdrawal of a profitable drug is rebuttable and is easily rebutted here. That presumption is based on the assumption that a manufacturer would not cause itself significant economic harm by withdrawing a profitable drug unless it had significant safety and effectiveness concerns. When Allergan withdrew Alphagan 0.2%, it did not cause itself significant economic harm because it waited until it was able to supply adequate amounts of Alphagan P 0.15% to cover Alphagan 0.2%'s prescriptions before implementing the withdrawal. If anything, Allergan's decision economically benefited the company by removing from the market a drug that was subject to imminent

generic competition (Alphagan 0.2%) and shifting the vast majority of prescriptions to the remaining drug (Alphagan P 0.15%), which was not facing imminent generic competition. Allergan is no doubt aware that even if an ANDA referring to Alphagan 0.2% is approved, it cannot be rated therapeutically equivalent (and therefore substitutable) to Alphagan P 0.15%, the product remaining on the market. Thus, even if Allergan's petition is denied, it has gained economic advantage through the withdrawal of Alphagan 0.2%. In sum, neither your arguments about physician preference nor those about the profitability of the drug prior to withdrawal support your position that Alphagan 0.2% was withdrawn because it was less safe or effective than Alphagan P 0.15%.[6]

4. Conclusion: Alphagan 0.2% Was Not Withdrawn for Safety or Effectiveness Reasons

In summary, we find unpersuasive your arguments that (1) the differences in clinical study results suggest that Alphagan P 0.15% is safer or more effective than Alphagan 0.2%, (2) physicians' willingness to prescribe Alphagan P 0.15% suggests it is more safe and effective than Alphagan 0.2%, and (3) Alphagan 0.2%'s profitability prior to withdrawal creates a presumption that it was withdrawn for safety and effectiveness reasons. Given the potential economic benefit to Allergan associated with the withdrawal of Alphagan 0.2%, and the lack of evidence of an inferior safety or effectiveness profile of Alphagan 0.2% (as compared to Alphagan P 0.15%) in the NDA files (including postmarket annual reports), adverse event databases, and published and unpublished literature, we conclude that Alphagan 0.2% was not withdrawn for safety or effectiveness reasons.[7]

Given this conclusion, Alphagan 0.2% will continue to be listed in the Discontinued Drug Product List section of the Orange Book and will be eligible to serve as an RLD for ANDAs.

B. Alphagan 0.2%'s Pediatric Labeling Exclusivity Does Not Prevent FDA From Ensuring That Generics Are Labeled for Safe Use in the Pediatric Population

In your petition, you express concern about the marketing of generic versions of Alphagan 0.2% without adequate pediatric labeling. You suggest that generics may only

[6] We also note that Allergan continues to market Alphagan 0.2%, as opposed to Alphagan P 0.15%, outside of the United States (e.g., in Canada). Although this fact alone is not determinative, it further undermines Allergan's position that Alphagan 0.2% was withdrawn because it is less safe or effective than Alphagan P 0.15%.

[7] Bausch & Lomb's comments and your responses discuss at length the appropriate legal interpretation of the "withdrawal from sale for safety or effectiveness reasons" standard. Specifically, the submissions offered different positions on whether the standard would be satisfied if, in fact, FDA concluded that Alphagan P 0.15% is more safe or efficacious than Alphagan 0.2%. However, we do not need to reach the issue of legal interpretation because we conclude that Alphagan P 0.15% and Alphagan 0.2% are comparably safe and effective.

be safely marketed if their labeling warns health care professionals about the risk of adverse events, including somnolence, in children treated with brimonidine tartrate ophthalmic solution 0.2%. Specifically, before its market withdrawal, Alphagan 0.2%'s labeling included the following pediatric warnings and precautions in the *Pediatric Use* subsection of the *Precautions* section of the labeling and in the *Adverse Events* section of the labeling:

> ***Pediatric Use***: In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50%-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence. The safety and effectiveness of ALPHAGAN® have not been studied in pediatric patients below the age of 2 years. ALPHAGAN® ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (Also refer to Adverse Reactions section).
>
> ***Adverse Reactions***: ...Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving ALPHAGAN®.

You contend that generic versions of Alphagan 0.2% cannot be safely marketed without including this important safety information in their labeling. We agree; the inclusion of this information in the labeling of generics is necessary to ensure their safe use in the pediatric population. However, we disagree with your conclusion that Allergan's exclusivity prevents FDA from approving any ANDAs until the exclusivity for this labeling expires on August 20, 2005.

To the contrary, section 11 of the Best Pharmaceuticals for Children Act (BPCA) specifically instructs FDA how to balance the competing goals of protecting intellectual property rights and speeding generic approvals when essential pediatric safety information is covered by exclusivity. Section 11 of the BPCA includes provisions designed to ensure that protection for pediatric labeling for an RLD will not block generics from entering the market. This section, codified at 21 U.S.C. 355a(o), is entitled *Prompt Approval of Drugs Under Section 505(j) When Pediatric Information Is Added To Labeling*, and specifically grants FDA the authority to require generics to include essential pediatric safety information that is included in the RLD's labeling, regardless of exclusivity. Section 11 provides, "a drug for which an application has been submitted or approved under 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling related to pediatric use when the omitted indication or other aspect of labeling is protected by patent or exclusivity" (21 U.S.C. 355a(o)).

Section 11 of the BPCA further provides that where appropriate, pediatric labeling protected by patent or exclusivity can be carved out and replaced with a disclaimer (21 U.S.C. 355a(o)(2)(a)). Section 11 states that in cases where, as here, FDA finds that pediatric labeling is essential to the safe use of the product, and cannot be carved out without jeopardizing the safety of the product, FDA may require that the labeling of a generic version of a drug "include a statement of any appropriate pediatric contraindications, warnings, or precautions that [the Agency] considers necessary" (21 U.S.C. 355a (o)(2)(B)). Under this authority, FDA plans to approve ANDAs for brimonidine tartrate ophthalmic solution 0.2%, incorporating the language from the *Pediatric Use* subsection of the *Precautions* section, and the *Adverse Events* sections of the Alphagan 0.2% label excerpted above.

In your petition and comments, you explain why you believe we cannot rely on the authority granted in section 11 of the BPCA. First, you state that section 11 does not apply because it "logically requires the listed drug to exist on the market. In the case of [brimonidine tartrate ophthalmic solution] 0.2%, the reference listed drug has been withdrawn from the market and is no longer listed in the Orange Book" (*see* Pet. at 6). This argument presumes that we believe the pediatric labeling can be carved out and suggests that where the RLD is not being marketed, no appropriate disclaimer can be crafted. We do not resolve whether and how we could craft an appropriate disclaimer where the RLD has been withdrawn from the market because no disclaimer is required here. As will be discussed in more detail below, we have concluded that all of the pediatric labeling for Alphagan 0.2% is covered by the exception created under 21 U.S.C. 355a(o)(B), which allows FDA to require an ANDA to include a "statement of any appropriate pediatric contraindications, warnings, or precautions" that the Agency considers necessary.

Second, in your comments, you suggest that section 11 of the BPCA only authorizes FDA to allow generics to bear information contained in a section of labeling with the word *Warnings*, *Contraindications*, or *Precautions* as the heading. Because the relevant information for Alphagan 0.2% is in the *Pediatric Use* and *Adverse Events* sections of the label, you suggest that this language is outside of the scope of section 11's reach. The language of the BPCA, however, does not support the interpretation you propose. The BPCA authorizes FDA to allow generics to bear, as necessary, "*any appropriate* pediatric contraindications, warnings or precautions" (21 U.S.C. 355a(o)(2)(B)) (emphasis added). Nothing in the language limits that authority to certain sections of labeling. Moreover, even if FDA were so limited in its interpretation of section 11, the *Pediatric Use* section is a subsection of the *Precautions* section of the labeling, and therefore falls squarely under the terms enumerated in section 11. It would be illogical to permit ANDA applicants to include important safety information in the *Pediatric Use* section of the labeling and to require them to carve out the same information when it appears in other sections such as *Adverse Reactions*. Thus, FDA's decision to require ANDA applicants to include this pediatric safety information in their labels is squarely within the BPCA's grant of authority.

Third, you suggest in your petition that generic products copying Alphagan 0.2%'s labeling could become unsafe since Alphagan 0.2% has been withdrawn and its labeling would not be updated if new pediatric side effects were discovered. We find this reasoning unpersuasive. The fact that generic versions of Alphagan 0.2% will copy the labeling of a discontinued product is not unique or even unusual; many generic products have been approved after their RLD has been withdrawn. In cases in which new pediatric or adult adverse events are discovered that necessitate a labeling change after the ANDA is approved, if there is no marketed RLD to initiate such a change, ANDA holders can amend their labeling by submitting a supplement to their ANDAs under section 505(b)(2) of the Act ((*see* 57 FR 17950 at 17961; April 28, 1992) (stating principle that ANDA holders can initiate changes to ANDA and RLD labeling when they discover new safety information)).

Finally, we note that section 11 of the BPCA is premised on the idea that pediatric labeling should not serve as a barrier to ANDA approval. In drafting the BPCA, Congress included the language authorizing FDA to permit ANDAs to bear, as necessary, pediatric safety information as part of a statutory provision entitled *Prompt Approval of Drugs Under Section 505(j) When Pediatric Information Is Added to Labeling* (21 U.S.C. 355a(o)). The section is structured so that all pediatric labeling information that receives 3-year exclusivity can either be carved out or be included in ANDA labeling without regard to exclusivity. Its clear intent is to ensure that changes in pediatric labeling do not block approval of generics that are otherwise eligible for approval. Allergan's interpretation, which would prohibit approval of ANDAs where the RLD has pediatric labeling that has been accorded exclusivity, is at odds not only with the language of the statute but also with Congressional intent.

Therefore, although we agree that generic versions of brimonidine tartrate ophthalmic solution 0.2% cannot be safely marketed without warning health care professionals about the risk of adverse reactions in the pediatric population, we disagree with your conclusion that generics may not be approved until after Allergan's pediatric labeling exclusivity expires. Under the authority provided in section 11 of the BPCA, FDA may approve generics with the same warnings and precautions language as contained in the labeling of Alphagan 0.2%.

III. CONCLUSION

Our approval of Alphagan 0.2% for use in lowering the IOP in patients with open-angle glaucoma or ocular hypertension was based upon a determination that it is safe and effective for that indication. We have not received from Allergan, nor have we found in our own search of NDA files, published and unpublished literature, and adverse event databases, any evidence to undermine that determination.

Moreover, our approval of Alphagan P 0.15% was based on evidence that it is similarly safe and effective when compared to its predecessor. We find any differences in study results between the two products to be typical of the variability seen in clinical trials and

do not find the differences in this case to be clinically significant. Therefore, we disagree with your assertion that Alphagan P 0.15% is safer and/or more effective than Alphagan 0.2% and reject your contention that Alphagan 0.2% was withdrawn for safety or effectiveness reasons. The Agency will continue to list Alphagan 0.2% in the Discontinued Drug Product List section of the Orange Book and ANDAs will be permitted to rely on Alphagan 0.2% as an RLD. Any generics approved in reliance on the finding of safety and effectiveness for Alphagan 0.2% will be required to include the language of the *Pediatric Use* subsection of the *Precautions* section and the language of the *Adverse Events* sections of the Alphagan 0.2% label relating to pediatric use. We believe the inclusion of this labeling is necessary to ensure the safe use of generic versions of Alphagan 0.2% in the pediatric population. For all of the reasons described above, your petition is denied.

Sincerely yours,

FOR Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research