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ACTELION

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***BY HAND DELIVERY***

Cherry Hill, 5 April 2013

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

**CITIZEN PETITION**

Actelion Pharmaceuticals Ltd. ("Actelion" or "the company") respectfully submits this citizen petition under 21 USC 355 and 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs take the actions described below with respect to any abbreviated new drug application ("ANDA") that references the Actelion product, Ventavis® (iloprost) inhalation solution ("Ventavis").

Ventavis is a complex, locally-acting, inhaled drug, approved as a combination product for use with specific nebulizers to treat pulmonary arterial hypertension. Because of the nature of the drug, its mechanism of action and the essential characteristics of the approved delivery devices, Ventavis presents issues that require particular, product-specific consideration with regard to ensuring that any proposed generic meets the standards for review and approval of an ANDA. These issues include the ratio of diastereoisomers that comprise the active ingredient, the formulation of the drug product, and the design, operation, and performance characteristics of the nebulizer.

As discussed herein, unless the active ingredient in a proposed generic iloprost inhalation solution consists of stereoisomers in the same ratio as Ventavis, the product does not contain the same active ingredient and therefore cannot be the subject of an ANDA referencing Ventavis. Additionally, because the drug component of this combination product is a solution that is nebulized and inhaled, unless the proposed product contains the same inactive ingredients in the same amounts as Ventavis, it must demonstrate bioequivalence. Similarly, any proposed generic version of Ventavis must be approved for use with a nebulizer that does not differ materially from those with which Ventavis is approved. Any different nebulizer must be shown to be equivalent by *in vitro* and *in vivo* data; moreover certain differences may require clinical data that preclude submission of an ANDA, and may mandate differences in labeling that prohibit approval via an ANDA.

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To Actelion's knowledge, the Food and Drug Administration ("FDA" or "the agency") has not issued approval standards that address these issues, nor are there any compendial standards for either the active pharmaceutical ingredient or the finished drug product. Accordingly, this petition seeks to have the agency enunciate and apply appropriate standards to ensure that any proposed generic product relying on Ventavis as the reference product is the "same as" Ventavis in all relevant characteristics, can be expected to have the same safety and effectiveness profile as Ventavis, and therefore qualifies for submission and approval by means of an ANDA.[1]

## ACTIONS REQUESTED

For the reasons discussed herein, Actelion respectfully requests that FDA not approve any ANDA referencing Ventavis unless:

(1) The active ingredient of the drug product consists of the same ratio of iloprost diastereoisomers as Ventavis;

(2) If the product does not contain the same inactive ingredients and in the same concentrations as Ventavis, the application contains the data described herein demonstrating equivalent performance by the nebulizer, as well as bioequivalence; and

(3) The product is approved for use with a nebulizer that, based on the analysis and data described herein, does not differ from those with which Ventavis is approved, in terms of performance characteristics or critical design features.

## STATEMENT OF GROUNDS

## I. PRODUCT BACKGROUND

### A. Pulmonary Arterial Hypertension

Ventavis is used to treat pulmonary arterial hypertension ("PAH"), an extremely serious, debilitating, and potentially fatal condition. PAH is a chronic condition that constricts the flow of blood through the pulmonary vasculature. It is characterized by an increase in pulmonary artery pressure, which can result from progressive changes in the arteries, including tightening of arterial walls or blood clots, that make it difficult for the heart to pump blood through the arteries and into the lungs. As a result, pressure in the pulmonary arteries rises, and the heart must work

[1] Actelion is not aware of any ANDA referencing Ventavis having been submitted.

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harder to overcome the increased pressure. Eventually, the heart becomes strained, which increases the risk of heart failure and death. As the disease worsens, its symptoms limit physical activity. Symptoms of PAH include dyspnea or shortness of breath, fatigue, angina or chest pain, heart palpitations, loss of consciousness, and heart failure.

Patients with PAH are stratified according to symptoms based on the New York Heart Association ("NYHA") functional classification system. The studies supporting approval of Ventavis included patients with NYHA Class III or IV symptoms – the most serious symptoms that have mortality implications. Patients with Class III symptoms are limited in their physical activity (*e.g.*, walking up stairs causes discomfort). Untreated Class III patients have a median survival of 2.5 years. Patients with Class IV symptoms are not able to do any physical activity without discomfort, and, if untreated, have a median survival of six months.

## B. Ventavis

### 1. Drug Product

Ventavis is a complex, locally acting, drug-device combination product designed to deliver precise quantities of drug substance to the alveolar region of the lung to exert pharmacological action directly upon the pulmonary vasculature. As PAH is incurable, therapy seeks to relieve the symptoms of PAH and reduce the progression of the disease. Ventavis is administered six to nine times per day during waking hours (*i.e.*, approximately every two hours).

The active ingredient, iloprost,[2] is a prostacyclin analogue that dilates both systemic and pulmonary arteries.[3] It works by reducing pulmonary vascular resistance, thereby increasing cardiac output and improving blood oxygenation, as seen in hemodynamic assessments.[4] Ventavis is delivered locally to the lung, and is primarily locally acting.[5] Although iloprost has both local and systemic effects, there is no clear relationship between serum levels (*i.e.*, pharmacokinetic ("PK") measurements) and pharmacodynamic ("PD") activity or clinical

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[2] The chemical name for iloprost is (E)-(3a*S*, 4*R*, 5*R*, 6a*S*)-hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4 methyl-1-octen-6-ynyl]-$\Delta^{2(1H0)\Delta}$-pentalenevaleric acid. Ventavis Package Insert, §11, Description, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021779s013lbl.pdf.

[3] *Id.* at §12.1, Mechanism of Action.

[4] *See id.* at §14, Clinical Studies.

[5] *See* Ventavis Approval Package, Administrative Documents and Correspondence, Project Manager Overview at 1 ("The rationale for the inhaled route of administration is to provide high local concentrations, while minimizing the systemic side effects."), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-779_Ventavis_admincorres.pdf.

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effect.[6] In reviewing the Ventavis NDA, the agency recognized that a "direct PK/PD correlation for iloprost may not be expected because iloprost drug concentrations decline rapidly shortly after inhalation is complete (<30 minutes post infusion); whereas, the PD effects are sustained for longer periods (>1 hour post infusion)."[7] Ultimately, FDA concluded that "there is no definitive evidence for a relationship of iloprost exposure (e.g. serum levels) to clinical response such as incidence rates of adverse events or efficacy. . . . Systemic iloprost exposure did not appear to be correlated to the timing and extent of local availability in the pulmonary vasculature."[8]

Due to its chiral centers, iloprost is an optically active diastereoisomeric mixture with geometric (Z-E) isomerism.[9] Specifically, iloprost consists of a mixture of the 4R and 4S diastereoisomers at a ratio of approximately 53:47.[10] The two diastereoisomers differ significantly in their potency in dilating blood vessels; the 4S isomer is four to twelve times more potent than the 4R isomer.[11] This pronounced difference is not surprising, given that diastereoisomers are not mirror images.

In fact, FDA generally considers diastereoisomers to be distinct active moieties. As the agency has explained:

> Diastereoisomers and geometric isomers are both chemically distinct and pharmacologically different (unless they are interconverted *in vivo*) and are generally readily separated without chiral techniques. Geometric isomers and diastereoisomers therefore should, with the rare exception of cases where *in vivo* interconversion occurs, be treated as separate drugs and developed accordingly. There is no reason to consider developing mixtures of geometric isomers or

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[6] *See* Ventavis Approval Package, Clinical Pharmacology and Biopharmaceutics Review, Part 2, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-779_Ventavis_biopharmr_P2.pdf.

[7] *Id.* at 55.

[8] *Id.* at 54.

[9] Stereoisomers are molecules that have the same atomic constitution and bonding, but different three-dimensional arrangement of atoms. Stereoisomers include enantiomers (mirror image isomers), geometric (cis/tran isomers), and diastereoisomers. Diastereoisomers are isomers with more than one chiral center that are not mirror images of one another. Iloprost possesses six asymmetrical carbon atoms, of which five are common with those in the natural prostacyclin. The configuration of the molecule is 8S, 9S, 11R, 12S and 15S. The methyl group at C16 causes two isomers to occur: 16R(4R) and 16S(4S). Iloprost also contains two defined configurations of carbon-carbon double bonds, 5E and 13E.

[10] Ventavis Package Insert, §11, Description.

[11] *See* Ventavis Approval Package, Chemistry Review at 9, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-779_Ventavis_chemr.pdf; Ventavis Package Insert, §12.1, Mechanism of Action.

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diastereoisomers unless they fortuitously represent a reasonable fixed dose combination (see 21 CFR 300.50).[12]

Consistent with this policy, FDA initially took the position that the 4R and 4S isomers in iloprost, which do not interconvert, should be isolated, characterized and developed as separate active ingredients.[13] However, on the basis of toxicology and pharmacodynamic data and an understanding that the isomers were not readily separable, the agency ultimately allowed Ventavis to be developed and approved as a diastereoisomeric mixture.[14] This decision was based in part on the degree of control over the 4R:4S ratio provided by the manufacturing process and product specifications.[15] The ratio of 4R and 4S has been maintained essentially unchanged from lot to lot since preclinical and clinical development began, through commercial manufacture to the present.

### 2. I-neb and Prodose Nebulizers

In addition to the stereoisomeric ratio, the functioning of the nebulizers with which Ventavis is approved is essential to ensuring that PAH patients receive precise doses of iloprost. Patients who receive an insufficient dose of iloprost could experience increased pulmonary arterial pressure, reduced activity and quality of life, and ultimately heart failure. Conversely, patients who receive higher doses of iloprost could suffer adverse effects, such as a drop in blood pressure and syncope.[16]

Ventavis is approved for use only with two specific nebulizer systems: the I-neb® Adaptive Aerosol Delivery® ("AAD") System ("I-neb") and the Prodose® AAD System ("Prodose").[17] There are a number of features of these two delivery devices that are essential to the safe and effective use of Ventavis, and on which patients are trained when Ventavis is first prescribed. The AAD platform technology generates aerosol only during inhalation and was

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[12] FDA Guidance on Development of New Stereoisomeric Drugs (May 1, 1992), *available at* http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm (last updated Apr. 27, 2011).

[13] *See* Ventavis Approval Package, Administrative Documents and Correspondence, FDA Minutes of March 9, 2004 Meeting at 2; Minutes of January 29, 2004 Meeting at 2; Minutes of November 20, 2003 Meeting at 2.

[14] *See* Ventavis Approval Package, Chemistry Review at 8-9; *see also* Ventavis Approval Package, Administrative Documents and Correspondence, Minutes of March 9, 2004 Meeting at 2; Minutes of January 29, 2004 Meeting at 2; Minutes of November 20, 2003 Meeting at 2.

[15] *See* Ventavis Approval Package, Administrative Documents and Correspondence, FDA Minutes of March 9, 2004 Meeting at 2.

[16] *See* Ventavis Package Insert, §6.1, Clinical Studies Experience.

[17] The I-neb and Prodose nebulizers reflect years of effort and collaboration between Actelion and Philips Respironics, the manufacturer and distributor of the devices. At present, Actelion has the exclusive right to distribute the nebulizers with iloprost drug product in the United States.

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developed in response to the need for patients to receive precise dosing during inhalation treatments.[18] The system analyzes pressure changes of airflow to the patient to ascertain the correct starting point for aerosol delivery during inhalation. It also monitors patient breathing throughout the treatment and continuously adapts to the patient's breathing pattern. By continuous adaption of aerosol delivery to actual patient breathing pattern, AAD reduces the loss of aerosol during exhalation, which is the greatest source of variability in nebulized drug delivery.[19] The AAD nebulizers also include user-interface technology that provides patients with visual and audible cues, providing feedback on effective use of the device. During treatment, the AAD nebulizers display different codes and symbols on a screen to help patients understand how the treatment is working. When the dose has been delivered, a signal indicates to the patient that the treatment is complete.

The nebulizers with which Ventavis is approved also have unique dosing features. Dosing is controlled with a computerized disc that is inserted into the nebulizer. The dosing discs are color-coordinated with corresponding medication chambers. For the Prodose system, the drug product is supplied in two ampules for use with 2.5 mg and 5.0 mg dosing discs. Two ampules are used for each treatment session. For the I-neb system, only one ampule is used for a treatment session. Patients must consult a doctor if they want to change the dosing disc or medication chamber. Additionally, for accurate dosing and to prevent contamination, the nebulizers must be cleaned regularly. The nebulizers have detailed cleaning instructions that require the patient to disassemble parts of the nebulizer, such as the mouthpiece, medication chamber, and drug guide.

The complexity of the nebulizer systems and the importance of proper use and maintenance to ensure precise dosing are reflected in the Ventavis approved labeling. Prescribers are directed to train patients "in proper administration techniques, including dosing frequency, ampule dispensing, I-neb® AAD® System or the Prodose® AAD® System operation, and equipment cleaning."[20] The Package Insert also includes detailed instructions and illustrations for opening, emptying, and disposing of the ampule.[21] Ventavis also has FDA-

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[18] *See* Dhand, R., "Intelligent Nebulizers in the Age of the Internet: The I-neb Adaptive Aerosol Delivery (AAD) System," *Journal of Aerosol Medicine and Pulmonary Drug Delivery* (2010) 23(1):iii-v, attached at Tab 1.

[19] *Id.* In contrast, conventional nebulizers provide continuous aerosol to a patient during the patient's normal breathing cycle. With such a device, the amount of drug actually inhaled by a patient during a treatment session varies, based on the patient's breathing pattern. Conventional nebulizers are intrinsically inefficient because as much as two-thirds of medication can be wasted during a patient's exhalation portion of his or her breathing cycle. *See* Mitchell, J.P., & Nagel, M.W., "Oral inhalation therapy: meeting the challenge of developing more patient-appropriate devices," *Expert Rev. Med. Devices* (2009) 6(2):147-55, 150, attached at Tab 2. In fact, some jet nebulizers have yielded only 12% of total dose to the lungs. *See* Yeo L.Y., *et al.*, "Ultrasonic nebulization platforms for pulmonary drug delivery," *Expert Opin. Drug Deliv.* (2010) 7(6):663-679, 666, attached at Tab 3.

[20] Ventavis Package Insert, §17, Patient Counseling Information.

[21] *Id.*, §17.1, Preparation Instructions.

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approved patient labeling that instructs patients to use only the I-neb or Prodose system ("You should not use other systems to take Ventavis as other systems may not give you the amount of Ventavis you need.") and highlights the necessity of physician-provided training ("**Do not use Ventavis until your doctor has showed you how to use one of these systems the right way.** Make sure you understand all the instructions or ask question until you do.")[22] The patient labeling also includes six pages of detailed instructions with text and multiple illustrations, including how to open the ampule, dispense the drug into the nebulizer, and dispose of the ampule, as well as instructions regarding operation and cleaning of the nebulizer, which comes with its own instructions for those tasks.[23]

## II. STATUTORY AND REGULATORY STANDARDS

Under section 505(j) of the Food, Drug, and Cosmetic Act ("FDCA"), an ANDA must demonstrate that the proposed generic product is the "same as" the reference listed drug ("RLD").[24] This generally requires the applicant to show, among other things, that the proposed product has the same active ingredient, dosage form, route of administration, strength, conditions of use, and (with certain exceptions) labeling as the RLD, and that the products are bioequivalent.[25] A product that meets this standard is approved without an independent showing of safety and effectiveness, because the demonstration of sameness allows FDA to conclude that the proposed generic is therapeutically equivalent to the RLD, meaning it will have "the same clinical effect and safety profile" as the reference product.[26] Moreover, this conclusion "reflects FDA's judgment that the products generally may be substituted for each other without physician intervention."[27]

### A. Active Ingredient

By regulation, FDA has explained that to be the "same as" a reference product, a proposed generic must be, *inter alia*, "identical in active ingredient(s)."[28] The active ingredient is the component of a drug product "that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the

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[22] *Id.*, Patient Labeling, "Patient Instructions for Using Ventavis" (emphasis in original).

[23] *Id.*

[24] *See* 21 USC 355(j).

[25] *See* 21 USC 355(j)(2)(A); 21 CFR 314.94(a).

[26] *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") at vii.

[27] *Id.* The agency's conclusions in this regard are expressed by means of an "A" rating in the Orange Book, which in turn forms the basis for generic substitution in most states.

[28] 21 CFR 314.92(a)(1).

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structure or any function of the human body."[29] The agency has said an active ingredient is considered to be the same "if it meets the same standards for identity."[30] Although standards for identity usually are described in the United States Pharmacopeia, that is not always the case, and in any event, the agency may establish "additional standards that are material to the ingredient's sameness."[31] In that regard, the agency has specifically recognized that there are circumstances in which FDA-established "standards for . . . stereoisomeric mixture may be required."[32]

### B. Inactive Ingredients

In addition, if a proposed generic product is (as a generic of Ventavis would be) a solution for nebulization, it generally is required to "contain the same inactive ingredients as the reference listed drug."[33] Different inactive ingredients are permitted only if "the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."[34] Additionally, there are circumstances under which FDA has required a proposed generic product to have the same formulation – *i.e.*, the same active ingredient and the same inactive ingredients, all in the same concentration – as the reference product.[35] This has been the case, for example, when there are toxicity concerns implicated by the route of administration or the dosage form presents potential bioequivalence challenges, such as with regard to generic versions of inhaled drugs.[36]

### C. Bioequivalence

Generally, a proposed generic product must demonstrate that it is bioequivalent to the reference product, meaning there is no significant difference between the products as to the rate and extent to which the active ingredient "becomes available at the site of drug action."[37] There

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[29] 21 CFR 314.3(b) (defining "drug substance").

[30] *Abbreviated New Drug Regulations*, Final Rule, 57 Fed. Reg. 17950, 17959 (April 28, 1992).

[31] *Id.*

[32] *Id.*

[33] 21 CFR 314.94(a)(9)(v).

[34] *Id.*

[35] *See* 21 CFR 314.127(a)(8).

[36] *See, e.g.*, Letter from Janet Woodcock, M.D., to AstraZeneca, Docket No. FDA-2006-P-0073 (November 18, 2008) ("Pulmicort Respules Petition Response") at 22; Draft Guidance on Budesonide (Sept. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf; Draft Guidance on Ciclesonide (Sept. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319983.pdf; Draft Guidance on Calcitonin-Salmon (Sept. 2012), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319979.pdf.

[37] *See* 21 CFR 320.1(e) (defining "bioequivalence").

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are a number of ways, variously involving *in vivo* and *in vitro* data, by which bioequivalence can be demonstrated.[38] The preferred methodology, and what is typically used with drugs that achieve therapeutic effect through systemic absorption, is to measure the rate and extent to which the active ingredient or active moiety is absorbed into the blood over time.[39] When the drug is locally acting, however, systemic absorption, if it can be measured, may not be relevant to understanding the rate and extent to which the active ingredient becomes available at the site of action. In such circumstances, alternative means of measuring bioavailability are required; they can include an *in vivo* test in humans to measure an appropriate pharmacological effect of the active moiety, or a comparative clinical trial with an efficacy endpoint.[40]

There also are circumstances in which bioequivalence can be assumed, and need not be proved. They include if the proposed generic drug product is a solution for nebulization and, as to the reference product, contains the same active ingredient in the same concentration and dosage form, and no difference in inactive ingredients "that may significantly affect systemic or local availability for products intended to act locally."[41]

[38] *See* 21 CFR 320.24.

[39] 21 CFR 320.24(b)(1)(i).

[40] *See* 21 USC 355(j)(8)(A)(ii) ("For a drug that is not intended to be absorbed into the bloodstream, [FDA] may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient . . . becomes available at the site of drug action."); 21 CFR 320.24(b)(3), (4).

[41] 21 CFR 320.22(b)(3).

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### D. Device Component of a Combination Product

With regard to a proposed generic product that is a drug-device combination product,[42] the agency's "sameness" analysis also must include the device component, where FDA considers whether there are differences in performance characteristics or design attributes that "significantly alter product performance or operating principles" or "result in impermissible differences in labeling."[43] The agency examines "whether any difference in materials, design, or operating principles introduces a new risk," looking at "both risks intrinsic to the new product and risks associated with switching from one product to the other without additional physician intervention or training."[44] More specifically:

> For ANDAs for a product with labeling that describes use by patients without physician supervision and further requires training of patients by a physician prior to initial unsupervised use, FDA considers whether patients can be safely switched to a new product without retraining by a physician or health care professional.[45]

Moreover, "[f]or products that require physician training before unsupervised patient use, differences in operation [between a reference listed drug and a proposed generic] that require retraining prior to use are not expected to be acceptable in an ANDA."[46]

The agency has recognized that differences between delivery devices may require "significant differences in labeling for safe and effective use" that fall outside the limited exceptions to the requirement that a generic product have the same labeling as the reference listed drug.[47] Further, FDA has acknowledged that device differences may have potential clinical consequences, such that clinical data are required to demonstrate the proposed product's

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[42] A combination product includes a drug product that, although packaged separately, is intended for use only with an individually specified device, where both the drug and device are necessary to achieve the intended use. 21 CFR 3.2(e)(3).

[43] Letter from Janet Woodcock, M.D., to King Pharmaceuticals, Inc., Docket Nos. FDA-2007-P-0128 and FDA-2009-P-0040 (July 29, 2009) ("King Petition Response") at 6.

[44] *Id.*

[45] *Id.*; *see also* Letter from Janet Woodcock, M.D., to Dey Pharma, L.P., Docket No. FDA-2009-P-0578 (May 27, 2010) ("Dey Petition Response") at 8.

[46] King Petition Response at 10-11.

[47] King Petition Response at 6. Generally, labeling differences are permitted if they are required because of product differences approved in a suitability petition or because the proposed generic drug and reference listed drugs are produced or distributed by different manufacturers. *See* 21 USC 355(j)(2)(A)(v); 21 CFR 314.94(a)(8)(iv).

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safety and effectiveness.[48] Such data may not be submitted in an ANDA; if they are necessary, such data would require submission of a 505(b)(2) NDA.[49]

## III. DISCUSSION

### A. The Active Ingredient of a Proposed Generic Referencing Ventavis Must Contain the Same Ratio of Diastereoisomers as Ventavis.

An ANDA must contain "information to show that the active ingredient of the new drug is the same as that of the listed drug."[50] Where, as here, there are no compendial standards defining the drug substance, FDA must establish standards identifying the characteristics that are "material to the ingredient's sameness."[51] This must mean characteristics that are material to the product's therapeutic effect. With regard to iloprost, this includes requiring the active ingredient of a proposed generic product to contain the 4R and 4S stereoisomers in the same 53:47 ratio as Ventavis. Because of the significant difference in potency between the two isomers, the ratio is a defining characteristic of the active ingredient; it is essential to the product's safety and effectiveness, and has been an unchanging product specification since product approval in 2004.

As discussed above, the agency's review and approval of Ventavis recognized that the iloprost stereoisomers were meaningfully different in terms of their pharmacologic effect. A proposed generic product with a different stereoisomeric ratio simply cannot be said to contain the same active ingredient, given the clinical significance of the difference. And because such a product would contain a different active ingredient, it could not be submitted for approval by means of an ANDA referencing Ventavis.[52] Moreover, precisely because of the clinical significance, a proposed product with a different ratio of stereoisomers could not be expected to have the same safety and efficacy profile as Ventavis. As such, even if it were considered to

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[48] King Petition Response at 7, 8.

[49] *See id.* at 7, Dey Petition Response at 9; *see* 21 USC 355(j)(2)(A).

[50] 21 USC 355(j)(2)(A)(ii)(I); *see also* 21 CFR 314.92(a)(1) (to be the subject of an ANDA, a drug product must contain the identical active ingredient as the RLD); 314.127(a)(3)(i) (FDA ***must*** refuse to approve an ANDA if the applicant fails to show that the active ingredient is the same as that in the RLD) (emphasis added).

[51] 57 Fed. Reg. 17959.

[52] This would be the case even if the product were considered to have demonstrated bioequivalence to Ventavis, because it still would not have the same active ingredient as Ventavis. Moreover, if such a product were the subject of a new drug application ("NDA") submitted under FDCA section 505(b)(2) and referencing Ventavis, the product would not be a pharmaceutical equivalent to Ventavis, and therefore could not be "A" rated to Ventavis as a therapeutic equivalent. *See* 21 CFR 320.1(c) (defining "pharmaceutical equivalents" as products containing "identical amounts of the identical active drug ingredient" and meeting "the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity"); Orange Book at vii (defining "therapeutic equivalents" as products that are pharmaceutical equivalents and "that can be expected to have the same clinical effect and safety profile" when used as labeled).

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have the same active ingredient (which Actelion does not concede), the proposed product would have to independently demonstrate its safety and effectiveness by means of clinical data, which would preclude submission under an ANDA.[53]

### B. Unless a Proposed Generic Referencing Ventavis Has the Same Formulation as Ventavis, it Must Demonstrate Bioequivalence by *In Vitro* and *In Vivo* Data.

As noted above, because Ventavis is a solution for nebulization, a proposed generic product referencing Ventavis must contain the same inactive ingredients, or demonstrate that any differences do not affect safety or effectiveness. Additionally, FDA has required proposed generic versions of certain drugs (including inhaled drugs) to have the same concentration of the same inactive ingredients as the RLD. In general, the agency has taken this position when either the route of administration is sensitive to potential toxicity issues or where the dosage form presents possible bioequivalence concerns. Because Ventavis falls squarely within this category of products, a proposed generic iloprost inhalation solution should be required to have the same formulation as Ventavis. And if the proposed product is formulated differently, the sponsor should be required to demonstrate the product's bioequivalence to Ventavis.

Ventavis is administered to extremely sensitive tissues within the lungs, in patients with compromised pulmonary function. Moreover, it is delivered by way of specific nebulizers that use sophisticated technology to deliver a precise dose for local activity in the airways. Generally, achieving deposition in the respiratory bronchioles and alveolar region requires generating droplets smaller than about 5 μm.[54] Numerous studies have shown that a formulation's fluid viscosity, surface tension, and ion concentration affect aerosol properties and

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[53] *See* 21 USC 355(j)(2)(A); 57 Fed. Reg. 17953 ("If investigations on a drug's safety or effectiveness are necessary for approval, an ANDA is not permitted.").

[54] *See* Ghazanfari, T., *et al.*, "The influence of fluid physicochemical properties on vibrating-mesh nebulization," *International Journal of Pharmaceutics* (2007) 339:103-111, attached at Tab 4. The fraction of droplets with aerodynamic diameters in this range is known as the fine particle fraction ("FPF"). In addition to FPF, other variables that affect inhalation therapy include particle mass median aerodynamic diameter ("MMAD"), total aerosol output, and the rate of aerosol output. Moreover, the inactive ingredients in a product formulation can affect nebulizer performance, and the possible use of a different delivery device presents a confounding factor. *See, e.g.*, Wilson, A.M., *et al.*, "Importance of drug-device interaction in determining systemic effects of inhaled corticosteroids," *Lancet* (1999) 353:2128, attached at Tab 5; Kendrick, A.H., *et al.*, "Selecting and using nebulizer equipment," *Thorax* (1997) 52(Suppl 2):s92-s101, attached at Tab 6; Hess, D., *et al.*, "Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer brand," *Chest* (1996) 110:498-505, attached at Tab 7; Loffert, D.T., *et al.*, "A comparison of commercial jet nebulizers," *Chest* (1994) 106:1788-1793, attached at Tab 8; Hardy, J.G., *et al.*, "Lung deposition from four nebulizers," *Respir. Med.* (1993) 87:461-465, attached at Tab 9.

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nebulizer performance.[55] Accordingly, Ventavis presents unique scientific challenges that the standards for approval of a generic product must take into account.

If a proposed generic product has the same formulation as Ventavis and is approved for use with the same device(s) with which Ventavis is approved, the product may qualify for a waiver of the requirement to demonstrate bioequivalence.[56] If the product varies from Ventavis with regard to inactive ingredients, however, the sponsor must demonstrate that those differences do not significantly affect systemic or local availability of the active ingredient.[57] This would require *in vitro* assessment of aerosolization properties and other delivery characteristics, as well as *in vivo* data demonstrating bioequivalence.

The following *in vitro* data are necessary to demonstrate that the formulation does not affect nebulizer performance:

- Mass Median Aerodynamic Diameter ("MMAD");
- Mass Median Diameter ("MMD");
- Geometric Standard Deviation ("GSD") for both MMAD and MMD;
- Nebulization time; and
- Dose of iloprost at the mouthpiece.

As a study submitted with the Ventavis NDA illustrates, even if nebulizer performance is sufficiently similar, the drug product may have different pharmacokinetics and pharmacodynamics. In that study, nebulizers that were comparable in terms of mean droplet size, exposure, and ratio of treatment effects "exhibited distinct PK, PD, and physical characteristics that may have impacted PK, PD, or PK/PD results."[58] In fact, the differences in pharmacodynamics among the devices led FDA to consider them not bioequivalent.[59]

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[55] For example, droplet size is inversely proportional to fluid viscosity. Increased fluid viscosity therefore increases total aerosol output and FPF. *See* Ghazanfari *et al.* (Tab 4) at 107. Viscosity and surface tension increase the amount of energy required to atomize the spray. An increase in in either property will therefore increase the droplet size. Additionally, a high ion concentration is inversely proportional to the volume median diameter of aerosol droplets and enhances FPF. *Id.* It has been postulated that the ions may prevent water adhesion to the internal device surfaces by repulsion of charges towards the bulk fluid and reducing the droplet surface charge, which in turn results in enhanced aerosol properties.

[56] *See* 21 CFR 320.22(b)(3).

[57] *See* 21 CFR 320.22(b)(3)(iii).

[58] Ventavis Approval Package, Clinical Pharmacology and Biopharmaceutics Review at 53.

[59] *Id.* at 52-53. Moreover, the difference in effect on mean systemic blood pressure was statistically significant, and resulted in a recommendation that patients' blood pressure be monitored. *Id.* at 53.

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For that reason, demonstrating that differences in formulation do not affect systemic or local availability of the active ingredient also requires bioequivalence data. This is consistent with the agency's views as expressed by Office of Generic Drugs and the Office of Pharmaceutical Science. Specifically, FDA has indicated that demonstrating bioequivalence for combination products intended to deliver drug to the airways and nasal passages generally requires (1) *in vitro* studies to determine comparative *in vitro* performance between the test and reference products; (2) where relevant, *in vivo* pharmacokinetic studies to establish equivalence in systemic exposure; and (3) either *in vivo* pharmacodynamics or clinical endpoint studies to demonstrate equivalence in products that are locally active.[60]

Although some iloprost is systemically absorbed, the drug is primarily locally acting, and there is no clear relationship between systemic levels of drug and either pharmacodynamic activity or therapeutic effect. Accordingly, demonstrating bioequivalence requires not only developing pharmacokinetic data (*i.e.*, $C_{max}$ and AUC of the drug in plasma), but also pharmacodynamic data. More specifically, the ANDA should include data demonstrating no statistically significant difference between test and reference products in the following:

- Mean pulmonary artery pressure ("mPAP");
- Pulmonary vascular resistance ("PVR");
- Cardiac output;
- Mixed venous oxygen saturation ("$SVO_2$");
- Systemic blood pressure;
- Systemic vascular resistance; and
- Heart rate.

The data should be collected from patients undergoing treatment for PAH, and should measure change, measured pre-dose, at some points during inhalation, and at the end of inhalation.[61]

### C. A Proposed Generic to Ventavis Must Be Approved for Use With a Nebulizer That Has the Same Performance Characteristics and Critical Design Attributes as the Nebulizers With Which Ventavis is Approved.

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[60] *See* Quality by Design for Orally Inhaled Drug Products, Lawrence X. Yu, Ph.D., Director for Science, Office of Generic Drugs, Food and Drug Administration, PQRI Workshop on Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products, March 9-11, 2009, attached at Tab 10; Adams, W.P, *et al.*, "Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products," *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 23:1-29 (2010) , attached at Tab 11; Draft Guidance for Industry: Bioavailability and Bioequivalence for Nasal Aerosols and Nasal Sprays for Local Action (Apr. 2003), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070111.pdf.

[61] Alternatively, a sponsor could conduct a comparative efficacy study evaluating a 6-minute walk.

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Aerosolization of a drug is a complex process affected by the formulation of the drug product and the performance attributes of the delivery system. The development of an inhaled therapy that is safe and effective depends not only on a pharmacologically active molecule, but also on a well-designed delivery system and formulation. Drug-device combinations must aerosolize the drug in the appropriate particle size distribution and concentration to ensure optimal deposition and dose in the desired region of the lung. Each inhalational device generates an aerosol with different properties; the particle size, respirable dose, lung deposition and distribution will differ. Consequently, the same drug at the same nominal dose delivered from different devices or in different formulations may not be bioequivalent.

Ventavis is approved for use only with the I-neb or Prodose nebulizer, each of which utilizes AAD technology that sets it apart from almost all other available nebulizers. The performance of these nebulizers is critical to the safe and effective use of Ventavis to treat PAH. That performance, in turn, is a function of a number of factors, including the interaction between drug and device, the design features and performance characteristics of the device, physician and patient familiarity with the device and the instructions for use, and patients' ability to use the device properly. That is why Ventavis is approved with physician and patient labeling with extensive instructions for use, the nebulizers themselves have extensive use instructions, and Actelion has an extensive patient training program.

Because of the essential and particular role of the nebulizer in the safe and effective use of Ventavis, any proposed generic iloprost inhalation solution must be approved for use with a nebulizer that (1) has the same performance characteristics and critical design attributes as the I-neb and Prodose devices, (2) patients will be able to use without additional instruction or training, and (3) will not require any material change in labeling from Ventavis. With that in mind, the agency must closely evaluate any ANDA that seeks approval with a different nebulizer, in order to understand the differences and their impact.

As a starting point, if a generic product referencing Ventavis is proposed for use with a different nebulizer, the agency should require the same *in vitro* and *in vivo* data outlined above, in order to demonstrate that the nebulizer performs to the same specifications as the I-neb or Prodose with Ventavis, and to show that the products are bioequivalent. Additionally, FDA must carefully evaluate the design attributes and manner of operation, and determine whether patients will be able to safely and effectively use the nebulizer without additional instruction or training from a healthcare professional. As the agency has recognized, such an evaluation may well require the applicant to provide data from human factors studies. If that is the case, the product cannot be submitted for review via an ANDA, but presumably would be the subject of an NDA under section 505(b)(2) of the FDCA.

The agency also must review the differences in labeling for the product, which would include differences in the extensive instructions for use in the physician and patient labeling. If the differences fall outside the narrow exceptions to the requirement for same labeling applicable

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to ANDA products, the proposed generic cannot be reviewed or approved under an ANDA and would not be eligible for an "A" rating if approved under a 505(b)(2) NDA.

## IV. CONCLUSION

For the reasons discussed above, Actelion requests that FDA not approve any ANDA referencing Ventavis without first taking the actions requested in this petition.

## ENVIRONMENTAL IMPACT

The actions requested in this citizen petition are subject to categorical exclusion under 21 CFR 25.31.

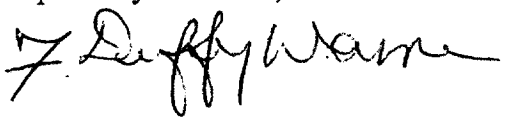
## ECONOMIC IMPACT

Information on the economic impact of this petition will be provided at the request of the Commissioner of Food and Drugs.

## CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, 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.[62]

Respectfully submitted,



Frances Duffy-Warren, PhD
VP US Regulatory Affairs

Attachments

cc: Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs

[62] Actelion is not aware of any ANDA or 505(b)(2) applications pending before the agency, and thus is providing certification under 21 CFR 10.30.

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