



New Medicines for New Times

Fujisawa Healthcare, Inc.
Theron Odlaug, Ph.D.

Executive Vice President, Operations
And Strategic Relations
Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8821 Fax (847) 317-7288
www.fujisawa.com

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VIA HAND DELIVERY

Dockets Management Branch
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on Apotex Corp.'s Suitability Petition, Docket Number
2004P-0326 (CP1)

Ladies and Gentlemen:

On July 21, 2004, Apotex Corp. filed a Suitability Petition pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (the "FD&C Act"). The Suitability Petition (Docket Number 2004P-0326 (CP1)) requests that FDA allow Apotex to file an abbreviated new drug application (ANDA) for 18 mg (6 ml vial) and 30 mg (10 ml vial) strength adenosine in reliance on Fujisawa Healthcare, Inc.'s approved product, Adenocard[®] (adenosine injection) as the reference listed drug. The products Apotex proposes, however, raise serious safety issues for patients, and FDA should therefore deny the Suitability Petition.

Contrary to Apotex's claims, the Suitability Petition requests a major change in drug strength. These higher strength products raise serious safety concerns due to the potential for overdose and/or contamination associated with the use of multidose vials in an emergency or pre-hospital setting. Because these concerns were not addressed in Fujisawa's original NDA,

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Apotex would need to conduct clinical trials to ensure that patient safety is not jeopardized. Moreover, Fujisawa's currently approved label is not designed for multi-use vials and, therefore, significant new warnings would be required to mitigate the risks posed by Apotex's proposed higher strength products. Under these circumstances, the FD&C Act and FDA's implementing regulations require that FDA deny the Suitability Petition.

I. Currently Available Adenosine Products for Treatment of Paroxysmal Supraventricular Tachycardia

A. Adenocard[®]

Adenocard[®] is indicated for conversion to sinus rhythm of paroxysmal supraventricular tachycardia ("PSVT"), including that associated with accessory bypass tracts (Wolff-Parkinson-White Syndrome). The active ingredient in Adenocard[®] is adenosine. Fujisawa markets Adenocard[®] (adenosine injection) pursuant to NDA 19-937, which was approved by FDA on October 30, 1989. Adenocard[®] is packaged in single dose prefilled syringes and offered at strengths of 6 mg and 12 mg.

B. Generic Adenosine

Patent protection for Adenocard[®] expired in June 2004, allowing the entry of generic substitutes. Currently, three companies are approved to market generic adenosine for treatment of PSVT. These manufacturers offer their generic product at the same strengths as Adenocard[®], 6 mg and 12 mg. Generic adenosine, like Adenocard[®], is offered in single dose packaging as prefilled syringes or individual vials.

II. Apotex's Suitability Petition Should Be Denied Because Its Proposed Products Would Require Clinical Investigation and Significant Labeling Changes

Generic manufacturers seeking market approval under an ANDA generally must offer the product in the same dosage form, strength, and route of administration as the reference listed drug.¹ A manufacturer seeking to change one of these characteristics in its product must obtain specific approval for the change through a suitability petition.² But the FDA must not approve such a petition if it finds that the change would require clinical or preclinical studies to show that the proposed generic product is safe or effective or if any newly introduced safety or effectiveness problems would necessitate significant labeling changes.³ As discussed below, the safety issues raised by Apotex's proposed products would require both clinical investigation and significant labeling changes. Therefore, Apotex's petition should be denied.

A. Higher-Strength Multidose Vials of Generic Adenocard® May Lead to Dosing Errors and Delays in Treatment

Apotex proposes offering generic adenosine in multidose vials in new strengths containing 18 mg or 30 mg of adenosine. Unlike the currently approved single dose, prepackaged product, these new multidose vials would require an end user to first open a separately packaged syringe and then draw an accurate bolus of adenosine for each dose injected into the patient--additional steps that could delay treatment and introduce a risk of dosing error. Fujisawa has never investigated the risks of such a dosing error because it has always sold Adenocard® exclusively at single dose strengths. Yet, because PSVT is usually treated under

¹ 505(j)(2)(A)(iii) of the FD&C Act, 21 U.S.C. § 355(j).

² *Id.*

³ Section 505(j)(2)(C) of the FD&C Act, 21 U.S.C. § 355(j)(2)(C); 21 C.F.R. § 314.93(e)(1-2).

emergency conditions, often in an ambulance or rescue setting by paramedics, there is a real risk of dosing errors or delay with multidose vials.

1. Current Treatment Methods for PSVT

The onset of PSVT is sudden and unpredictable. It is characterized by symptoms that may include one or more of the following: pounding in the chest; rapid pulse rate (150-250 beats per minute); shortness of breath; lightheadedness or dizziness; tightness or pain in the chest; and pallor or fainting. Although the symptoms associated with PSVT vary in their severity, depending on the age, physical condition, and cardiac health of a patient, PSVT can be life threatening in those with underlying cardiac disorders. At least one study reported loss of consciousness in 20% of those treated for an episode of PSVT and the need for external direct-current shock to correct arrhythmia in 16%.⁴

Although not every patient requires pharmacological intervention for PSVT, for those whose symptoms are severe enough and who meet other treatment criteria, adenosine is the drug of choice to reduce the elevated heart rate. According to the approved label, Adenocard[®] should be administered initially as a 6 mg rapid intravenous bolus given over a 1 to 2 second period.⁵ This single 6 mg dose is sufficient to convert tachycardia to a normal sinus rhythm in most patients (approximately 60 percent).⁶ For the minority of patients who fail to convert to sinus rhythm within 1 to 2 minutes after a single dose of adenosine, the Adenocard[®] label directs

⁴ See K.A. Wood, et al., Frequency of Disabling Symptoms in Supraventricular Tachycardia, 79 American Journal of Cardiology 145-149 (1997).

⁵ See Adenocard[®], Prescribing Information (Aug. 2003) (Attached at Appendix A).

⁶ See *id.*

administration of a second rapid intravenous bolus of 12 mg of the drug.⁷ Two doses of adenosine will eliminate supraventricular tachycardia in the vast majority of patients (approximately 92%).⁸ The label recommends a third dose--12 mg--only for patients who do not respond to the first two injections. It is important to note, however, that in clinical practice, paramedics and physicians often switch to alternate treatment modalities if patients do not respond to one or two adenosine injections.⁹

Adenocard®'s current strength and packaging is ideal for rapidly and reliably administering the correct dose of adenosine to patients.¹⁰ Individually wrapped, prefilled syringes are offered at two dosage strengths--6 mg and 12 mg.¹¹ When emergency personnel need to administer Adenocard®, they simply unwrap a single prefilled syringe and administer its full contents to the patient. If a second dose is needed, a second full syringe is administered. The individual packaging virtually eliminates the possibility of dosing error. Moreover, there is no wasted drug and no time spent opening a vial or assembling and filling a syringe. Since most

⁷ *See id.*

⁸ *See id.* Although the studies cited in the package insert also involved doses of 3 mg and 9 mg, post-approval studies reach similar conclusions using only the 6 mg and 12 mg doses. *See* L.K. Wittwer and M.D. Muhr, Adenosine for the Treatment of PSVT in the Prehospital Arena: Efficacy of an Initial 6 mg Dosing Regimen, 12 *Prehospital and Disaster Medicine* 64-66 (1997).

⁹ *See* Declaration of Marvin A. Wayne, M.D., F.A.C.E.P, F.A.A.E.M. (Attached at Appendix B).

¹⁰ *See id.*

¹¹ *See* Adenocard®, Prescribing Information (Aug. 2003) (Attached at [Appendix A](#)).

patients require only one, or, at most, two doses, the only waste produced with Adenocard® is a single, or occasionally two, empty syringes.¹²

2. Apotex's Proposed Change

With the proposed new 18 mg and 30 mg strength vials, by contrast, ER personnel and paramedics will be forced to measure out the proper dose (either 6 mg or 12 mg) from the vials before administering adenosine. Particularly in a critical situation, this can easily result in dosing errors.¹³ Such dosing errors may put patients at unnecessary risk of complications and adverse events such as hypotension, bronchospasm, or high-grade atrioventricular (AV) node block. In some cases, these dosage errors could become life threatening. For example, a period of prolonged asystole could well be created by such a dosing error. A prolonged period of asystole could allow life threatening rhythm disturbances to occur which may result in dangerously accelerated ventricular rates.¹⁴

¹² See Declaration of Marvin A. Wayne, M.D., F.A.C.E.P, F.A.A.E.M. (Attached at Appendix B).

¹³ See *id.* The issues involved in the use of multidose vials have been studied by various groups concerned with safe medication practices. See, e.g., "Patient safety movement calls for reexamination of multidose vial use," ISMP Medication Safety Alert!, June 14, 2000. To avoid such errors, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Official Handbook (2004) recommends procedures for safe administration of medications. One of these recommendations is that "Medications are dispensed in the most ready-to-administer forms available from the manufacturer or if feasible, in unit-doses that have been repackaged by the pharmacy or licensed repackager." Joint Commission on Accreditation of Healthcare Organizations, Comprehensive Accreditation Manual for Hospitals: The Official Handbook, Standard MM(M4)(2004).

¹⁴ See Declaration of Marvin A. Wayne, M.D., F.A.C.E.P, F.A.A.E.M.

The potential for dosing error in the absence of single dose (unit) packaging is more than a mere theoretical possibility. A 1999 report by the Institute of Medicine of the National Academies found that “[u]nit dosing was a major systems change that significantly reduced dosing errors when it was introduced nearly 20 years ago.”¹⁵ Indeed, since its approval in 1989, Adenocard has *always* been supplied in single dose packaging, as are all of the generic products currently on the market. ER personnel and paramedics, accustomed to administering entire 6 mg or 12 mg vials or prefilled syringes of adenosine, may mistakenly inject full 30 mg vials of adenosine into patients.¹⁶

Fujisawa has never fully studied the effects of such a large dose of adenosine in a single rapid bolus injection administered over 1-2 seconds. Although the Adenocard® label states that adverse events should generally be self limiting due to the short half-life of adenosine, Adenocard® has never been offered at strengths as high as those sought by Apotex. By offering adenosine in multidose form at higher strengths than are currently available, Apotex would create a new and unknown safety risk that was never studied in Fujisawa’s original NDA.

Apotex should not be allowed to bring this new, higher strength form of adenosine to market under an ANDA without conducting additional testing to determine the risk to patients of exposure to adenosine doses as high as 30 mg. At the very least, Apotex would have to make labeling changes to address this newly-introduced safety problem. Because Apotex must take

¹⁵ Committee on Quality of Health Care in America, Institute of Medicine, *To Err is Human: Building a Safer Health System* 193 (Linda T. Kohn et al., eds., 1999).

¹⁶ See Declaration of Marvin A. Wayne, M.D., F.A.C.E.P, F.A.A.E.M.

these additional measures to ensure the safety of the proposed products, the FD&C Act and FDA's regulations require that FDA deny the Suitability Petition.

B. 18 mg and 30 mg Strength Vials Could Subject Patients to Contamination Risks

The 18 mg and 30 mg strengths proposed by Apotex also present significant risks of product contamination. Neither Adenocard®, the three generic products currently on the market, nor Apotex's proposed generic product are formulated to contain a preservative.¹⁷ The lack of a preservative is not an issue with the current Adenocard® product or the generic adenosine products currently on the market for treatment of PSVT because all these products are maintained in a sterile prefilled syringe or vial, the entire contents of which are administered in a single dose. Thus, there is no real likelihood that a single syringe or vial would be used more than once. By contrast, emergency department personnel and paramedics will rarely use all, or even most, of the generic adenosine in 18 mg and 30 mg vials.¹⁸ As discussed above, in most cases, patients return to normal sinus rhythm after only a single 6 mg dose of adenosine. Moreover, as previously noted, as a matter of clinical practice, clinicians often switch treatment options if patients do not respond to the first or second adenosine injections. Thus, the majority of the contents of an 18 mg or 30 mg vial would remain unused, with the unused portion constituting sufficient drug to give as many as four additional 6 mg doses. Although Apotex may not intend for its product to be stored and reused at various times for multiple patients, the

¹⁷ See Suitability Petition, appendix B (proposed labeling for Apotex products stating that the products do not contain a preservative).

¹⁸ See Declaration of Marvin A. Wayne, M.D., F.A.C.E.P, F.A.A.E.M.

large amounts of drug remaining in the proposed larger vials could tempt ER personnel and paramedics to return the vials to the shelf for use in the next patient or patients over an indeterminate amount of time.

There is a significant risk that, if not discarded, these products would become contaminated before being used in the next patient or patients.¹⁹ Incidents of PSVT are infrequent, with typical emergency department and paramedic teams often going days or even weeks between cases.²⁰ As a result, excess amounts of generic adenosine from the proposed 18 mg and 30 mg strength vials may sit on the shelf for significant periods of time between uses. The next patient or patients could then be injected with contaminated product.

Fujisawa has not conducted studies to assess the contamination rate of adenosine, the risks of injecting patients with contaminated adenosine, or even the stability of an adenosine vial once it has been penetrated with a needle. Further clinical investigation is required to determine the safety of providing vials capable of multidose use where the multidose product is not intended to be reused. For this reason, FDA must deny the Suitability Petition.

In the absence of additional clinical studies, at the very least, Apotex should be required to add heightened warnings to its product labels to account for this new safety risk. These

¹⁹ The CDC, for example, has linked multidose vials to nosocomial outbreaks. G. Krause, et al. Nosocomial transmission of hepatitis C virus associated with the use of multidose saline vials. *Infect. Control Hosp. Epidemiol.* 24(2):122-127 (2003) (from the CDC); L.K. Archibald, et al. Enterobacter cloacae and Pseudomonas aeruginosa polymicrobial bloodstream infections traced to extrinsic contamination of a dextrose multidose vial. *J. Ped.* 133(5):640-644 (1998) (from the CDC).

²⁰ See Declaration of Marvin A. Wayne, M.D., F.A.C.E.P, F.A.A.E.M.

warnings should make clear that ER personnel and paramedics must dispose of unused product from 18 and 30 mg product, and cannot re-use it on successive patients. The Adenocard[®] package insert does direct that unused portions of the product should be discarded. But, this warning is made in the context of 6 mg and 12 mg vials or prefilled syringes of Adenocard[®], where “unused portions” represent only minute, residual amounts that cannot be re-used in the first place. Because anywhere from 12 mg to 24 mg may be left over in Apotex’s products, ER personnel and paramedics may believe that these larger vials are intended for reuse. In the absence of data supporting the ability to safely reuse these therapeutic doses of adenosine, additional warnings should be required to account for this newly introduced safety risk. For this reason, FDA must deny the Suitability Petition.

III. Apotex’s Rationale for the Proposed Product Cannot Be Substantiated

Weighed against the potential risks posed by Apotex’s proposed products is the fact that nowhere in the Suitability Petition does Apotex contend that its 18 mg and 30 mg products present any medical benefit over that already offered by Fujisawa or the other generic manufacturers. Apotex argues only that its products are “more cost-efficient than 2 ml vials, and 2 ml and 4 ml syringes”, and that “[v]ials are also space-efficient and produce less waste than single-use syringes.”²¹ Apotex, however, provides no factual support for its claims. Indeed, as discussed above, in the vast majority of cases there will be substantial amounts of drug product leftover after a patient is successfully treated. Moreover, medical personnel will need to use a

²¹ See Suitability Petition, p. 2-3.

needle and syringe to remove the adenosine from the proposed large vials.²² These syringes and needles would need to be carried and stored along with the proposed Apotex vials, taking up additional space.²³ In addition, this type of packaging could lead to inadvertant needle-stick injuries.²⁴ Thus, the greater likelihood is that large, multidose vials of adenosine would be *less* cost and space efficient and produce *more* waste than the current approved strengths.

In short, Apotex seeks permission to market a product that would require the health care system to spend large amounts of money on drug product that it has no reasonable expectation of using. Far from providing a practical advantage, the higher strength products that Apotex proposes are completely ill-suited for use as a generic substitute for Adenocard® and would provide no meaningful benefit to physicians or patients over that offered by the current product.

IV. Additional Reasons to Deny Apotex's Petition

In the absence of any substantial benefit associated with the marketing of a multidose drug, it is reasonable to ask what motivation Apotex might have for offering such a product. As the FDA is aware, Fujisawa markets a second adenosine-based product, Adenoscan®, which is used as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately. Adenoscan® differs from Adenocard® in several key respects. First, unlike Adenocard®, Adenoscan® is administered as a slow infusion of adenosine at 140 mcg/kg/minute over a period of 6 minutes. Second, also unlike Adenocard®, Adenoscan® is

²² See Declaration of Marvin A. Wayne, M.D., F.A.C.E.P, F.A.A.E.M.

²³ See *id.*

²⁴ See *id.*

administered as part of a routine diagnostic procedure rather than an emergency treatment of a cardiac condition. Third, while the patent for Adenocard® expired in June 2004, Adenoscan® has years of patent protection remaining.

Despite the differences between the products, the active ingredient of Adenoscan® is an adenosine solution at the same concentration used in Adenocard®, raising the possibility that individuals or organizations might attempt to use the generic adenosine labeled for use as a low-dose bolus in the treatment of PSVT as a substitute for the high dose adenosine infusion used for Adenoscan®. Adenoscan® is marketed at strengths of 60 mg and 90 mg, as compared to the 6 mg and 12 mg doses of Adenocard® or generic adenosine for treatment of PSVT. Thus, using current products, it would be inconvenient at best to combine 5 to 8 single dose 12 mg syringes or vials of Adenocard® or generic Adenocard® to yield sufficient material for 60 mg or 90 mg of Adenoscan®.

Yet introduction of multidose generic adenosine in strengths of 18 mg or 30 mg would all but eliminate the inconvenience of combining doses of adenosine labeled for treatment of PSVT as a substitute for Adenoscan®. Indeed, such products would actively encourage substitution if priced sufficiently low.²⁵ Although such substitution of generic adenosine or Adenocard® for

²⁵ The objective intent of persons responsible for labeling of a prescription drug is determined by their expressions or the circumstances surrounding distribution of the drug. 21 C.F.R. § 201.128 Thus, a drug is intended to treat a given disease (and must therefore apply for FDA approval for treatment of that disease) if that intent is objectively manifested by its manufacturer. By creating a product that is suitable for use as generic Adenoscan®, but not as generic Adenocard®, Apotex has manifested its intent that the product be used as generic Adenoscan®. As a result, should FDA accept the suitability petition, the FDA should require Apotex to label its drug for the new (continued...)

Adeoscan® would be an infringement of Fujisawa's patent rights, an even more compelling concern from the FDA's perspective is the fact that substitution carries potential serious health risks for patients due to differences in the USP formulation of the two drugs.

Off-label use of generic Adenocard® as Adenoscan® could expose patients to unsafe levels of bacterial endotoxins. The USP for adenosine permits 11.62 USP Endotoxin Units per mg of Adenocard®, but permits only 5.95 USP Endotoxin Units per mg of Adenoscan®.²⁶ This difference is due to the fact that Adenoscan® is administered in much larger doses than is Adenocard®. Under the current manufacturing specification, Apotex's proposed 30 mg generic Adenocard® could have endotoxin levels of up to 11.62 endotoxin units per mg. If this product were used off-label in place of Adenoscan®, patients could potentially receive up to twice the level of endotoxin deemed safe by USP.²⁷

Patients exposed to such high levels of endotoxins would be put at an unacceptable risk of serious side effects. High levels of endotoxin can cause adverse effects including fever, chills, myalgia, increase in heart rate, decrease in mean arterial pressure, and decrease in left ventricular

intended use, to reference Fujisawa's Adenoscan® NDA, and to make the appropriate certifications for corresponding patents listed in the Orange Book.

²⁶ U.S. Pharmacopeial Convention, Inc., U.S. Pharmacopeia 2- National Formulary 4774(18) (23rd ed.) (May 15, 1999).

²⁷ For example, a patient receiving three 10 ml vials (total 30 ml) of generic adenosine in place of Adenoscan® could potentially receive 1,045.8 endotoxin units (30 ml x 3 mg/ml x 11.62 units/mg) rather than the recommended total maximum of 535 units (5.95 USP Endotoxin Units per mg of Adenoscan®).

function.²⁸ Once again, Apotex should be required to conduct additional investigations to assess this safety risk associated with its proposed multidose products. At the very least, additional warnings regarding such risk of serious side effects should be required on the product labels to ensure that pharmacists and physicians are not tempted by the larger vial sizes to use these products off-label as generic Adenoscan[®]. The FD&C Act and FDA's implementing regulations therefore require that FDA deny the Suitability Petition.

V. Any ANDA For Apotex's Products Should Be Denied Under Section 505(j) of the FD&C Act

In addition to providing grounds for denial of the Suitability Petition, the safety concerns highlighted above require denial of any ANDA for Apotex's products, should FDA determine that it is acceptable for filing. For example, section 505(j)(4)(A) states that FDA must deny an ANDA if "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity."²⁹ Because 18 mg and 30 mg generic Adenocard[®] may be reused after the initial patient, the failure to include a preservative in the product renders Apotex's method of manufacture, processing, and packing inadequate to preserve the product.

Most importantly, the risk benefit analysis for Apotex's proposed products requires that FDA refuse to approve them. As has been explained above, there is no medical benefit to producing adenosine for Adenocard[®] in new strengths of 18 mg and 30 mg when the largest

²⁸ R. Burrell, Human responses to bacterial endotoxin, 43 *Circulatory Shock* 137-153 (1994).

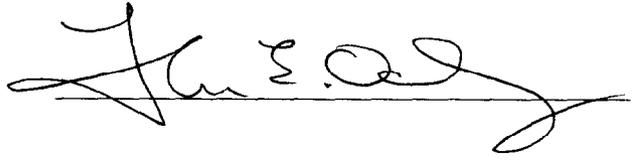
²⁹ 21 U.S.C. § 355(j)(4)(A).

labeled dose is 12 mg and majority of patients require only a single 6 mg dose. Far from being cost and space efficient, such a product would create waste and force the health care system to purchase large amounts of product that it will only throw away. In light of the total lack of benefit for these new strengths of adenosine, there is no justification for subjecting patients to the additional safety risks highlighted in these comments.

VI. Conclusion

The changes proposed by the Suitability Petition raise serious safety concerns for Apotex's proposed generic products. Supplying generic Adenocard® in new strengths of 18 mg and 30 mg raises the very real possibility of overdose and contamination, and could lead to exposure to unsafe levels of endotoxins. To ensure that Apotex's products do not jeopardize patient's safety, Apotex must conduct additional animal or human testing. At the very least, Apotex's proposed products would require "significant labeling changes to address the newly introduced safety or effectiveness problem[s]." As a result, the FD&C Act and FDA's regulations require that FDA deny the Suitability Petition.

Respectfully Submitted,



Theron Odlaug
Executive Vice President
Fujisawa Healthcare, Inc.

cc: (w/attachments): Daniel E. Troy, Esq., Chief Counsel, FDA
Gary J. Buehler, Director, OGD