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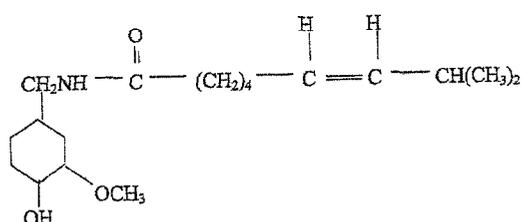
Citizen's Petition

The undersigned submits this petition under Section 508 of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to designate an official name for cis-8-methyl-N-vanillyl-6-nonenamide (the "Compound") different than "zucapsaicin," which is the current official United States Adopted Name for the Compound. Winston Laboratories, Inc. ("Winston") currently has several Investigational New Drug Exemptions (42,979, 46,669, 47,007, and 66,266) on file with the Food and Drug Administration (FDA) to study different dosage forms of the Compound for various clinical indications. These include intranasal civamide for the treatment of episodic cluster headaches and neuropathic pain syndrome, and civamide cream for the treatment of the signs and symptoms of psoriasis and relief of pain due to osteoarthritis. Winston has sought relief from the United States Adopted Names Council ("USAN") and the USAN Review Board with no success. Winston, therefore, requests the Commissioner of Food and Drugs designate an official name for the Compound different than the USAN name.

A. Action requested.

The requested action concerns a novel synthetic chemical, cis-8-methyl-N-vanillyl-6-nonenamide, whose chemical structure is depicted below:

Structure of Civamide



Capsaicin, a naturally occurring chemical derived from the pepper plant, is the trans isomer of the above Compound. By this petition, Winston hereby requests that the Commissioner of Food and Drugs designate an official name for the Compound different than the current official United States Adopted Name for the Compound which is "zucapsaicin." The *de facto* established name for the Compound by the medical and scientific communities is "civamide" (see Appendix 1, Exhibit B). Although "civamide" is Winston's preferred name for the Compound, this petition requests that FDA change the established name of the Compound from "zucapsaicin" to civamide or some other non-confusing name not containing "capsaicin."

Winston believes that the name "zucapsaicin" unnecessarily exposes patients, physicians, pharmacists, health-care and scientific professionals and our company to various types of risk, including the potential for medication errors arising from confusion between the names "zucapsaicin" and "capsaicin."

To maintain consistency in nomenclature across nations, Winston also requests that the Commissioner of Food and Drugs notify the World Health Organization (WHO) of the newly established official name in order to change the International Nonproprietary Name (INN) of the Compound to "civamide" or to some other non-confusing name not containing "capsaicin." If it is not possible to change the INN, Winston nevertheless maintains that the benefit from changing the established name of the Compound in the United States outweighs possible inconsistencies between a new, non-confusing U.S. established name and the existing INN (viz. the case of atomoxetine, whose established name was changed by FDA from tomoxetine, even though the latter remains the INN).

B. Statement of grounds

As stated in its petition to the USAN Review Board (Appendix 1), Winston believes that the name "zucapsaicin" is an inappropriate nonproprietary name for the Compound and violates several fundamental Guiding Principles for Coining United States Adopted Names for Drugs ("Guiding Principles", attached in Appendix 1, Exhibit A), namely:

1. General Rule #4: "A name should be free from conflict with other nonproprietary names and with established trademarks; it should be neither confusing nor chemically misleading."
2. General Rule #5: "Preference should be given to names of established usage provided they conform to these guiding principles and are determined to be free from conflict with existing nonproprietary names and trademarks."

3. Specific Rule #14: "A name coined for a new chemical entity routinely does not specify the stereoisomeric form of the molecule in the nonproprietary name. If the stereochemical configuration has been determined, this information is presented in the chemical name(s) and is reflected in the structural formula..."

In addition to violating several fundamental Guiding Principles, the name "zucapsaicin" unnecessarily exposes patients, physicians, pharmacists, health-care and scientific professionals, and our company to various types of risk:

1. potential damage from medication errors, arising from confusion between the names "zucapsaicin" and "capsaicin";
2. potential damage to the public from non-use of the Compound in cases where it would be beneficial;
3. potential damage to any product(s) incorporating the Compound and thereby to Winston as a corporation; and
4. confusion within the medical and scientific communities, where "civamide" is the *de facto* name of established usage for the Compound.

Below, as presented in the petition to the USAN Review Board, Winston elaborates on the inappropriateness of the name "zucapsaicin" as measured against the Guiding Principles, the negative consequences of the name "zucapsaicin" to numerous parties, and the desirability of changing the Compound's nonproprietary name to a non-confusing alternative, preferably "civamide."

“Zucapsaicin” Violates Several Key Guiding Principles for Nonproprietary Drug Names

The name “zucapsaicin” violates several fundamental Guiding Principles for Coining United States Adopted Names for Drugs.

1. The name “zucapsaicin” violates General Rule #4: “A name should be free from conflict with other nonproprietary names and with established trademarks; it should be neither confusing nor chemically misleading.”

The name “zucapsaicin” is similar to “capsaicin,” the name of the active constituent in several marketed drugs and a term that is already surrounded by considerable confusion as to whether it encompasses synthetic capsaicin, capsaicinoids, and/or capsaicin oleoresin. Indeed, disputes involving the name “capsaicin” have found their way into court. For example, in GenDerm Corp. v. Biozone Labs., Case No. 92C2533, 1992 WL 220638 (N.D. Ill. Sept. 3, 1992), the court enjoined the defendant from labeling its products as capsaicin when the product actually contained “synthetic capsaicin” (a/k/a nonivamide), which has a different composition, formula, and chemical weight than does capsaicin. There is also potential for confusion with the proprietary name Capzasin® which is currently used to market a line of topical analgesic products containing capsaicin.

To further support our concerns regarding the confusability of “zucapsaicin,” Winston commissioned Bruce Lambert, Ph.D. of the University of Illinois –

Chicago, to undertake an assessment of the comparative confusability of the name “zucapsaicin.” Dr. Lambert has developed a computer program that searches databases of drug names to determine how similar, in terms of spelling or pronunciation, a specified drug name is to existing drug names. Dr. Lambert’s program has been used by various organizations including the Institute for Safe Medication Practices to screen proposed drug names for possible look-alike and sound-alike confusion.

For this assessment, Dr. Lambert searched the Multum Lexicon, a large database of brand and generic drug names, and returned a list of existing drug names ranked in descending order of similarity to “zucapsaicin.” He used four different search strategies, two based on spelling and two on pronunciation. Dr. Lambert writes that his research “suggests that searches based on normalized edit distance provide a better approximation to human expert judgments of similarity than do searches based on trigram measures of similarity.” Hence we have provided only the results of the search based on normalized edit distance, though the other searches produced nearly identical results (Appendix 2).

The results show that, as Winston maintains, “zucapsaicin” and “capsaicin” are extremely similar, and consequently there is likely to be confusion between this pair of drug names. The normalized edit distance, for both spelling and pronunciation, between the two names is 0.1818, putting zucapsaicin/capsaicin in the 99.95th percentile of all possible pairs of one-word USAN names, according to Dr.

Lambert. In other words, a mere 0.048% of pairs of one-word USAN names are as similar or more similar than the zucapsaicin/capsaicin pair.

(We note parenthetically that none of the names that the USAN Council cited as having a potential to be confused with civamide, namely “rifamide, cisapride, cinitrapide, cinflumide, and cintramide,” had normalized edit distances as close as that between zucapsaicin/capsaicin).

It is our understanding that FDA has recently implemented a new system, known as Phonetic and Orthographic Computer Analysis (POCA), for evaluating proprietary drug names. Winston is not aware of the technical differences between Dr. Lambert’s methodology and POCA; however, it seems quite likely that, if used to evaluate the name “zucapsaicin,” POCA would produce similar results to those obtained by Dr. Lambert.

The potential for medication error between “zucapsaicin” and “capsaicin” is heightened by the fact that one of the indications the Compound is being developed for is the same indication and with the same method of administration and similar dosage strength as certain capsaicin-containing products currently marketed. Hence factors that, in some cases, might mitigate the linguistic similarity and reduce the prospect of look-alike and sound-alike errors, in this particular instance tend to increase the likelihood of medication errors between zucapsaicin and capsaicin.

2. The name "zucapsaicin" violates General Rule #5: "Preference should be given to names of established usage provided they conform to these guiding principles and are determined to be free from conflict with existing nonproprietary names and trademarks."

The name used almost exclusively by the medical and scientific communities for the Compound is "civamide." The enclosed list of references in Appendix 1, based on a literature search conducted in calendar year 2004, shows that "civamide," not "zucapsaicin," is the *de facto* name of established usage. On this basis, "civamide" would appear to be a preferable name for the Compound. At the very least, "zucapsaicin" appears inconsistent with this Guiding Principle.

3. The name "zucapsaicin" violates Specific Rule #14: "A name coined for a new chemical entity routinely does not specify the stereoisomeric form of the molecule in the nonproprietary name. If the stereochemical configuration has been determined, this information is presented in the chemical name(s) and is reflected in the structural formula...."

The Compound is a new chemical entity; it is not found in nature and must be chemically synthesized. Accordingly, Specific Rule #14 clearly states that it is not routine for the stereoisomeric form of a new chemical entity such as the Compound to be identified in the nonproprietary name. Contrary to this rule, the USAN Council has maintained, "The name zucapsaicin is appropriate for a stereo-isomer

of capsaicin.” (letter dated July 26, 2000, Appendix 1, Exhibit C). Winston’s letter dated June 20, 2003 to the USAN Review Board (Appendix 3) pointed out that “the Council’s selective reading of Specific Rule #14 ignores the essence of the rule and inappropriately lumps geometric isomers with optical isomers, when the two are usually treated quite differently in practice (cf. the FDA’s Policy Statement for the Development of New Stereoisomeric Drugs)” (Appendix 4). In essence, the USAN mistakenly treats the Compound, which is a geometric isomer of capsaicin, as if it were an optical isomer.

“Zucapsaicin” Has Potential to Cause Harm

Winston’s major concern is that the inappropriateness of the name “zucapsaicin” may cause harm, as a result of potential confusion between “zucapsaicin” and “capsaicin.” We believe that the prospect of such confusion unnecessarily exposes patients, physicians, pharmacists, health-care and scientific professionals, and Winston to various risks:

1. potential damage from medication errors arising from confusion between the names “zucapsaicin” and “capsaicin”

Given the similarity in the names, “zucapsaicin” and “capsaicin,” Winston has significant concerns that physicians, pharmacists, or other health professionals might confuse the two. This concern is reinforced by a survey of pain specialists

commissioned by Winston and conducted by International Research Services, Inc. (“IRSI”) (Appendix 5). IRSI, a contract research organization, was commissioned to conduct a survey of physician, pharmacist or nursing members of the American Pain Society, examining whether the nonproprietary names “zucapsaicin” and “capsaicin” might create confusion among specialists in pain management. It is worth emphasizing two points that emerge from the survey results.

First, the name zucapsaicin appears likely to cause significant *substantive* confusion, in direct contrast to assertions made by the USAN Council. For instance, in its letter dated July 24, 2003 (Appendix 6), the USAN Council alleged that “. . .any health care practitioner can clearly understand that capsaicin and zucapsaicin are related.” Yet among a random sample of pain specialists, who are assuredly better informed about medications in the pain area than the average health-care practitioner, nearly 85 percent of respondents *incorrectly* indicated that zucapsaicin and capsaicin were different names for the same compound. This finding rebuts the USAN Council’s claim (again in its letter dated July 24, 2003) that “[z]ucapsaicin obviously shows the relationship to capsaicin”; conversely, it supports Winston’s contention that zucapsaicin and capsaicin are likely to be mistaken in practice.

Second, the survey results indicate that when asked the question, “If zucapsaicin and capsaicin are names for different compounds used to treat the same pain indication, would there be a chance of confusion between the names in writing or

reading a prescription?”, greater than 90 percent of the respondents indicated that there would be confusion with just under two-thirds responding that it would cause “major confusion.” This survey result is consistent both with the linguistic evidence presented above and with Winston’s experience as a company whose subsidiary markets a capsaicin-containing product.

This survey of specialists in the pain area strongly suggests that zucapsaicin would be confused with capsaicin in the health-care arena. This provides further support for the arguments that Winston is making in this Citizen’s Petition and has made repeatedly to the USAN Council and in its petition to the USAN Review Board.

The USAN Council’s response dated October 24, 2003 to the report prepared by Bruce Lambert, Ph.D. and the survey conducted by International Research Services Inc. is contained in Appendix 7. It is worth noting that although the USAN Council criticizes the validity of Dr. Lambert’s methodology and of the IRSI Survey, the USAN Council does not offer any evidence to support its contention that healthcare practitioners and patients would not confuse the names “zucapsaicin” and “capsaicin.”

Potential confusion between the Compound and capsaicin is important because even though they are stereoisomers, their pharmacological and toxicological properties are different. Notably, the Compound is ten times more potent as a neuropeptide depletor than capsaicin; high doses of the Compound have no

anatomical or physiological adverse effects on neurons, while capsaicin at similarly high doses has been demonstrated to be neurotoxic; and the Compound produces significantly less burning and stinging on topical application than does capsaicin in double-blind tolerance studies.

Given that the Food and Drug Administration in recent years has emphasized the problem of medication errors and the importance of avoiding look-alike and sound-alike names, Winston requests that FDA designate an official name for the Compound different than "zucapsaicin." Winston has made requests on several occasions to the USAN Council and petitioned the USAN Review Board for a name change without success. 21CFR§ 299.4(e) states that "The Food and Drug Administration will continue to publish official names under the provisions of section 508 of the act when the agency determines that: (1) The USAN or other official or common name is unduly complex or is not useful for any other reason. . . ."

2. potential damage to the public from non-use of the Compound in cases where it would be beneficial

Above we have noted the problem of medication error, whereby patients erroneously use a product incorporating capsaicin rather than the Compound, or vice versa. In addition to this problem of inappropriate drug use, there is a potential problem of non-use arising from drug name confusion. There is a reasonable probability that some of the negative side effects of capsaicin, especially the

burning and stinging associated with capsaicin application, might be mistakenly attributed to the Compound, so that some physicians might elect not to prescribe the Compound and some consumers might not use the Compound if it were prescribed for them. Such patients would thereby be deprived of the positive benefits that the Compound might have in any indication(s) for which it might be approved.

Additionally, some physicians and patients may not have experienced efficacious use of capsaicin for its indication(s), and may be unwilling to try a similar-sounding compound, again depriving some individuals of the potential benefits of the Compound.

3. material damage to any product(s) incorporating the Compound and thereby to Winston

Confusion such as that described in the points immediately preceding could materially damage any products that Winston may introduce incorporating the Compound. Indeed, Roger Williams, the executive vice president and CEO of USP, a sponsoring organization of the USAN Council and the Review Board, articulated the significant commercial impact that a nonproprietary name can have:

“[T]he naming of therapeutic ingredients and products has a role that is much larger and more important than one might expect . . . *Naming controls your marketplace. You can either create or deny a market based on a name.* Names are also vitally

important as a means of preventing medical errors.” (Appendix 1, Exhibit D, italics added)

4. confusion within the medical and scientific communities, where “civamide” is the *de facto* name of established usage for the Compound

As noted above and documented in Appendix 1, Exhibit B, the medical and scientific communities know the Compound as “civamide.” Although it would be possible to expend resources to re-educate practitioners and researchers, it would be easier and faster to change the nonproprietary name of the Compound to the name of established usage.

CONCLUSION

As mentioned several times in this Citizen’s Petition, Winston has sought relief from the USAN Council and the USAN Review Board to change the name of the Compound from “zucapsaicin” to a less-confusing name. On September 10, 2001, USAN sent a letter (Appendix 8) informing Winston that the USAN Council was denying Winston’s request and would retain the official USAN “zucapsaicin” adopted in 1993.

Winston subsequently brought a Complaint against the USAN Council and its constituent members in the Circuit Court of Cook County, Illinois County Department, Chancery Division on April 15, 2002. Judge Richard J. Billik, on November 8, 2002, dismissed without prejudice Winston's complaint, encouraging Winston to pursue a review of the nonproprietary drug name "zucapsaicin" by the USAN Review Board and/or seek an appropriate administrative remedy at FDA (Appendix 9).

Winston, following the Court's recommendation, petitioned the USAN Review Board on March 17, 2003, requesting the official United States Adopted Name for the Compound be changed from "zucapsaicin" to "civamide" or to some other non-confusing name not containing capsaicin that was mutually acceptable to Winston and to the Review Board. On December 19, 2003, Winston received a letter (Appendix 10) from the USAN Review Board denying Winston's petition dated March 17, 2003, and upholding the decision of the USAN Council to retain the name "zucapsaicin." Provided in Appendix 11 is the May 23, 2003 letter from the USAN Council to the USAN Review Board, setting forth the basis of its opposition to Winston's appeal of the Council's decision to retain "zucapsaicin" as the official USAN for cis-8-methyl-N-vanillyl-6-nonemide. Appendix 3 contains Winston's response dated June 20, 2003 to the May 23, 2003 letter from the USAN Council. Appendix 6 contains USAN Council's response to Winston's June 20, 2003 letter.

As noted above, before appealing to FDA in this Citizen's Petition, Winston requested reconsideration by the USAN Council. Although Winston expressed its willingness to negotiate a new, non-confusing name for the Compound, the USAN Council reiterated its position that "zucapsaicin" had been adopted according to the proper process and would not work with Winston to find a mutually acceptable alternative. Winston then appealed to the USAN Review Board, which rejected Winston's appeal without giving any specific grounds for its decision (Appendix 10).

Winston is thus left with no recourse but to file this Citizen's Petition with FDA. As the USAN Council's attorneys note, ". . . the FDA has exclusive authority to designate 'official name[s]' for drugs. (Sec 21 U.S.C. §358(a)). Where the FDA designates an 'official name,' that name must be used on the drug label. (21 U.S.C. 352(e)). Also, if the FDA has designated an 'official name' for a drug, then federal law requires that 'official name' 'shall be the only official name of that drug . . . used in any official compendium published after such name has been prescribed...' (See 21 U.S.C §358(a)). The FDA has responsibility to review both previously assigned 'official names' and those drugs without 'official names' in order to ensure that no drug bears an inappropriate name (21 U.S.C. §358(c)). The FDA then may choose either a name suggested by the compilers of the official compendium (if it finds such names to have 'usefulness and simplicity') or identify a different 'official name' (Id)."

Based on the arguments made by USAN Council's own attorneys to the Circuit Court of Cook County, Illinois, Winston requests the Commissioner of Food and Drugs to designate an official name for the Compound that is different from "zucapsaicin" and that is a non-confusing name not containing "capsaicin."

C. Environmental Impact

Winston claims a categorical exclusion under §25.31(e) of Title 21 Code of Federal Regulations since the action requested of the Commissioner of Food and Drugs is the designation of an official name for the Compound which is currently being investigated under several Investigational New Drug Exemptions with the Agency. A categorical exclusion is also claimed under §25.30(k) since the designation of an official name will have a direct consequence on the labeling for the product once approved for marketing.

D. Economic Impact

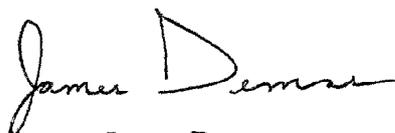
Winston will provide this information upon request. It is Winston's opinion that a name change imposes no costs on any party and potentially benefits many. A name change would benefit a wide spectrum of parties, from patients to health-care providers to researchers to Winston itself. The requested action would not impose costs on any party, including the USAN Council, other than the administrative costs to the Council associated with changing the name, which Winston has offered to defray.

It would be optimal to change the Compound's nonproprietary name now, while products incorporating the Compound are still in the investigational stage, rather than after any such products are introduced to the market. To change the nonproprietary name now would be far less costly and much less disruptive than it would be once any products containing the Compound have been approved and marketed.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and view on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Signature:



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