

3

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 15, 1994
FROM: James Ramsey, Ph. D.
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THROUGH: David Feigal, M.D., M.P.H.
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TO: Murray Lumpkin, M.D.
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Center for Drug Evaluation and Research
SUBJECT: Cyclosporine-Request for Reclassification

I have reviewed the data submitted by Sandoz in their submission of October 14, 1994, wherein they responded to CDER's request to provide a scientific basis for the language "in dilute solution" as a criterion for an antibiotic. In this review, I have responded point-by-point to the rationale and discussion (vol. 1, pp.001-004) provided by the sponsor to support their request for reclassification. For clarity purposes in the text provided below, rationale and discussion provided by the sponsor are in bold type, my comments in response are in non-bolded type.

Sandoz:

Sandimmune[®] (cyclosporine)
NEORAL[™] (cyclosporine, microemulsion)
Request for Reclassification

INTRODUCTION

Section 507 (a) of the Federal Food, Drug, and Cosmetic Act defines an antibiotic drug as "any drug intended for use by man containing any quantity of any chemical substance which is produced by a microorganism and has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance)."

The key phrase from the above definition is "has the capacity to inhibit or destroy microorganisms in dilute solution" (emphasis added). There have been various interpretations of dilute solution to mean either "in vitro" plate levels or "animal in vivo" plasma or serum levels or "human in vivo" plasma or serum levels. The different interpretations of dilute solution create confusion and may lead to classification of drugs with no clinically relevant antimicrobial activity as antibiotics.

FDA COMMENT:

There are 4 key phrases in the above definition of an antibiotic which are the following:

- 1) any chemical substance which is produced by a microorganism
- 2) has the capacity to inhibit or destroy microorganisms
- 3) in dilute solution
- 4) including the chemically synthesized equivalent of any such substance.

As will become apparent in the following discussion, the relative importance of all of these key phrases, not just "in dilute solution" are pertinent to the sponsor's request for reclassification and will be referred to where appropriate. Regulations are, by necessity, written in a manner that leaves them subject to broad interpretation. The exclusive focus on a specific or exact definition of circumstances described in regulations often creates more problems than are solved. Consequently, it has always been the policy of this Agency to interpret regulations based upon the collective body of evidence available upon which to make decisions.

Sandoz:

Proposed Definition by Regulation

As a clinically relevant and valid interpretation of "in dilute solution" we propose that minimal inhibitory concentrations (MIC's) of the chemical substance against human pathogens be achievable in human serum, plasma or other relevant body solution (eg, urine) following administration of recommended doses of the drug in the target patient population.

This definition would insure that drugs with in vitro antimicrobial activity only at concentrations that cannot be safely achieved and maintained in man would not be inappropriately classified as antibiotics for human use.

FDA COMMENT:

This argument presupposes that MIC's can be determined for all relevant human pathogens and, furthermore, that clinically relevant antibiotic activity is always highly correlated with patient plasma drug levels approximating MIC values determined in in vitro preclinical assays.

The supposition that MIC's can be determined for all relevant human pathogens is false. Minimum inhibitory concentration is a term appropriately applied to bacterial, fungal and some parasite cell culture assays only. For microorganisms requiring a host cell to support their replication in in vitro cell culture, such as viruses

abbreviated as IC_{50} or IC_{90} (i.e., the concentrations of drug necessary to inhibit growth 50% or 90%, respectively), are used to express drug activity, not MIC values. Furthermore, some microorganisms, such as *Mycobacterium leprea*, cannot be cultivated in vitro and, therefore, an MIC value cannot be determined.

In addition, the suitability of assay methodologies used in the determination of MIC values is highly relevant to characterization of drug activity. Variations in culture media, organism load, organism strain, incubation conditions, drug exposure time, and experimental design have the capacity to influence MIC values. Acceptance of MIC values without knowledge of how they were determined may satisfy the specific focus on the definition of "inhibition in dilute solution" but knowing how they were determined still requires an evaluation of the collective body of evidence available upon which to make a decision with respect to relevance.

Another concern is that the focus on in vitro MIC's for determining antimicrobial activity completely ignores data from animal model studies. For some microorganisms and for some drugs, in vitro MIC values are less reliable than animal model data for predicting relevant human drug activity. Drug activity in animal studies is usually expressed in terms of effective dose (ED_{50} and ED_{90}) or protective dose (PD_{50} and PD_{90}) and are defined as the drug dose that reduces microorganism load or protects survival in infected animals 50% and 90%, respectively. The terms effective or protective dose are preferred because following drug administration, the drug concentration in the target organ(s) may vary over time or be unknown, depending upon the organ(s) examined. Thus, an MIC value for animal dosing is not a valid parameter to calculate.

The assumption that clinically relevant antibiotic activity will correlate with in vitro MIC values determined for all human pathogens is unwarranted. While MIC values often are predictive of potential human clinical activity, some antibiotics are known to be clinically active against some species of Enterobacteriaceae even though achievable plasma drug concentrations are substantially below the MIC values determined for these microorganisms. On the other hand, it is not uncommon to encounter circumstances where human plasma drug concentration exceeds in vitro MIC values in the absence of clinical efficacy. The reasons for these observed lack of correlations between MIC values and human antibiotic activity are frequently unclear and unpredictable.

Another problem in specifically focusing on the fact that plasma drug concentrations must be equal to in vitro MIC values before one could expect to demonstrate clinically relevant antibiotic activity is that host drug metabolism is not considered. For example,

cyclosporine is extensively metabolized in the host liver and the

parent drug concentration in plasma drops between dosing. However, the plasma concentration of cyclosporine metabolites may rise in some patients and actually exceed the plasma concentration of the parent drug (Sandoz submission Ref 2 - Yee GC, Solomon DR. Cyclosporine. In: Evan WE, Schentag JJ, Jusko WJ, eds. Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring. 3rd ed. Vancouver, Washington: Applied Therapeutics, Inc; 1992:28-1 - 28-40).

The antimicrobial activities of cyclosporine metabolites have not been adequately characterized although it is known that many retain their immunosuppressive activity. If these metabolites maintain antimicrobial activity as well, matching only parent drug concentration in plasma to preclinical MIC values (determined only for the parent drug) to estimate potential clinical relevance is not valid. Potential clinical antibiotic activity would be the sum of the contributions made by the parent drug and the active metabolites, not just parent drug.

Sandoz:

Classification of Cyclosporine-A: Drug or Antibiotic?

Cyclosporine-A was originally filed as both an oral solution and an intravenous solution in 1982 under the provisions of 505(b) of the Act. The original NDA numbers were 18-773 and 18-772, respectively. A detailed submission chronology for all pending and approved applications is included as Appendix I.

Possibly due to an early publication by Sandoz Pharmaceuticals Division (Ref. 1), which appeared to demonstrate weak antifungal activity in vitro in "dilute solution", these applications were subsequently reclassified as antibiotics (Form 5's 50-574 and 50-573). In addition some animal infection models were studied at extremely high doses (not achievable in man without lethality). It is now clear, however, that maximal plasma concentrations of cyclosporine A, obtained with the highest recommended doses of Sandimmune, do not reach MIC's for any human pathogen for which cyclosporine A has been shown to exhibit in vitro antifungal activity.

FDA COMMENT

The conclusion that animal infection model studies utilized extremely high doses of cyclosporine, not achievable in man without lethality, is premature. Information on bioavailability, pharmacokinetics and pharmacodynamics of cyclosporine in animal species utilized in published studies and how these parameters compare to human circumstances were not addressed by the sponsor. Because of known differences for many drugs with respect to adsorption, distribution, metabolism, and elimination kinetics

among animal species and humans, human equivalent doses for animals often vary substantially when administered on a mg/kg body weight basis. Without including these kind of data in these analyses, correlation of efficacy and toxicity profiles between animal and human studies is less certain (see below). Therefore, without analysis of these parameters, rejection of animal data from being considered in the definition of clinically relevant antibiotic activity, as proposed by Sandoz, is unwarranted.

Sandoz:

In Phase I antibiotic drug development, serum or plasma levels, rather than whole blood levels, of the drug are always evaluated because the serum or plasma is the compartment in which (1) the drug is available to bind to blood borne bacterial or fungal organisms and (2) the drug is available to supply third compartments (e.g., the middle ear). Although drug bound to the cellular elements of blood may be in equilibrium with the plasma and serum, C_{max} levels in the plasma or serum are more relevant than in whole blood.

Cyclosporine levels are usually measured in whole blood to reduce variability of the assay, but can also be measured in plasma. Plasma levels of cyclosporine are approximately equal to 40% of whole blood levels (Ref. 2). Since there is little data on serum concentrations of cyclosporine, plasma concentrations are appropriate to assess the antimicrobial activity of cyclosporine.

The highest plasma levels of cyclosporine are obtained during the time immediately prior to and for 1-2 weeks following transplant. Current Sandimmune labeling indicates that the maximum recommended doses are 14-18 mg/kg/day. Peak (C_{max}) whole blood cyclosporine levels are generally in the range of 1000-1500 ng/mL (as determined by HPLC) although occasionally levels of 2000 ng/mL are observed (Ref. 2, 3, and Appendix II). Since plasma levels of cyclosporine are 40% of whole blood levels, maximal plasma levels of cyclosporine are in the range of 400-800 ng/mL. Maintenance whole blood levels of cyclosporine are usually below 350 ng/ml consistent with plasma levels of up to 140 ng/ml.

FDA COMMENT

In general, these statements by the sponsor give a balanced opinion of published information relevant to their content. The important aspects of these facts are as follows: 1) there is a difference in blood and plasma cyclosporine levels, 2) concentrations stated are for parent drug and do not include metabolites, 3) peak levels of parent drug are substantially higher than trough levels, 4) assays for the measurement of cyclosporine give variable results (comparisons of results are valid if performed by the same

procedure), 5) bioavailability of oral doses is approximately 30% (range, 5%-90%), 6) therapy is long-term, and 7) the maximum recommended human initial doses are 14-18 mg/kg/day given orally.

Sandoz

Cyclosporine has not been shown to have activity against bacteria. MIC's for common pathogenic bacteria including *Streptococcus faecalis*, *Bacillus subtilis*, *E. Coli* K12, *Salmonella typhimurium* and *Pseudomonas aeruginosa* are all over 100,000 ng/mL (Ref. 1) Therefore, maximal achievable plasma levels are over 100 times less than the MIC for any of these potential pathogenic bacteria. Therefore, cyclosporine should not be classified as an antibacterial agent.

FDA COMMENT

After review of the data submitted by the sponsor and that retrieved from the National Library of Medicine database by this reviewer, no credible evidence or rationale was identified that would support the conclusion that cyclosporine has any clinically relevant antibacterial activity.

Sandoz

In vitro activity against selected pathogenic fungi has also been reported (Ref. 1 and 4). Table 1 lists the MIC's for these fungal pathogens.

Table 1. MIC's (ng/ml) for Cyclosporine for Fungal Pathogens

<u>Pathogen</u>	<u>MIC</u>	<u>Reference</u>
<i>Saccharomyces cerevisiae</i>	> 100,000	1
<i>Kloekera apiculata</i>	> 100,000	1
<i>Hansenula anomala</i>	> 100,000	1
<i>Pythium debaryanum</i>	> 100,000	1
<i>Rhodoturla rubra</i>	100,000	1
<i>Anixopsis steracoraria</i>	100,000	1
<i>Cospora lactis</i>	31,600	1
<i>Aspergillus flavus</i>	> 10,000	2
<i>Aspergillus fumigatus</i>	> 10,000	2
<i>Candida albicans</i>	> 10,000	2
<i>Candida tropicalis</i>	> 10,000	2
<i>Histoplasma capsulatum</i>	> 10,000	2
<i>Blastomyces dermatidis</i>	> 10,000	2
<i>Neurospora crassa</i>	10,000	1
<i>Trichophyton quickaneum</i>	10,000	1
<i>Aspergillus niger</i>	3,000	1
<i>Curvularia lunata</i>	1,000	1
<i>Coccidioides immitis</i>	1,000	2

As stated above, the maximum plasma concentrations of cyclosporine that may be achieved with recommended doses are in the order of 400-800 ng/mL. Therefore, cyclosporine should also not be classified as an antifungal agent.

FDA COMMENT

The sponsor's conclusion that cyclosporine should not be classified as an antifungal agent, even when using their own proposed definition of "dilute solution", is premature.

The sponsor cited only 2 references in which in vitro determined MIC's for fungal pathogens were reported. Two others, both highly relevant to this report, are summarized below.

Reference 1 - Mody, Christopher H., Galen B. Toews, and Mary F. Lipscomb. 1988. Cyclosporin A Inhibits the Growth of Cryptococcus neoformans in a Murine Model. Infection and Immunity. 56:7-12.

In this study, Mody et al. reported the effect of cyclosporine (Sandimmune IV) on the growth of Cryptococcus neoformans strains 145A, ATCC 36556, and H99 in cell culture and in mice.

For in vitro studies, C. neoformans was cultured for 48 hr in both neopeptone or yeast nitrogen base broth in the presence of cyclosporine at 0.1 or 1.0 ug/ml. Growth of C. neoformans in broth cultures without additives or with Cremaphor-EL (the vehicle for Sandimmune IV) at a concentration equal to that present in the 1.0 ug/ml cyclosporine broth cultures, served as controls. The pH of the culture media with Sandimmune IV, Cremaphor-EL, or without additives was 6.6, 6.7 and 6.2, respectively. Growth inhibition was determined by plating serial 10-fold dilutions of the 48 hr broth cultures onto agar medium and enumerating the number of colony forming units (CFU's) observed after an additional incubation for 48 hr.

Results showed that for strains 145A, ATCC 36556 and H99, 0.1 ug/ml cyclosporine inhibited growth approximately 95, 75 and 98%, respectively; whereas, at 1.0 ug/ml, inhibition was 100% for all strains. Concentrations between 0.1 and 1.0 ug/ml were not evaluated. Similar results were observed with both broth culture media utilized. Growth in media containing Cremaphor-EL and in media without additives was equivalent, suggesting that the pH differences in these cell cultures did not affect fungal growth.

However, many drugs are known to exhibit significantly different antimicrobial activity as a function of pH and blood pH is approximately 7.3. Thus, the possibility exists that cyclosporine

MIC values would be less if evaluated at pH 7.3. Activity determined in mice (see below) at cyclosporine blood concentrations comparable to MIC values shown above would suggest that antifungal activity is maintained at pH 7.3.

These results establish that cyclosporine is fungicidal for C. neoformans in vitro with an MIC value of ≤ 1.0 ug/ml. Different types of assays are used to differentiate fungistatic from fungicidal activity of drugs. However, results from this fungicidal assay suggest that cyclosporine fungistatic MIC values for C. neoformans strains could be ≤ 0.1 ug/ml.

Mody et al. also evaluated the antifungal activity of cyclosporine against C. neoformans infection in C57BL/6 mice at 20, 50 and 75 mg/kg administered subcutaneously for 7 days. Because cyclosporine administered to mice via this route had not been previously reported, they determined levels of cyclosporine in blood 24 hr after the last dose. Cyclosporine was extracted and quantified by high-performance liquid chromatography (HPLC). Results showed that trough blood levels of 0.30 ± 0.03 , 1.50 ± 0.10 , and 2.75 ± 0.85 ug/ml were achieved for the above doses, respectively. Corresponding plasma values would be expected to be 0.12, 0.60, and 1.10 ug/ml based upon the observation that plasma cyclosporine concentrations are 40% of blood concentrations. Concentrations of cyclosporine metabolites in mouse blood were not reported.

These results show that trough blood/plasma cyclosporine concentrations in mice following 20 mg/kg subcutaneous injection are comparable to that observed for human transplant patients receiving recommended oral dosing. However, no data were provided to compare peak concentrations between species or to determine concentrations or antimicrobial activities of metabolites present in blood/plasma.

In addition to in vitro studies, Cyclosporine antifungal activity was evaluated by these investigators in mice inoculated intratracheally with C. neoformans. Results obtained with 20 mg/kg s.c. treatment show a highly significant reduction in fungal CFU's within 4 days of treatment (Table 2). Data derived from studies utilizing 50 and 75 mg/kg were not critically reviewed because blood levels produced at these doses were at or above the upper range of levels achievable in humans without inducing severe toxicity. Without additional pharmacokinetics data in mice to compare to human data, assessment of antimicrobial relevance at these higher doses is impaired.

TABLE 2. Effect of cyclosporine on *C. neoformans* in the lungs of mice after intratracheal inoculation^a.

Cryptococcal strain	CFU (log ₁₀)/organ in lungs at:		Animal treatment
	Deposition	Day 4	
145A	3.79 ± 0.12	2.60 ± 0.12 ^b	Cyclosporine
		4.56 ± 0.05	Control
36556	4.21 ± 0.05	2.62 ± 0.19 ^b	Cyclosporine
		4.76 ± 0.11	Control
H99	5.41 ± 0.05	4.92 ± 0.02 ^b	Cyclosporine
		5.41 ± 0.06	Control

^aMice received Cyclosporine (20 mg/kg per day s.c.) or Cremaphor-EL (control solution) equivalent to 20 mg/kg per day beginning on the day before inoculation. n = 5 in each group.

^bp<0.001.

These results show that the MIC of cyclosporine against *C. neoformans*, determined *in vitro* and shown to be active in an infected animal model, is achievable in human plasma following administration of recommended doses of cyclosporine in transplant patient populations.

Reference 2 - Hoepfich, Paul D. and Joanne M. Merry. 1987.

Comparative Efficacy of Forphenicol, Cyclosporine, and Amphotericin B in Experimental Murine Coccidioidomycosis. *Diagn. Microbiol. Infec. Dis.* 6:287-292.

Hoepfich and Merry, utilizing a broth dilution assay, determined the *in vitro* MIC and minimum fungicidal concentrations (MFC) of cyclosporine and Amphotericin B against *Coccidioides immitis* strain *Silveria* and 10 clinical isolates as shown in the Table 3 below.

Table 3. Susceptibility of Strain *Silveria* (Geometric Means of Triplicate Determination ± SE) and 10 Clinical Isolates (Geometric means ± SE) of *C. immitis* was Tested *In Vitro* Against Cyclosporine and Amphotericin B used to Treat Experimental Murine Coccidioidomycosis

Drug	<i>C. immitis</i>	MIC (range)	MFC (range)
		ug/ml	
Cyclosporine	<i>Silveria</i>	0.3	>20
	10 isolates	0.3 ± 0.04 (0.15-0.60)	>20
			>20
Amphotericin B	<i>Silveria</i>	0.56	NR
	10 isolates	0.56 ± 0.21 (0.30-2.50)	>20
			>20

NR - not reported

In this study, *in vitro* MIC values indicated that cyclosporine possessed antifungal activity against *C. immitis* greater than that

observed for Amphotericin B, an antibiotic drug approved for the treatment of disseminated forms of coccidioidomycosis in human patients. A minimum fungicidal concentration of cyclosporine against *C. immitis* was not elicited even at concentrations of 20 ug/ml. However, these *in vitro* results demonstrate that fungistatic MIC values, determined for a laboratory strain and 10 clinical isolates of *C. immitis*, are achievable in human plasma following administration of recommended doses of cyclosporine in transplant patient populations.

Antifungal activity was also determined in mice injected intratracheally with 100 arthroconidia of strain Silveria. Seventy-two hours after inoculation, groups of 10 mice were intravenously administered the following treatments: a) 0.1 ml of 5% glucose/day for 23 doses (controls); b) cyclosporine at 50, 100, or 200 mg/kg body wt/day for 23 doses; c) Amphotericin B at 0.75 or 1.50 mg/kg body wt on alternate days for 12 doses. Mice surviving at 24 days post-treatment were sacrificed and fungal burden determined in lungs, livers and spleens.

Results obtained showed that survival of controls, 50, 100, and 200 ug/kg cyclosporine, and 0.75 and 1.50 ug/kg Amphotericin B treated mice was 20%, 90%, 60%, 60%, 100% and 100%, respectively. Fungal growth in necropsied tissue from cyclosporine treated mice was slightly less than controls. Cultures of lung tissue from 60% of Amphotericin B treated animals were negative for fungal growth; remaining Amphotericin B treated animals with culture positive lung tissue showed significantly reduced fungal growth.

Survival of cyclosporine treated mice was higher than untreated mice. However, because survival was less at high doses of cyclosporine (100 and 200 mg/kg, survival of 60%) than at the lowest dose evaluated (50 mg/kg, survival of 90%), it is possible that a lower dose with less immunosuppressive activity would prove to have greater benefit but, unfortunately was not evaluated.

Adequate and well controlled human clinical studies for the evaluation of cyclosporine antifungal activity were not found in the literature. Data from published human clinical studies, reporting observations that fungal infections were less/more prevalent in transplant patients or in patients undergoing cyclosporine treatment for autoimmune disease, were insufficient to clearly establish cyclosporine's contribution to changes in fungal prevalence in these patient populations.

Published literature reports relative to potential or actual cyclosporine antifungal activity were scant, but certainly greater than that found for antibacterial activity. Data from these *in vitro* MIC and *in vivo* animal studies demonstrated that cyclosporine possessed antifungal activity for at least two human pathogens,

Cryptococcus neoformans and Coccidioides immitis, at concentrations achievable in plasma following administration of recommended doses of the drug in target patient populations. With respect to fungi, there is rationale to classify cyclosporine as an antibiotic, even if the definition of dilute solution as proposed by Sandoz is used.

Sandoz

Cyclosporine has also been reported to exert weak activity against a variety of human parasites (Ref. 5-23) including malaria. However, activity against malaria is only observed at doses of cyclosporine that are nephrotoxic in animals (Ref. 24, 25, and 26). Therefore, Sandoz believes that cyclosporine should be not classified as an antiparasitic agent.

FDA Comment

The claim that activity against malaria is only observed at doses of cyclosporine that are nephrotoxic in animals (Ref. 24, 25, and 26) is inaccurate. Nephrotoxicity was only reported in studies with owl monkeys and was thought to be due to the combined effects of malaria and drug toxicities (Ref. 24).

In mice inoculated with Plasmodium yoelii or Plasmodium berghei and administered 25 mg/kg cyclosporine s.c. for 4 consecutive days, parasitemia and death in 15 of 15 and 9 of 10 mice, respectively, was prevented (Ref. 25). Nephrotoxicity was not reported. In an additional experiment, these authors investigated the potential of cyclosporine to cure existing parasitemia produced by P. yoelii (L), P. yoelii (NL), and P. berghei. Two consecutive cyclosporine doses of 25 mg/kg administered s.c. 6 or 8 days after infection was initiated was effective at reducing parasitemia to below detectable levels. However, after 5 days parasitemia reappeared, persisted at relatively low levels for another 5 days and subsequently became undetectable. This pattern was seen even if treatment was extended from 2 days to several weeks except for infections with P. yoelii (NL) in which recrudescence did not re-occur. Resistance to cyclosporine in malaria parasites in animals that relapsed was common. Although not investigated, it would be of interest to determine if combination therapy with 2 or more effective drugs would prevent resistance emergence.

Again bioavailability and pharmacokinetics of cyclosporine was not reported in these studies. However, if blood levels in this study were comparable to those determined in the C. neoformans study described above, these data suggest that cyclosporine has antimalarial activity at plasma cyclosporine levels achievable in transplant patients.

There is a considerable body of literature available on cyclosporine effects in parasite infected animal models, not just

with respect to malaria. Before discounting the weight of evidence from these studies in the effort to determine that cyclosporine is not an antiparasite drug, a comprehensive evaluation of relevant animal and human bioavailability, pharmacokinetics and pharmacodynamics data should be conducted.

Sandoz

Cyclosporine exerts some activity against HIV (Ref. 27). However, approved antiviral drugs are not classified as antibiotics. Therefore, reported antiviral activity of cyclosporine is not relevant to the classification of cyclosporine as an antibiotic.

FDA Comment

The conclusion that reported antiviral activity of cyclosporine is not relevant to the classification of cyclosporine as an antibiotic is incorrect. For example, Vidarabine is a purine nucleoside obtained from fermentation cultures of Streptomyces antibioticus. It possesses in vitro and in vivo antiviral activity against Herpes simplex types 1 and 2, Varicella-Zoster, and Vaccinia viruses. Vidarabine is an FDA approved antibiotic drug indicated for the treatment of acute keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types 1 and 2. The sponsor failed to consider all of the 4 key phrases in the definition of an antibiotic drug illustrated in the beginning part of this report. Because Vidarabine, an antiviral drug, meets all of the requisite conditions it is considered an antibiotic drug.

Reference 27 in the Sandoz submission indicates that cyclosporine possesses anti-HIV activity at a concentration of 0.1 ug/ml when added to cell cultures prior to or during acute infection. In addition, numerous reports are in the literature that are relevant to determining cyclosporine antiviral activity. In view of the oversight that antivirals are not classified as antibiotics, the sponsor should consider further the status of cyclosporine's antiviral activity before concluding that cyclosporine antiviral activity is irrelevant to reclassification.

Sandoz

It is also noteworthy that cyclosporine is an immunosuppressive agent and that the risk of some bacterial, fungal and viral infections is increased during cyclosporine therapy (Table 2, Sandimmune[®] package insert, and Ref. 28, 29, and 30). It is also well recognized that most infections occur within the first two to eight weeks after transplant, at the time when cyclosporine levels are highest. This provides further evidence that plasma, blood and tissue levels of cyclosporine obtained during cyclosporine therapy provide no relevant antimicrobial activity.

Table 2. From Approved Sandimmune[®] Package Insert

Infectious Complications in the Randomized Renal Transplant Patients

Complication	Sandimmune [®] Treatment	Standard Treatment [*]
	(N = 227) % of Complications	(N = 228) % of Complications
Septicemia	5.3	4.8
Abscesses	4.4	5.3
Systemic Fungal Infection	2.2	3.9
Local Fungal Infection	7.5	9.6
Cytomegalovirus	4.8	12.3
Other Viral Infections	15.9	18.2
Urinary Tract Infections	21.1	20.2
Wound and Skin Infections	7.0	10.1
Pneumonia	6.2	9.2

*Some patients also received ALG.

FDA Comment

Reports in the literature suggest that the magnitude of infections in transplant patients may depend upon the level of immunosuppression produced during therapy to prevent organ rejection. The animal model data reviewed above suggest that better antimicrobial activity is achieved at doses that are high enough to elicit antimicrobial effects but low enough that severe immunosuppression is not in evidence. The argument that infections are most severe during early periods following transplantation when dosing of patients is higher is consistent with this observation. Continued research efforts incorporating antimicrobial activities of immunosuppressive drugs may contribute significantly to improvements in clinical care of transplant patients.

CONCLUSIONS:

Credible data to demonstrate that cyclosporine has clinically relevant antibacterial activity was not found in the literature.

Cyclosporine has been shown to possess antifungal activity against 2 relevant human pathogens, Cryptococcus neoformans and

13

Coccidioides immitis at MIC's achievable in human plasma following administration of recommended doses of the drug in transplant patient populations. Moreover, MIC values for cyclosporine, reported for C. immitis strain Silveria and 10 clinical isolates, were shown to be lower than that determined for Amphotericin B, an antibiotic drug approved for the treatment of disseminated forms of coccidioidomycosis in human patients.

Data in the published literature suggest that cyclosporine has antiviral activity at relevant clinical concentrations. The sponsor discounted these data based upon the incorrect premise that approved antiviral drug products were not classified as antibiotic drugs. These data should be comprehensively evaluated by the sponsor and submitted for review.

Published reports on cyclosporine antiparasite activity are numerous. However, due to several inaccurate assumptions made by the sponsor, the data in this literature was discounted in their response to the FDA request to define "in dilute solution" to support their request for reclassification. To continue the pursuit of this reclassification objective, data relevant to cyclosporine bioavailability, pharmacokinetics and pharmacodynamics in conjunction with efficacy determinations in animals and humans must be comprehensively addressed.

In summary, even if the sponsor's proposed definition of "in dilute solution" is used as the interpretative criterion for cyclosporine reclassification, data are available in the published literature that would support its continued classification as an antibiotic drug.

RECOMMENDATION

Cyclosporine should remain classified as an antibiotic drug.

