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SOPHIA V. FUERST, Director
312-464-4045

May 23, 2003

Joseph G. Valentino, Esq.
Senior Vice President, Secretary, and General Counsel
United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

Re.. USAN Review Board / Winston Laboratories

Dear Mr. Valentino:

This letter is in response to your request, in your role as Secretary to the USAN Review Board, that the USAN Council (Council) set forth the basis of its opposition to Winston Laboratories' (Winston) appeal of the Council's decision to retain "zucapsaicin" as the official USAN for *cis*-8-methyl-*N*-vanillyl-6-nonenamide. The Council's responses to each of Winston's allegations (indicated by **bold face** or *italics*) are set forth below.

The name "zucapsaicin" violates several key USAN Guiding Principles for Nonproprietary Drug Names (Guiding Principles).

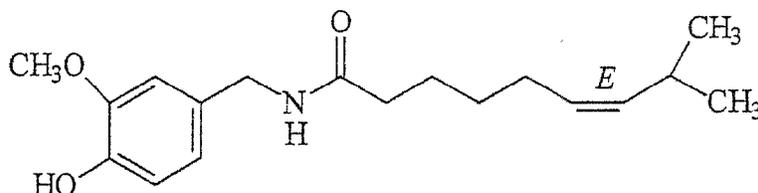
On the contrary, the name "zucapsaicin" was coined by USAN, in collaboration with Winston's predecessor, following the Guiding Principles:

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.""*

Any name selected that does not contain "capsaicin" would be chemically misleading. "Zucapsaicin" clearly identifies this product as an isomer of "capsaicin". The relationship between the two compounds is clearly indicated by their chemical names, chemical structures, molecular formulas, and molecular weights:

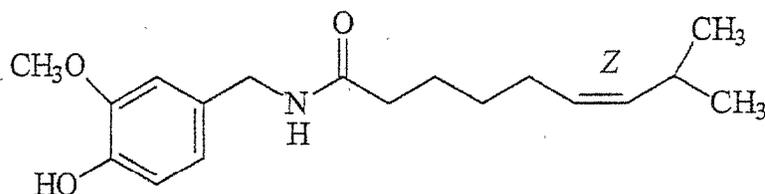
➤ **capsaicin**

- chemical name: (*E*)-8-methyl-*N*-vanillyl-6-nonenamide
- molecular formula: $C_{18}H_{27}NO_3$
- molecular weight: 305.41
- structural formula:



➤ **zucapsaicin**

- chemical name: (*Z*)-8-methyl-*N*-vanillyl-6-nonenamide
- molecular formula: $C_{18}H_{27}NO_3$
- molecular weight: 305.41
- structural formula:

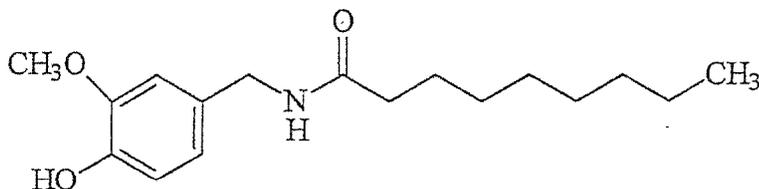


As can be clearly noted, the only difference between the two compounds is the question of stereochemistry. The “*E*” in the chemical name of capsaicin refers to the stereochemical indicator *entgegen* which means “opposite”; the “*Z*” in the chemical name of zucapsaicin refers to the stereochemical indicator *zusammen* which means “together”.

The compound in question in the case cited by Winston, GenDerm Corp. v. Biozone Labs., is a completely different situation. The compound identified as “nonivamide” is structurally and chemically different than capsaicin and zucapsaicin:

➤ **nonivamide**

- chemical name: *N*-vanillyl-nonamide
- molecular formula: $C_{17}H_{27}NO_3$
- molecular weight: 293.40
- structural formula:



The registered mark, Capzasin[®] refers to products containing capsaicin, not zucapsaicin. The prefix zu-, pronounced zoo-, gives a clear indication that although this compound is related to capsaicin, there is some inherent difference between the two.

Winston points out that the stem "zu" is used as an identifier in the monoclonal antibody nomenclature scheme. The infix "zu" is indeed used to identify monoclonal antibodies of a humanized source. However, this syllable is ONLY used as an infix in monoclonal antibody nomenclature, and would never appear without the "mab" suffix and a unique prefix (e.g., *felvizumab*, *epratuzumab*). The nomenclature scheme for monoclonal antibodies is a very detailed, complicated scheme, for a very specific type of product, and the possibility of confusion with the use of the prefix "zu" in zucapsaicin is most unlikely.

Additionally, there is precedence in the use of the prefix "zu" in two other nonproprietary designations to indicate the Z isomer:

- clomiphene (the racemic form) and its Z isomer zuclophene:
 - clomiphene - 2-[p-(chloro-1,2-diphenylvinyl)phenoxy]triethylamine
 - zuclophene - (Z)-2-[p-(chloro-1,2-diphenylvinyl)phenoxy]triethylamine

 - clopenthioxol (the racemic form) and its Z isomer zuclopenthioxol:
 - clopenthioxol - 4-[3-(2-(chlorthioxanethen-9-ylidene)propyl)-1-piperazineethanol
 - zuclopenthioxol - (Z)- 4-[3-(2-(chlorthioxanethen-9-ylidene)propyl)-1-piperazineethanol.
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."*

USAN Response

Zucapsaicin was adopted as a USAN on November 23, 1993 after a successful negotiation between the Council and GenDerm Corporation (Winston's predecessor). GenDerm's acceptance of the name zucapsaicin is documented in its letter of July 13, 1993, to the USAN program (attached).

Zucapsaicin was approved by the International Nonproprietary Name (INN) Committee and published as the proposed International Nonproprietary Name in INN List #71 (*WHO Drug Information*, Vol. 8, No.2, 1994). The name, zucapsaicin, was republished as the recommended INN in List # 35 (*WHO Drug Information*, Vol. 9, No.3, 1995) and is recommended for use in all World Health Organization (WHO)-

member countries. Zucapasaicin has been included in the *USP Dictionary of USAN and International Drug Names* since 1994 and as such, by law, is the Food and Drug Administration (FDA)-recognized, established nonproprietary name for this entity.

The name, civamide, was not an acceptable nonproprietary name in 1992 and it is not acceptable in 2003. Civamide conflicts with the nonproprietary designations rifamide, cisapride, cinitapride, cinflumide and cintramide. Indeed, there are close to 200 nonproprietary designations ending in -amide.

Only Winston (and previously GenDerm), and not the regulatory agencies, has repeatedly used the name civamide. Thus, Winston's claim of *de facto* usage of the name civamide is misleading in itself (no such usage was claimed at the time the Council adopted the USAN in 1993).

3. *The name "zucapsacin" 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...."*

USAN Response

The chemical entity in question is not a new entity. It is the *cis* or *Z* isomer of capsaicin. Capsaicin, as it exists in nature, is the *trans* or *E* isomer. The two compounds are diastereoisomers or geometric isomers. Geometric isomers are isomers that are caused by the presence of a carbon-carbon double bond which does not rotate. Both compounds have the same atom groups attached; the only difference is that they are orientated in different directions.

The Rule in question goes on to state:..."Subsequently, if a name is needed for a different enantiomer or for the racemic form, the following prefixes should be added to the existing name:..." The Council and the INN would have been remiss in not identifying the chemical relationship to capsaicin when recommending a non-proprietary name for *cis*-8-methyl-*N*-vanillyl-6-nonenamide. In fact, during the initial negotiations, the name *ciscapsaicin* was suggested by the Council and rejected by the manufacturer. This is documented in a series of letters dated December 23, 1992, March 24, 1993, and July 13, 1993 (attached). The name *zucapsaicin* was a compromise agreement reached after negotiation with the duly appointed representative of GenDerm (Winston's predecessor). As stated previously, the prefix *zu-* as well as the prefix *cis-*, have been previously used to identify diastereoisomers.

"Zucapsaicin" has potential to cause harm, and various risks result from the possible confusion between "zucapsaicin" and "capsaicin".

USAN Response

There would be no reason for pharmaceutical companies to investigate the properties of stereoisomers if there was no medical or economic benefit to do so. There are various examples:

- omeprazole and esomeprazole
- citalopram and escitalopram
- albuterol and levalbuterol
- methylphenidate and dexmethylphenidate
- fenfluramine and dexfenfluramine
- ofloxacin and levofloxacin

One should note that all of the above USAN names are coined in a similar manner to capsaicin and zucapsaicin. The Council is unaware of any "harm" to patients resulting from the use of any of these names, and many of these drugs have been widely used in the treatment of patients. Thus, absent data to the contrary, the Council has no reason to conclude that having the names "capsaicin" and "zucapsaicin" will result in harm to patients. (Note: While fenfluramine and dexfenfluramine have been removed from the market because of side effects, this was unrelated to problems with nomenclature.)

While isomers have identical molecular weights and physical properties, they can show remarkable selectivity within biological systems. Therefore, isomers can have different biological actions. In many cases, only one isomer of the racemic drug is responsible for the drug's efficacy. The other may be an unnecessary component or may cause side effects.

Therefore, it is not unexpected that zucapsaicin and capsaicin would have some different selectivity, although both compounds do have analgesic properties. It is important for physicians and other health care practitioners to know that zucapsaicin is an isomer of capsaicin. More confusion would be caused by giving zucapsaicin a nonproprietary name that does not reflect any relationship to its optical isomer. For example, some of the side effects inherent in capsaicin may, even if in a lesser form, exist in its isomer. Any information on products containing zucapsaicin would be handled in the FDA-approved labeling, which would be released by Winston only after approval of a New Drug Application by the FDA.

There would be confusion within the medical and scientific communities if zucapsaicin is retained, as "civamide" is the *de facto* name of established usage for the Compound.

In the attached correspondence, the manufacturer states "we are aware of at least two articles in print which use the name civamide." As indicated earlier, the name "civamide" has no status other than as a trivial name used by the manufacturer in the literature. Once zucapsaicin became the adopted USAN in 1993, the manufacturer

should have used, and encouraged others to use, this "official" name in scientific publications. Unfortunately, Winston (and its predecessor) continued to use the name civamide even after zucapsaicin was adopted as the officially recognized USAN in 1993. For the record, it should be noted that this compound is also referred to in the literature by the trivial name *cis*-capsaicin.

The official nonproprietary name both in the United States (US) and overseas is "zucapsaicin." This is the name that must appear in all legal documentation for this compound, and it also must appear in the labeling information, subsequent to marketing approval, in the US, the European Union (EU), and other WHO member states. It would certainly cause more confusion for regulatory agencies if the name were changed at this point, especially to a name that is clearly in conflict with other nonproprietary designations.

The USAN Council did not address Winston's substantive arguments.

USAN Response

The majority of Winston's substantive arguments were addressed as early as 1993, prior to the adoption of zucapsaicin (see attached correspondence). However, each time the manufacturer requested that the Council again deliberate this issue, the Council noted that no new, compelling information was presented by Winston to re-examine the selection of zucapsaicin as a USAN. Even so, this issue was discussed at the June 26, 2000 and June 26, 2001 meetings of the Council. During both consultations, the Council reaffirmed its decision that, because this substance is an isomer of capsaicin, the name zucapsaicin is appropriate and free of conflict.

A discussion of the process regarding the adoption of zucapsaicin as the USAN for its compound is not germane to this issue.

USAN Response

The Council disagrees with this allegation. The fact remains that the manufacturer approved this name after prolonged negotiation. Unfortunately, instead of using the name zucapsaicin in company publications after its adoption as the official USAN, Winston continued to use the trivial name civamide, and now is claiming *de facto* usage of the name.

As pointed out by Winston, the Council is not inflexible to changing a USAN if it is deemed in conflict or if a potential for medication errors is foreseen. Hydrocortisone probutate and atomoxetine were adopted to replace hydrocortisone buteptrate and tomoxetine, respectively. Both of these changes were made before either compound became a recommended INN (rINN) or a marketed entity.

The Council also initiated the change of amrinone to inamrinone, because it was believed that retaining the name amrinone could cause medication errors. There were no fees associated with this change. The name was changed in order to protect the safety of patients. Moreover, this name change was made long after this compound attained status as a rINN, and it had been marketed for several years.

It should also be pointed out that the INN Programme currently does not have a method in place to change a rINN. For example, the change of amrinone to inamrinone was only done in the US. Therefore, if the name zucapsaicin was changed in the US, it would remain zucapsaicin in all other member states of the WHO – this would cause even more confusion. Even if the INN Committee could consider changing the name at this time, the arguments to change the name are not substantive, and the possibility of acceptance of a name change is minimal.

Failure to change the name, zucapsaicin, could potentially damage any products incorporating the compound and, therefore, damage Winston.

USAN Response

The Council recognizes that manufacturers may prefer nonproprietary names that offer a marketing advantage to their drug products. While this is not a consideration for the Council, the negotiation process leading to the adoption of a USAN provides ample opportunity for a manufacturer to include this factor in its decision to accept or not accept a proposed USAN. In 1993, GenDerm accepted zucapsaicin as the adopted USAN for its compound after such a negotiation.

Frankly, the only perceived benefit to changing the name, zucapsaicin, at this time would be a marketing benefit to Winston. The Council contends this is not an appropriate reason to change an established USAN. Unlike trademarked (brand) names, which manufacturers select primarily to distinguish and promote their products, USANs must satisfy other purposes (e.g., to properly classify a chemical compound).

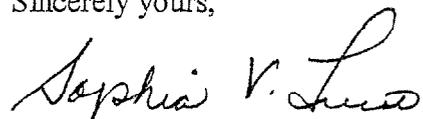
Conclusion

In conclusion, the Council strongly believes that the name zucapsaicin is appropriate for this geometric isomer of capsaicin, and that the name was coined in accordance with its Guiding Principles. The prefix, zu-, serves to differentiate this name from capsaicin. The name zucapsaicin clearly indicates that this substance is related to capsaicin, which is appropriate. Selecting another name without reference to capsaicin would be misleading to health care practitioners. In fact, it would be in violation of the Council's first General Rule, which states: "A nonproprietary name should be useful primarily to health care practitioners...". The Council is unaware of any evidence to suggest the name, zucapsaicin, will cause medication errors and harm to patients. The name civamide is inappropriate for this compound, and is in conflict with existing nonproprietary nomenclature.

Response to USAN Review Board request
May 23, 2003
Page 8

The Council respectfully contends that the name zucapsaicin be retained.

Sincerely yours,



Sophia V. Fuerst
Secretary, USAN Council and
Director, USAN Program

Enclosures

cc: ~~Winston Laboratories~~
Winston Laboratories
USAN Council Members

GenDerm Corporation
600 Knightsbridge Parkway
Lincolnshire, IL 60069
Telephone: 708-634-7373
FAX: 708-634-2008

GENDERM

DEC 29 1992

December 23, 1992

Sophia V. Fuerst
Assistant Secretary
USAN Council
American Medical Association
515 North State Street
Chicago, IL 60610

Dear Ms. Fuerst:

We have reviewed the recommendation that the USAN council has made following its deliberation of our submission for civamide/mevamide.

We request that ciscapsaicin not be the USAN name assigned to this drug for the following reasons:

We acknowledge that FDA has several INDS for capsaicin, GenDerm alone currently has four INDS active for the trans-isomer Capsaicin. FDA, under its recent stereoisomer policy, recognizes the isomers to be distinct chemical entities and, in fact, GenDerm has submitted a data package to the agency and held a pre-IND meeting on this product as Civamide.

We prefer to use the name Civamide also to indicate that this is not an isomer of a mixed product but a separate entity. Further, this product is only available as a synthetic material, whereas the trans-isomer is typically used as a natural material with naturally occurring analogs present. Because USAN policy appears to have been to use the ci- or cis- prefix when referring to a single isomer of a mixed product (e.g. cidoxepin hydrochloride and doxepin hydrochloride), we feel that the use of this convention in naming this product, which has never been identified in natural capsaicin, would be misleading. In order to avoid considerable confusion between these isomers, we request a distinguishing name-Civamide.

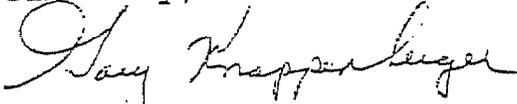
We are unaware of previous cases where synthetic isomers of a previously identified single isomer product have been identified by the cis- or trans- prefix.

Research conducted to date indicates considerable differences in biologic and clinical activity, as well as toxicology, may be found between the two isomers.

Sophia V. Fuerst
USAN Council
American Medical Association
December 23, 1992
Page 2.

We are aware of at least two articles in print which use the name civamide for this isomer. In the interest of patient safety and to eliminate considerable confusion, we respectfully request that the council submit the name Civamide to the WHO Nomenclature Committee for review and approval, instead of ciscapsaicin.

Sincerely,



Gary Knappenberger
Director, Regulatory Affairs

GK/mmp

USAN

American Medical Association
515 North State Street
Chicago, Illinois 60610

UNITED STATES ADOPTED NAMES COUNCIL

RUTA FREIMANIS, Pharm.D., R.Ph., Secretary
(312) 464-4045

SOPHIA V. FUERST, Assistant Secretary
(312) 464-5352

March 24, 1993

Telefax: 312-464-4154
Telex: 280248 AMA CGO

EE-81

GenDerm Corporation
600 Knightsbridge Parkway
Lincolnshire, IL 60069

Attn: Gary Knappenberger
Director
Regulatory Affairs

Dear Mr. Knappenberger:

Your December 23, 1992 request for the reevaluation of the name ciscapsaicin has been forwarded to the USAN Council for review and comment. The USAN Council has reconfirmed its position that the name ciscapsaicin is appropriate for this compound.

The following comments have been made regarding Genderm's position that ciscapsaicin is not suitable:

- 1) FDA states that stereoisomers are distinct chemical entities.

Isomers are distinct chemical entities; however, if the activity is the same, then the same class name is needed.

- 2) Pre-IND meeting with FDA using civamide as nonproprietary name.

This is irrelevant; manufacturer can call their product whatever they want at this phase.

- 3) EE-81 is not an isomer of a mixed product but a separate entity.

Capsaicin is not a mixed product; it is clearly defined in the Merck Index as the trans- form.

- 4) EE-81 is synthetic; trans- form is typically a natural material with other analogues present.

Synthetic capsaicin is certainly available; again, other analogues are not in question here.

Gary Knappenberger
Page 2 EE-81
March 24, 1993

- 5) Previous USAN comparison given — doxepin/cidoxepin. No other cases such as this one.

Doxepin defined as a specific mixture of Z- and E- (or cis- and trans-) isomers. Cidoxepin is the name assigned to the cis- isomer.

There has been precedence. The naturally occurring form of tretinoin is all -trans; in fact, it is defined as all -trans-retinoic acid. The 13-cis- form is isotretinoin. The entire name tretinoin is used.

- 6) Misleading as cis- is not in naturally occurring capsaicin.

It is more misleading not to identify this product as related to capsaicin.

- 7) Different clinical activity.

Questionable, both are listed as topical analgesic. Differences in toxicology ... handled in product inserts and description of drug.

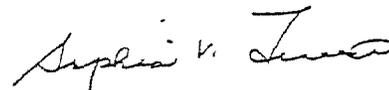
- 8) Two articles in which EE-81 is referred to as civamide.

Civamide as a trivial name would be added as note to adoption statement.

I have run across the enclosed article in the literature. The literature indicates confusion in the nomenclature of capsaicin; adding other names at this point could generate more confusion.

Please reconsider the name ciscapsaicin and let me know if it is acceptable to GenDerm for this entity. If so, I will transmit the name and pertinent nomenclature information to the World Health Organization (WHO) Nomenclature Committee for review and clearance. If there are no objections from the WHO Committee members, ciscapsaicin can be formally adopted as USAN within twelve to sixteen weeks.

Sincerely yours,



Sophia V. Fuerst
Assistant Secretary
USAN Council

SVF/gat

Enclosures

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600 Knightsbridge Parkway
Lincolnshire, IL 60069
Telephone: 708-634-7373
FAX: 708-634-2008

GENDERM

USAN COUNCIL

JUL 16 1993

July 13, 1993

Sophia V. Fuerst
Assistant Secretary
USAN Council
515 North State Street
Chicago, IL 60610

EE-81

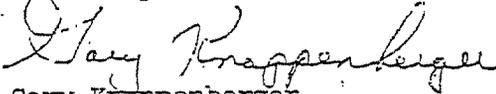
Dear Ms. Fuerst:

We wish to thank you and Dr. Freimanis for your assistance and explanations at our May 13 meeting. Subsequently we have had several internal discussions and would like to request approval of the name zucapsaicin for the cis-isomer of capsaicin. We prefer the zu - prefix to the cis - prefix and understand that the USAN Council would consider it as an option.

I am available to discuss this further should you have any questions.

Again, we thank you for your assistance.

Sincerely,



Gary Knappenberger
Director, Regulatory Affairs

GK/mmp