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Academic Pharmaceuticals, Inc.

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OFFICE OF ORPHAN PRODUCTS DEVELOPMENT

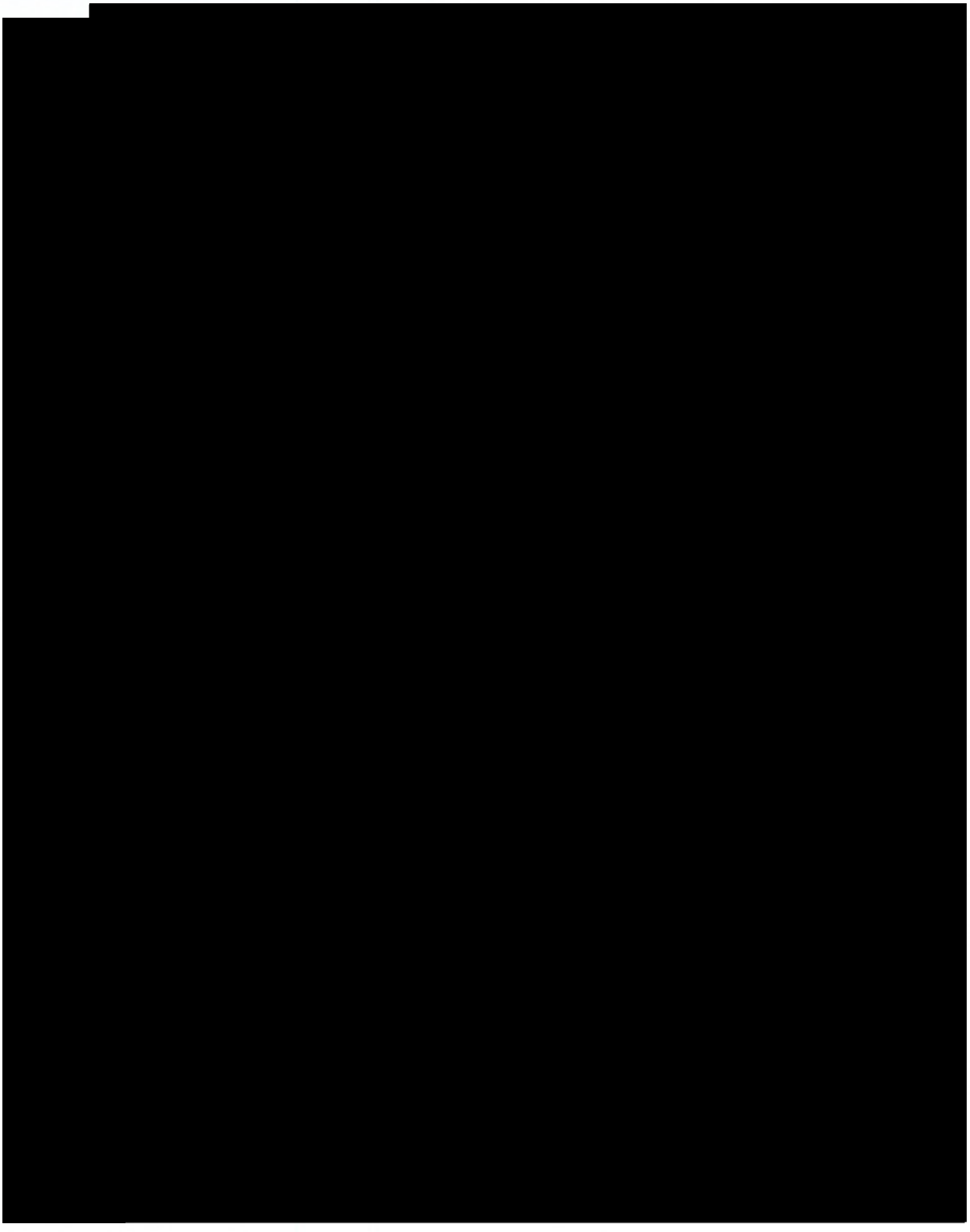
Timothy R. Cote, MD, MPH
Director, Office of Orphan Products Development
FDA
5600 Fishers Lane
Rockville, MD 20857

Re: Designation Request [redacted]

We are in receipt of your letter of April 9, 2008 denying Orphan Drug Designation to Sotalol IV. [redacted]

21 NORTH SKOKIE HIGHWAY, SUITE G-3, LAKE BLUFF, IL 60044
PHONE: 847-735-1170, FAX: 847-735-1173

(1) Sotalol hydrochloride is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of a physician is life threatening.



[redacted]

The Agency for Healthcare Research and Quality list 695,000 patients with a diagnosis of arrhythmias at hospital discharge. Of the 695,000, 7,830 patients have ventricular fibrillation and ventricular flutter and 7,718 patients are listed with a cardiac arrest. It is not possible to determine if the 7,800 patients with VF/flutter are also coded for cardiac arrest, although it is likely, since VF invariably initiates a cardiac arrest. Adding all the categories together (with possible over counting) the numbers point to a possible 15,518 patients who could receive IV sotalol (7,718 CA, 7,800 VF/VT).

One can also evaluate the projected use of sotalol IV based on a disease specific condition, cardiac arrest that are treated in a hospital. The proposed use of IV sotalol for life threatening ventricular arrhythmias could be based on the number of cardiac arrests in the U.S., approximately 174,000 (American Heart Association, statfact sheet, 2007 update, http://www.americanheart.org/downloadable/heart/1168639579314outofhosp07.pdf). The survival of cardiac arrest patients is reported to be less than 5% (Prystowsky EN Circ 2004:109(9)1073-5). Sotalol could be initiated IV for survivors of cardiac arrest who reach the hospital or approximately 8,700, a number close to that reported in the National Discharge Survey. A separate source reports the number of cardiac arrest in-hospital, to be approximately 6,000, American Heart Assoc. (Heart disease and stroke statistics 2007 update http://circ.ahajournals.org/cgi/reprint/115/5/e69). There is a possible significant overlap in the number between cardiac arrest survivors 8,700 and in-hospital cardiac arrest discharges, 6,000; since out of hospital arrest patients, if resuscitated, are hospitalized and become part of the hospital arrest statistic. These numbers presented are incidence figures, since sotalol would be used for the patients acute problem, on a one time basis, to prevent acute recurrence or to continue sotalol therapy when oral therapy can't be administered in-hospital.

Sotalol is also employed to prevent recurrence of atrial fibrillation or atrial flutter. It is **not** used for acute conversion. Patients are not loaded with large oral loading doses of sotalol to convert AF patients, because the large doses

could cause a prohibitively high incidence of life threatening Torsade de Pointes ventricular tachycardia that can be fatal. The drug is currently started in the hospital at a low dose, once a patient is in sinus rhythm (NSR) and then continued after discharge to prevent AF recurrence or to prolong the time to AF recurrence. Supraventricular arrhythmias such as sick sinus syndrome, AV node tachycardia, proximal atrial tachycardia (PAT), and multifocal atrial tachycardia either don't respond, are made worse or the risk of proarrhythmia from sotalol so outweighs the benefits that the medical community does not employ oral sotalol for therapy (an example would be the arrhythmia proximal atrial tachycardia). Thus the disease target is atrial fibrillation or atrial flutter. Additionally, because of the serious consequences of proarrhythmia, sotalol is recommended and used in medical therapy for highly symptomatic patients. This is clearly stated in the product label for oral sotalol and in the AHA/ACC Society guidelines for arrhythmia management. Atrial flutter is much less prevalent condition than atrial fibrillation, often treated today by ablative invasive electrophysiologic procedure and most data bases combine AF with A flutter. From CDC data, the incidence of flutter is less than 10% of AF (CDC vital and Health Care Statistics Series 13, Number 162 Oct 2006). The prevalence of AF/A flutter is estimated to be 2.3 million in the U.S. (Go,AS,JAMA2001;285(18):2370-5). Many patients are managed in the U.S., employing the strategy of leaving the patient in AF, treating with anti-coagulant therapy and drugs to control the ventricular rate. Sotalol is not a drug used for rate control, but rather to maintain NSR once the patient is cardioverted. The incidence of cardioversion is 23,000 as reported by ICD-9 codes for 2004 in CDC procedure frequency listings (CDC Vital and Health Stat:Series 13 Number 162,Oct 2006). Cardioversion converts AF in about 70% of patients to NSR and 95% successes rate in A flutter. Estimating 10% of patients have flutter or 2,300 cardioversions would result in 2,185 in NSR. Of the 20,700 in AF, cardioversions would result in 14,490 converted to NSR, yielding a total of 16,675 patients eligible for sotalol therapy, patients in NSR that could be put on sotalol therapy to continue to maintain NSR. Sotalol is only used and indicated for patients that are highly symptomatic. Highly symptomatic patients

are difficult to estimate, but one study reports that only 30% of patients with AF are symptomatic or 30% of the 16,675 or 5,003 patients would be eligible, if that many (Fetsch T, Eur Heart J 2004,25(16):1385-94). If one considered the total AF population in the U.S. of 2.3 million patients and admitted all these patients into the hospital, 1,610,000 patients could be converted to NSR and 483,000 may be symptomatic. Placing 100% on oral sotalol therapy one then could estimate (based on rate of AF hospitalizations) that 10% would be re-hospitalized and thus eligible to receive IV sotalol. The prevalence of eligible patients would be 48,000 patients. However, of the 2-3 million AF patients most have persistent AF that is a different condition and not treated by sotalol, only those Cardioverted to maintain sinus rhythm would receive oral sotalol and be candidates to receive IV sotalol, a small fraction of the 2-3 million (50,000 patients).

A third approach to estimate the disease specific target population would be to use the Agency for Healthcare Research and Quality report on the web site http://hcupnet.ahrq.gov listing 392,619 patients with AF (ICDM code) in hospital. Estimating that 70% can be cardioverted to NSR that would give 274,833 patients of which 30% would be symptomatic (even less highly symptomatic) or 82,450 patients.

Thus the range of eligible patients for IV sotalol for AF/flutter runs from as low of 5,000 to as high as 83,000 patients.

Taking the high estimate of the potential use of sotalol for patients with VT/VF of 15,500, which includes all eligible patients and combining it with the high estimate of potential use of sotalol IV in AF/A flutter patients 83,000, yields a combined total of 98,500, less than the 200,000 patients comprising the "cut off" for orphan designation. While one can look at the total number of patients with hospital discharge diagnosis that have an arrhythmia condition and come up with a number in the 600,000 to 700,000 patient range, those patients having an arrhythmia disease type that is appropriate for sotalol therapy, the use of sotalol thus constitutes 15% of the total arrhythmia population, or approximately 100,000 patients, not 696,551 patients with a diagnosis of arrhythmias in 2005.

(3) "Per the Agency for Healthcare Quality and Research, in 2005 there were a total of 696,551 patients with hospital disease diagnosis of some form of cardiac dysrhythms. As the two previously approved indications for sotalol are for treatment of life threatening ventricular arrhythmias and maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation or flutter who are currently in normal sinus rhythm, it is not unreasonable to predict whether IV sotalol might make for a reasonable agent to induce normal sinus rhythm in patients with arrhythmias".

Please see our analysis on disease number above showing that the use of IV sotalol would be in the 100,000 range. The IV drug would be unreasonable to use for the induction of NSR. It is not approved for this purpose; has a high incidence of Torsade, a life threatening arrhythmia; and has not been studied or reviewed by FDA for this purpose. Additionally, the use of shock – cardioversion (ICD – 9 code) is 24,000 and shock is safer than drugs for conversion (CDC Vital and Health Statistics, Series 13, Number 162, Oct. 2006). Clearly 696,000 plus patients don't receive shock, so why would they receive IV sotalol. Thus even if IV sotalol was used in an unreasonable manner, off label, without studies justifying its use, it still would not put the use of sotalol over the range of 200,000, since only 24,000 patients receive shock for this purpose and are conceivably eligible for IV sotalol.

[redacted]

Sincerely,

John Somberg, MD
President API

REVIEW OF REQUEST FOR ORPHAN DRUG DESIGNATION

Date Received by FDA:	08/16/2007
Date Received by Reviewer:	08/31/2007
Date Review Completed:	10/15/2007
Designation Number:	[redacted]
Drug Generic Name:	Sotalol
Trade Name:	So-Aqueous™
Chemical name:	n/a
Code name:	n/a
Sponsor:	Academic Pharmaceuticals. 21 N. Skokie Highway, Suite G-3 Lake Bluff, IL 60044
Contact Information:	John Somberg, MD President Academic Pharmaceuticals. 21 N. Skokie Highway, Suite G-3 Lake Bluff, IL 60044 Tel: (847) 735-1170 Fax: (847) 735-1173 e-mail: jsomberg.api@comcast.net
Source of Drug Product:	[redacted]
Regulatory Status:	Sotalol has been designated twice before by this office, once for the treatment of life-threatening ventricular tachyarrhythmias, and once for the prevention of life-threatening ventricular tachyarrhythmias. The designation for prevention of life-threatening ventricular tachyarrhythmias was subsequently administratively withdrawn by this office. The designation for treatment of life-threatening ventricular tachyarrhythmias was approved to market October 30th, 1992. In addition to this indication, sotalol has also been approved for the indication of maintenance of normal sinus

	rhythm in patients with symptomatic atrial fibrillation or flutter who are currently in normal sinus rhythm. Sotalol, per the sponsor has been approved for marketing in more than 50 foreign countries.
Proposed Indication:	Initiating or continuing sotalol administration when oral administration is indicated by sotalol product labeling, but is not possible.

1. Background of Disease or Condition

Arrythmias refer to abnormal heart rhythms which may arise from a variety of etiologies and vary in severity from generally inconsequential (premature atrial contraction) to life threatening (sustained ventricular tachycardia). If the abnormal signal arises in the atria the dysrythmia is referred to as atrial (atrial flutter, atrial fibrillation, multifocal atrial tachycardia) or superventricular. Aberrant rhythms such as torsaddes de pointes or Wolf Parkinsons White syndrome may arise from the ventricles. Any ventricular aberrant rhythm leading to sustained ventricular tachycardia is life threatening and must be treated immediately.

Arrymthias may arise from one of three basic mechanisms, re-entrant dysrhythmias, abnormal automaticity and triggered dysrhythnias. Of the three the re-entrant arrhythmias are the most common. Such arrhythmias basically involve a "short" of the normal cardiac conduction pathway such that a shorter and self-sustaining pathway becomes established.

Sotalol is a class II and class III antiarrythmic with both beta-blocking effects and effects on cardiac action potential duration.[i],[ii]

2. Scientific Rationale

The Office of Orphan Products awards designation based off the active moiety of small molecules such as Sotalol.

[redacted]

[redacted]

For this reason, though there has been a change in formulation, this office considers intravenous sotalol to be identical to oral Sotalal,. Oral Sotalol has been evaluated by the FDA and considered safe and effective for marketing in the treatment of life threatening ventricular arrhythmias as well as maintenance of normal sinus rhythm in patients with symptomatic atrial flutter or fibrillation. Therefore, IV sotalol is considered to have adequate scientific rationale for use in these indications.

3. Disease Prevalence

The sponsor presents data from a proprietary marketing database that in 2006 there were 1,657,000 total prescriptions written for sotalol. The sponsor then estimates that each prescription would last from an eighth to a quarter of the year which would give a range of 276,166 to 414,250 patients on sotalol in a given year. The sponsor then states, though without references, that the rate of heart failure per year in this patient group could be as high as 25%. As only hospitalized patients would receive IV sotalol, this would place an upper limit on prevalence of 25% * 414,250, or 103,562.

The sponsor also presents the written testimony of four experts in the field that the prevalence of use of IV sotalol would be under 200,000 patients. Unfortunately none of the queried experts provides an exact figure for prevalence. The sponsor presents various other methodologies, starting from number of cardiac arrests, number of implanted defibrillators and estimates of prevalence of atrial flutter/fibrillation, for attempting to estimate the prevalence of IV sotalol. However, none of these approaches is as direct or compelling as the estimate from total sotalol prescriptions or the testimony of numerous experts in the field. For the purposes of Orphan designation the prevalence of IV sotalol use is considered to be 104,000.

Reviewer Comment:

As was noted in the regulatory section, sotalol has previously received Orphan Designation and subsequent approval to market for the indication, "treatment of life-threatening ventricular tachyarrhythmias". The, market approval and therefore start of Orphan exclusivity occurred on October 30th of 1992 and ran for seven years until October 30th of 1997. Therefore, the former Orphan approval for sotalol in no way blocks the sponsor of the current application from bringing the identical product to market for the same indication. Thus while the current sponsor is not blocked from marketing IV sotalol, the question still remains as to whether the current application may be granted Orphan designation or is blocked by the previous Orphan designation of oral sotalol.

There are two ways to view the sponsor's current application. One is to take the position that the current indication is different from the previous one. This position is supported by the finding that sotalol has by this time not only been approved for its Orphan indication of sustained ventricular tachycardia but also for the more highly prevalent condition of maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation or atrial flutter. As detailed above, the sponsor does a

reasonable job of deriving a prevalence estimate for where IV sotalal might be of use in these two groups of patients.

The second way of viewing this application is that, because the indication fundamentally overlaps that of the approved Orphan product they are blocked from receiving Orphan designation. In such cases of having an identical product for an identical marketed Orphan product a sponsor may make a claim of clinical superiority. By demonstrating clinical superiority the sponsor avoids the necessary refusal to grant Orphan designation detailed in CFR § 316.25(a)(3) for

> *"A drug that is otherwise the same drug as one that already has orphan drug exclusive approval for the same rare disease or condition and the sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug."*

Clinical superiority is itself addressed and defined in CFR § 316*.3(3)(i-iii). The same drug may be considered clinically superior if in comparative studies there is demonstrated greater safety or efficacy, or*

> *"In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care" CFR § 316.3(3)(iii)*

The sponsor does not provide any peer-reviewed articles bolstering their contention that in certain cases patients will not be able to receive oral sotalol. Likely such studies have not been performed. It would seem obvious, however, that such a minority of patients with ventricular or atrial arrhythmias exist and are likely some of the most serious patients. Moreover, despite the absence of peer-reviewed medical literature the sponsor does obtain the testimony of more than three experts in this field. In fact five letters of expert testimony are provided by the sponsor. Not only do all these experts offer an opinion on the prevalence of the requested indication but all of them also explicitly testify that a minority of their patients are unable to receive oral sotalol and these patients would benefit from the availability of IV sotalol.

In view of the clarity of the sponsor's argument that some patients with ventricular or atrial arrhythmias will be NPO and thus require an IV formulation of sotalol, as well as the testimony of five experts in the field that this is in fact an issue of clinical relevance, it is accepted that the IV formulation of sotalol comprises a major contribution to patient care.

Therefore, the sponsor might be approved for Orphan designation both by considering the current indication to be different than the original Orphan designation, which did not include atrial arrhythmias, or by considering the IV formulation to be a major contribution to patient care. Likely because of the closeness, and areas of clear overlap, between the currently requested indication and the previously approved Orphan indication it is best to emphasize the major contribution to patient care provided by this change in formulation.

4. **Evaluation and Recommendation**

Pursuant to 21 CFR ¶316.24, it is recommended that the sponsor be awarded Orphan drug designation for So-Aqueous™ in initiating or continuing sotalol administration when oral administration is indicated by sotalol product labeling, but is not possible.

_____

Paul D. Maher, MD MPH
LT CMDR, USPHS

Concurrence:

_____ Date: _____

Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development

[redacted]

[i] Stahmer Sarah A., MD*, Cowan Robert MD. Tachydysrhythmias. Emerg Med Clin N Am 24 (2006) 11–40

[ii] Center for Drug Research and Evaluation, Sotalol approved drug labeling. Accessed at: http://redpoll.pharmacy.ualberta.ca/drugbank/drugBank/FDA_labels/075237.pdf

[iii] Wishart DS et al., DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 1;34

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Review of Orphan-Product Designation Request Amendment

Application number: [redacted]

Date received: 06-19-2008
Date assigned: 07-07-2008
Date completed: 07-11-2008

Proposed indication: Ventricular tachycardia, ventricular fibrillation, or the maintenance of sinus rhythm in patients converted from atrial fibrillation or atrial flutter when initiating or continuing sotalol administration when oral administration is not possible

Drug generic name: sotalol

Drug trade name: So-Aqueous

Sponsor: Academic Pharmaceuticals
21 N. Skokie Highway, Suite G-3
Lake Bluff, IL 60044

Sponsor's contact: John Somberg, M.D.

Background

This submission is a request for re-consideration of denied orphan designation for intravenous sotalol [redacted]. The stated indication is "ventricular tachycardia, ventricular fibrillation, or the maintenance of sinus rhythm in patients converted from atrial fibrillation or atrial flutter when initiating or continuing sotalol administration when oral administration is not possible". OOPD's points in the denial letter are reproduced below, followed by the sponsor's reply and/or my review comment.

(1) "This office designates orphan products for a specific disease or condition. The requested indicate as currently worded does not appear to be a disease or condition".

The sponsor has responded that the requested indication(s) are those in FDAS approved labeling for orally administered sotalol, and therefore qualify as specific diseases or conditions (sustained ventricular tachycardia that is life threatening/maintenance of normal sinus rhythm in highly symptomatic patients with atrial flutter or fibrillation). I agree.

(2) "You would need to clarify why IV sotalol would not be expected to be used to induce normal sinus rhythm in a significant percentage of patients with cardiac arrhythmias."

The sponsor has presented a cogent discussion of the drug's safety profile which makes it unsuitable for cardioversion, as opposed to maintenance of normal sinus rhythm following successful cardioversion using other agents or devices. The sotalol entry in 2008 AHFS Drug Information® specifically notes that because of the drug's arrhythmogenic potential, use of sotalol for less severe arrhythmias, even if symptomatic, is not recommended by the manufacturer, and that treatment of asymptomatic ventricular premature complexes should be avoided. This is even more compelling for the intravenous formulation, since the risk of Torsade ventricular tachycardia is greater when delivered by this route.

(3) "Per the Agency for Healthcare Quality and Research, in 2005 there were a total of 696,551 patients with hospital disease diagnosis of some form of cardiac dysrhythmias. As the two previously approved indications for sotalol are for treatment of life threatening ventricular arrhythmias and maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation or flutter who are currently in normal sinus rhythm, it is not unreasonable to predict whether IV sotalol might make for a reasonable agent to induce normal sinus rhythm in patients with arrhythmias".

As noted above under item 2, the safety profile of this drug precludes most of the ~700,000 patients with cardiac arrhythmias. Using hospital discharge diagnoses, the sponsor estimated the potential use of sotalol for ventricular patients at 15,500. They then added the high estimate of potential use in atrial cases (83,000) for a total of 98,500. Thus, they estimate that appropriate use of sotalol would be 15% of the total arrhythmia population, or approximately 100,000 patients.

An alternative approach to this calculation would be to obtain drug usage data from a vendor, and then attempt an estimate of the proportion likely to need IV administration in a year. This approach, however, would not necessarily be more accurate, given the limitations of utilization data, and the assumptions needed to estimate the IV subset. Even if the sponsor's estimate is low, it seems very unlikely that the subset of patients needing an intravenous formulation would exceed 200,000 per year.

(4) "Finally, this office designates a product based on a drug's active moiety without regard to drug formulation. CFR § 316.25(a)(3) elaborates on the requirement to deny Orphan Designation for the following",
"A drug that is otherwise the same drug as one that already has orphan drug exclusive approval for the same rare disease or condition and the sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug". Clinically superiority is itself addressed and defined in CFR § 316.3(3)(i-iii). The same drug

[redacted]

may be considered clinically superior if in comparative studies there is demonstrated greater safety or efficacy, or "In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care" CFR § 316.3(3)(iii). Therefore, if the designation for IV sotalol is requested for the same disease as the previously marketed Orphan oral sotalol, it would prove necessary to provide a medically plausible hypothesis for the clinical superiority of IV sotalol in order to receive Orphan Designation".

The sponsor provides a compelling case that patients who cannot receive oral sotalol constitute an orphan population needing the IV formulation. They state that the very small market size explains the lack of an IV formulation after 15 years of oral formulation marketing. The submission includes information supporting their assertion that nasogastric drug administration of the oral formulation results in greater drug concentration variability and diminished absorption, a particular problem for drugs such as sotalol that have a limited concentration range for achieving efficacy while avoiding toxicity.

Evaluation and recommendation

I recommend that the sponsor, Academic Pharmaceuticals, be granted Orphan-Drug Designation of So-Aqueous (sotalol intravenous) for ventricular tachycardia, ventricular fibrillation, or the maintenance of sinus rhythm in patients converted from atrial fibrillation or atrial flutter when oral administration is not possible. The basis for this recommendation is that the sponsor has provided a plausible hypothesis for the clinical superiority of intravenous sotalol in an Orphan population.

Kathryn O'Connell 7/18/08
Kathryn O'Connell MD PhD
Reviewing Medical Officer
OOPD/OC/FDA

I/H 5
7/18/08

Concurrence:

Timothy R. Coté 21 JUL 08
Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development

[redacted]