



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

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RE: Docket No. 2003N-0233 SUP3 (Symrise, Inc.) and RPT 1 (Ego Pharmaceuticals Pty. Ltd.); Safety and Effectiveness of Amiloxate in Over-the-Counter Sunscreen Drug Products

Dear Ms. Scharlat and Dr. Oppenheim:

In accordance with 21 CFR 330.14(g)(4), this letter provides FDA's initial determination and feedback on safety and effectiveness data submitted by Symrise, Inc. and Ego Pharmaceuticals Pty. Ltd. to demonstrate the safety and effectiveness of the sunscreen active ingredient amiloxate (also known as NeoHeliopan® E 1000) at concentrations up to 10 percent (the amiloxate submissions) for use in over-the-counter (OTC) sunscreen products. These data were provided in response to our announcement that amiloxate was found eligible to be considered for inclusion in the OTC sunscreen monograph (21 CFR part 352, currently stayed) based on our review of a Time and Extent Application (TEA) submitted by Haarman and Reimer Corp. under 21 CFR § 330.14(c) (the TEA regulation), and our related call for submission of safety and effectiveness data.<sup>1</sup>

We have reviewed the available public data on amiloxate for use in OTC sunscreens. Based on that review, we have made an initial determination that the scientific record is not sufficient to establish that amiloxate is generally recognized as safe and effective (GRASE) for OTC sunscreen use. However, in accordance with the TEA regulation, we are including a copy of this letter in the public docket and providing you and any other interested parties with an opportunity to submit additional data. This letter describes our review of the amiloxate data

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<sup>1</sup> 68 FR 41386 (July 11, 2003).

submissions, identifies additional data needed to demonstrate that amiloxate is GRASE, and explains our rationale for specific data requirements.

### Background

The TEA regulation creates a process through which a sponsor can request that an active ingredient or other condition<sup>2</sup> be added to an OTC drug monograph. First, the sponsor must provide a TEA application package containing the information on time and extent of marketing (eligibility information) described at 21 CFR 330.14(c)(1). If the condition is found eligible, then FDA will publish a notice of eligibility in the *Federal Register* requesting that the sponsor and other interested parties provide data to demonstrate the safety and effectiveness of the condition for its intended OTC use, as was done for amiloxate.<sup>3</sup> After evaluating the safety and effectiveness data provided, FDA will make an initial determination as to the status of the condition (i.e., whether it is generally recognized as safe and effective (GRASE) for use in the United States).<sup>4</sup> If we make an initial determination that the condition is GRASE, we will propose to amend or establish a relevant OTC monograph regulation to include the condition, followed by publication of a final rule reflecting our consideration of public comments on the proposed rule.<sup>5</sup> If we initially determine that the condition is not GRASE, we will so inform the sponsor (and other interested parties that have submitted data) by way of a feedback letter that will also be placed in the public docket.<sup>6</sup> (As noted above, this letter provides that feedback.) Where FDA initially determines that the condition is not GRASE, FDA also will publish a proposed rule to codify this determination by adding the condition to 21 CFR 310.502, Certain Drugs Accorded New Drug Status Through Rulemaking Procedures, followed by publication of a final rule (or a new proposed rule to add the condition to the monograph) after consideration of public comments on the proposed rule.<sup>7</sup>

In order for FDA to propose to amend the OTC sunscreen monograph to include amiloxate, we must make an initial determination, based on appropriate scientific evidence, that any sunscreen product that could be formulated using the active ingredient concentrations, permitted combinations, or other applicable limitations specified in the monograph (including the proposed amendment) would be GRASE for use under the conditions prescribed, recommended, or suggested in its labeling.<sup>8</sup> We have reviewed the amiloxate data submissions. We also have performed a search for published scientific literature on amiloxate, which did not yield any additional data to address our outstanding questions. Based on our review, we have made an initial determination that the data currently available in the public record are not sufficient to

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<sup>2</sup> For purposes of the TEA regulation, "condition" is defined as "an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration marketed for a specific OTC use", with specific exclusions. See 21 CFR 330.14(a).

<sup>3</sup> 21 CFR 330.14(e); for the notice of eligibility for amiloxate, see 68 FR 41386 (July 11, 2003).

<sup>4</sup> 21 CFR 330.14(g). This determination is governed by the same safety, effectiveness, and labeling standards that apply to existing monograph ingredients under 21 CFR § 330.10(a)(4).

<sup>5</sup> 21 CFR 330.14(g)(3), 330.14(g)(5).

<sup>6</sup> 21 CFR 330.14(g)(4).

<sup>7</sup> 21 CFR 330.14(g)(4), 330.14(g)(5). OTC drugs and conditions listed in 21 CFR 310.502 may not be marketed without an approved NDA or ANDA.

<sup>8</sup> 21 CFR 330.14(g); see also Food, Drug, & Cosmetic Act § 201(p).

support the requisite GRASE determination; therefore, FDA cannot propose to amend the OTC sunscreen monograph (21 CFR part 352) to include amiloxate. However, because our thinking about the necessary safety data for OTC sunscreen active ingredients has evolved over time, we are not at this time proposing to preclude monograph status.<sup>9</sup> Rather, we are providing you and any other interested parties with an opportunity to submit additional data to address the current data gaps.<sup>10</sup> Nonetheless, we remind you that at present, sunscreens containing amiloxate require an approved new drug application in order to be legally marketed in the United States.<sup>11</sup>

In accordance with the TEA regulation, we are placing a copy of this feedback letter in the public docket, and we invite you and any other interested parties to submit additional data and/or comments on appropriate data requirements for amiloxate. We also are planning a public meeting to discuss current considerations in FDA's evaluation of OTC sunscreen active ingredients, to be scheduled for Spring of 2014, which we encourage you to attend. A *Federal Register* notice will provide more detail about this public meeting. At another public meeting, scheduled for March 25 and 26, 2014, we will be seeking public input on how to improve the regulatory processes for establishment and revision of FDA's OTC drug monographs (also referred to as the OTC Drug Review; generally found at 21 CFR Part 330), including the TEA process. Information about this public meeting is available on the Internet at <https://www.federalregister.gov/articles/2014/02/24/2014-03884/over-the-counter-drug-monograph-system-past-present-and-future-meetings>.

A general discussion of the type and extent of data we believe would be sufficient to support the necessary safety determination for amiloxate, as well as our assessment of the currently available safety data on amiloxate, is explained in Section I below. Section II contains the corresponding discussion on efficacy data requested for amiloxate, as well as our assessment of the currently available efficacy data. Data gaps for amiloxate based on the assessments described in Sections I and II are summarized in Section III.

## Discussion

### **I. Safety Data Considerations for OTC Sunscreen Products Containing Amiloxate**

In evaluating the safety of a proposed monograph active ingredient, FDA applies the following regulatory standard:

Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low

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<sup>9</sup> See 21 CFR 330.14(g)(4), indicating that the agency will propose to include any TEA-eligible condition that is not found to be GRASE in 21 CFR 310.502, Certain Drugs Accorded New Drug Status Through Rulemaking Procedures.

<sup>10</sup> See 67 FR 3067 (Jan. 23, 2002) ("Parties can respond to a feedback letter and supplement their submissions."). If we issue a proposed rule to amend 310.502, then the process of comment on that proposal would provide an additional opportunity for supporting data to be submitted. 21 CFR 330.14(g)(5); see also 67 FR 3067 (Jan. 23, 2002) ("Parties will have another opportunity to respond when the agency publishes a notice of proposed rulemaking to include the condition in § 310.502.").

<sup>11</sup> 21 CFR 330.14(h).

potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.<sup>12</sup>

FDA's OTC drug regulations generally identify the types of information that may be submitted as evidence that OTC drugs are generally recognized as safe (GRAS).<sup>13</sup> To apply the general OTC safety standard to each potential new condition, FDA uses its scientific expertise to determine what constitutes "adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use." In assessing what specific testing or other data are needed to adequately demonstrate the safety of amiloxate for use in sunscreen, FDA considers the circumstances under which OTC sunscreen products that could contain amiloxate would be used by consumers.

When used as directed with other sun protection measures, broad spectrum OTC sunscreen products with a sun protection factor (SPF) value of 15 or higher strongly benefit the public health by decreasing the risk of skin cancer and premature skin aging associated with solar ultraviolet (UV) radiation, as well as by helping to prevent sunburn. (Sunscreens with lower SPF values, or without broad spectrum protection, also help prevent sunburn.) When used as directed by the required labeling, all OTC sunscreen products are applied liberally to the skin and reapplied frequently throughout the day.<sup>14</sup> Because the effects of UV exposure are cumulative, to obtain the maximum benefit, users of broad spectrum sunscreens with an SPF value of 15 or higher are directed to use such products regularly - on a routine basis.<sup>15</sup> Given these conditions of use, our safety evaluation of an OTC sunscreen active ingredient such as amiloxate must consider both short-term safety concerns (such as skin sensitization/irritation and photosafety) and potential concerns related to long-term sunscreen use, including potential systemic exposure via dermal absorption.

The purpose of the safety testing described below is to establish whether an OTC sunscreen product containing amiloxate and otherwise meeting all requirements applicable to OTC sunscreens under 21 CFR 330.1 would be GRAS for use as labeled. To demonstrate that these requirements are met for amiloxate, initial safety testing should be performed using amiloxate as the sole active ingredient up to the highest concentration for which monograph status is sought and eligibility has been established: 10%. If initial testing suggests a particular safety concern associated with amiloxate (e.g., a hormonal activity), FDA may request additional studies to address that concern.

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<sup>12</sup> 21 CFR 330.10(a)(4)(i).

<sup>13</sup> 21 CFR 330.10(a)(2).

<sup>14</sup> 21 CFR 201.327(e).

<sup>15</sup> *Id.*

## A. Human Safety Data

### 1. Human Irritation, Sensitization and Photosafety Studies

Studies of skin irritation, sensitization, and photosafety are standard elements in the safety evaluation of topical drug products that, like amiloxate-containing sunscreens, are applied to the skin repeatedly over long periods of time. FDA recommends separate studies for skin irritation and sensitization. Skin irritation studies should generally include at least 30 evaluable subjects and should evaluate the test product (i.e., amiloxate in an appropriate test vehicle), the vehicle alone, and both negative and positive controls. Skin sensitization studies generally should include at least 200 subjects and should evaluate the product containing amiloxate, the vehicle, and a negative control. For both irritation and sensitization studies, test site applications should be randomized and the test observer blinded to the identities of the test products.

FDA recommends that photosafety evaluation generally involve studies of skin photoirritation (phototoxicity) and skin photosensitization (photoallergenicity). General principles for designing and conducting photosafety studies are described in FDA guidance.<sup>16</sup> Photosafety studies, like sensitization and irritation studies, should be conducted using amiloxate 10% in an appropriate test vehicle, the vehicle alone, and a negative control. In addition, phototoxicity studies should include at least 30 evaluable subjects and photoallergenicity studies should include at least 45 evaluable subjects.

#### Data Available for Amiloxate: Human Irritation, Sensitization and Photosafety Studies

The amiloxate submissions included two expert opinions describing summary results of human irritation, sensitization, and photoirritation studies.<sup>17</sup> Based on the summary information provided, the experts concluded that amiloxate is not a primary irritant, sensitizer, photosensitizer, or photoirritant. However, none of the submissions provided the underlying studies. In the absence of data from the underlying studies, we cannot evaluate the validity of these conclusions, and therefore, cannot accept them as evidence that amiloxate at concentrations up to 10% is GRAS for use in sunscreen products. Either complete data from existing studies or data from additional studies are needed in the record to demonstrate that an OTC sunscreen product containing up to 10% amiloxate is not an irritant, sensitizer, photosensitizer, or photoirritant.

### 2. Human Dermal Pharmacokinetic (Bioavailability) Studies

Because OTC sunscreens are topically applied, another important safety consideration for amiloxate for use in sunscreens is whether dermal application may result in skin penetration and systemic exposure to amiloxate and, if so, to what extent. A well-designed and -conducted human dermal pharmacokinetic study can be expected to detect and quantify the presence in blood or other bodily fluids of amiloxate and/or any metabolites that may have a bearing on

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<sup>16</sup> FDA, Guidance for Industry: "Guidance on Photosafety Testing," May 2003, available on the Internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079252.pdf>.

<sup>17</sup> SUP3, Vol. 1, Haarman & Reimer (H&R) Tests No. 1976022-24 and 1986014.

safety, using recognized parameters such as percent bioavailability,  $C_{max}$ ,  $T_{max}$ , AUC, half-life, clearance, and volume of distribution. This information can help identify potential safety concerns and help determine whether an adequate safety margin for sunscreens containing amiloxate exists. FDA recommends that the pharmacokinetic studies performed on amiloxate also collect additional safety-related data from regularly scheduled physical examinations, collection of vital signs, and other measures, which may help capture adverse skin events or other potential safety signals. Studies should continue until steady state is reached, to ensure that maximum penetration of amiloxate has taken place and chances of it being detected are optimal.

General information and recommendations on the design and conduct of human pharmacokinetic studies can be found in FDA's guidance entitled "Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application."<sup>18</sup> In order to support a GRAS determination for amiloxate (up to 10%), such a study should be conducted under maximal use conditions using amiloxate 10% in various vehicles, including vehicles that would be expected to enhance absorption. We encourage study sponsors to consult with FDA before conducting pharmacokinetic studies, as the properties of amiloxate may bear on the optimal design.

#### Data Available for Amiloxate: Human Dermal Pharmacokinetic (Bioavailability) Studies

No human dermal pharmacokinetic studies for amiloxate were submitted in response to our call for data. We received and reviewed three dermal penetration studies that used other models: an in vivo study in rats,<sup>19</sup> an ex vivo study using pig skin,<sup>20</sup> and an in vivo study in humans that used a tape stripping method for drug recovery from the skin.<sup>21</sup> The ex vivo pig skin study and the human tape stripping model were not designed to detect or quantify amiloxate in blood or other body fluids, and thus provide no useful information about systemic exposure. In the case of the in vivo rat model, systemic exposure did occur, but these findings cannot readily be correlated to the potential for, and extent of, absorption through human skin. While human and rat skin have the same general structural organization, the thickness of the stratum corneum, the presence/absence of glandular apparatus, and the density and distribution of hair follicles are quite different. Therefore, while this study provides some preliminary evidence that amiloxate penetrates the skin of rats, the relevance of this preliminary evidence to absorption through human skin is not clear. Accordingly, we request data from human pharmacokinetic studies to assess the potential for and the extent of systemic absorption. These studies should be performed under expected maximal use conditions with your proposed maximum concentration as discussed above.

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<sup>18</sup> This guidance is available on the Internet at <http://www.fda.gov/downloads/drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072112.pdf>.

<sup>19</sup> SUP3, Vol. 2, H&R Test No. 1986017.

<sup>20</sup> SUP3, Vol. 2, H&R Test No. 1995030.

<sup>21</sup> SUP3, Vol. 2, H&R Test No. 1986059.

### 3. Human Safety Data to Establish Adverse Event Profile

An evaluation of safety information from adverse event reports and other safety-related information derived from commercial marketing experience of sunscreen products containing amiloxate, as well as from other sources, is a critical aspect of FDA's safety review of amiloxate. The TEA regulation specifically calls for submission of information on all serious adverse drug experiences, as defined in §§ 310.305(a) and 314.80(a), from each country where the active ingredient or other condition has been or is currently marketed as either a prescription or OTC drug; in addition, it calls for submission of all data generally specified in 21 CFR 330.10(a)(2), which itself includes documented case reports and identification of expected or frequently reported side effects.<sup>22</sup> To evaluate amiloxate, FDA thus seeks individual adverse drug experience reports, a summary of all serious adverse drug experiences, and expected or frequently reported side effects of the condition.<sup>23</sup> To assist in the Agency's safety evaluation of amiloxate, FDA emphasizes our need for the following data:

- A summary of all available reported adverse events potentially associated with amiloxate;
- All available documented case reports of serious side effects;<sup>24</sup>
- Any available safety information from studies of the safety and effectiveness of amiloxate in humans; and
- Relevant medical literature describing adverse events associated with amiloxate.

Submissions of adverse event data should also include a description of how each country's system identifies and collects adverse events, unless this information, like that for Australia, has been previously submitted as part of amiloxate's TEA package.

While we recognize that adverse event data from foreign marketing experience may reflect patterns of use and regulatory reporting requirements that differ from those in the United States, we nonetheless consider such information to be strongly relevant both to our overall GRASE assessment of amiloxate for use in sunscreens and to our consideration of potential product labeling. FDA recognizes that such information may not be available from all countries; where that is the case, please provide a written explanation for the lack of data. Overall, we seek sufficient data to characterize amiloxate's adverse event profile.<sup>25</sup>

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<sup>22</sup> 21 CFR § 330.14(f)(2), 330.14(f)(1).

<sup>23</sup> *Id.*

<sup>24</sup> 21 CFR 330.14(f)(2).

<sup>25</sup> 67 FR 3060, 3070 (Jan. 23, 2002) ("The agency agrees that the absence of an adverse experience reporting system in a foreign country for drugs or cosmetics does not necessarily mean that a condition cannot be GRAS/E. The GRAS/E determination will be based on the overall quality of the data and information presented to substantiate safety and effectiveness.").

### Data Available for Amiloxate: Human Safety Data to Establish Adverse Event Profile

One of the amiloxate submissions (RPT 1) contained a table of consumer complaints for amiloxate sunscreen products marketed in Australia. The submission noted some complaints related to skin reactions/sensitivity for these products. However, no photographs, medical reports or other corroborating data were provided. The submission did not explain the lack of such information.

Based on information in the amiloxate TEA submissions, we understand that OTC drug products marketed in Australia are required to submit adverse event reports to the Australian Therapeutic Goods Administration (TGA), the regulator of such products. We did not receive any adverse event reports that were submitted to the database maintained by the TGA. We also did not receive any adverse event reports from other countries in which amiloxate-containing sunscreens were previously documented to have been marketed to support the eligibility of amiloxate for evaluation for inclusion in the monograph, such as Spain and Germany. The submissions did not provide any explanation for the limited scope of adverse event-related safety information provided, given the extent of marketing previously documented to establish eligibility of amiloxate for potential inclusion in the sunscreen monograph. To support the evaluation of the safety of amiloxate for use in OTC sunscreens, we request that submitters either supplement the data already submitted, including more recent adverse data, or explain why such information cannot be provided.

#### B. Nonclinical (Animal) Studies

Another important element of FDA's GRAS review of amiloxate for use in sunscreens is an assessment of data from nonclinical (animal) studies that characterize the potential long-term dermal and systemic effects of exposure to amiloxate. Even if the bioavailability data discussed above at Section I.A.2 suggest that dermal application is unlikely to result in skin penetration and systemic exposure to amiloxate, FDA still considers data on the effects of systemic exposure to be an important aspect of our safety evaluation of amiloxate. The addition of amiloxate to the OTC sunscreen monograph would permit its use in as-yet-unknown product formulations, which might in turn alter the skin penetration of the active ingredient. Therefore, an understanding of the effects of amiloxate, were systemic exposure to occur, is critical to determine whether and how regulatory parameters can be defined to assure that all conforming amiloxate-containing sunscreens would be GRASE as labeled.

FDA recommends animal testing of the potential long-term dermal and systemic effects of exposure to amiloxate because these effects cannot be easily assessed from previous human use. Taken together, the carcinogenicity studies, developmental and reproductive toxicity studies, and toxicokinetic studies described below at subsections I.B.1-3 should provide the information needed to characterize both the potential dermal and systemic toxic effects and the levels of exposure at which they occur. These data, when viewed in the context of human exposure data, can be used to determine a margin of safety for use of amiloxate in OTC sunscreens.

### Data Available for Amiloxate: Nonclinical (Animal) Studies Generally

The amiloxate submissions included data from the following types of nonclinical safety studies:

- Acute dose dermal toxicity<sup>26</sup>
- Genotoxicity/mutagenicity<sup>27</sup>
- Embryotoxicity/teratogenicity/uterotrophic toxicity<sup>28</sup>
- Acute and repeat dose oral toxicity<sup>29</sup>
- Androgen and estrogen receptor binding<sup>30</sup>
- Animal skin irritation and sensitization<sup>31</sup>
- Animal photoirritation and photosensitization<sup>32</sup>

Some of the studies<sup>33</sup> provided are of the type generally conducted as screening studies prior to long term studies, and thus provide only limited information. Specifically, while the acute oral dermal toxicity tests indicate little toxicity from amiloxate, these were, in general, incomplete assessments with no clinical chemistry, hematology, or histopathology. Thus, their utility is very limited. For example, in a 3-week study in rats,<sup>34</sup> toxicity was apparent at an amiloxate volume of 2.7 mL/kilogram (kg); however, the limited assessment of this study did not permit identification of target organs and did not provide a concentration to calculate the dose. A dose of 2,000 milligram (mg)/kg was toxic when administered by oral gavage to rats for 3 months,<sup>35</sup> but a dose of 200 mg/kg appears to be the no observed adverse effect level (NOAEL). Based on this study, the primary target organs appear to be the liver, blood, and the spleen. In the context of amiloxate's use as a sunscreen, these studies are of limited utility and data from other studies, such as carcinogenicity, will be most relevant.

Other studies were provided including skin irritation studies in rabbits and rats, skin sensitization studies in guinea pigs, and photoirritation and photoallergenicity studies in guinea pigs. These studies did not reveal any significant irritation or sensitization in terms of erythema or edema.<sup>36</sup> These studies constitute a good beginning in the exploration of the safety of amiloxate; the next step would be to corroborate the results of the irritation and sensitization studies by human clinical testing, as discussed in Section I.A.1.

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<sup>26</sup> SUP3, Vol. 1, H&R Tests No. 1982040 and 1986024.

<sup>27</sup> SUP3, Vols 1&2, H&R Tests No. 1980096, 1988065, 1987025, 1989139, 1997041, 1991002, 1986016, 1994018, and 1994263.

<sup>28</sup> SUP3, Vol. 2, H&R Tests No. 1987126, 1988034, and 2001155.

<sup>29</sup> SUP3, Vol. 1, H&R Tests No. 1975001, 1979004, and 1983014.

<sup>30</sup> SUP3, Vol. 2, H&R Tests No. 2002031, 2992077, and 2001155.

<sup>31</sup> SUP3, Vol. 1, H&R Tests No. 1994254, 1976019, 1976020, and 1994255.

<sup>32</sup> SUP3, Vol. 2, H&R Test No. 1990129.

<sup>33</sup> SUP3, Vol. 1&2, H&R Tests No. 1982040 1986024, 1975001, 1979004, 1983014, 1980096, 1988065, 1987025, 1989139, 1997041, 1991002, 1986016, 1994018, and 1994263.

<sup>34</sup> SUP3, Vol. 1, H&R Test No. 1979004.

<sup>35</sup> SUP3, Vol. 1, H&R Test No. 1983014.

<sup>36</sup> SUP3, Vol. 1, H&R Tests No. 1994254, 1976019, 1976020, 1994255, and 1990129.

## 1. Carcinogenicity Studies: Dermal and Systemic

FDA guidance recommends that carcinogenicity studies be performed for any pharmaceutical that is expected to be clinically used continuously for at least 6 months or “repeatedly in an intermittent manner.”<sup>37 38 39</sup> Because the proposed use of amiloxate in OTC sunscreens falls within this category, these studies should be conducted to help establish that amiloxate is GRAS for its proposed use. Carcinogenicity studies assist in characterizing potential dermal and systemic risks by identifying the type of toxicity observed, the level of exposure at which toxicity occurs, and the highest level of exposure at which no adverse effects occur, referred to as the “no observed adverse effect level” (NOAEL). The NOAEL would then be used in the determination of the safety margin for human exposure to sunscreens containing amiloxate.

Systemic carcinogenicity studies can also help to identify other systemic or organ toxicities that may be associated with amiloxate, such as hormonal effects. For example, the effect of persistent disruption of particular endocrine gland systems (e.g., hypothalamic-pituitary-adrenal axis), if any, can be captured by these assays.

### Data Available for Amiloxate: Genotoxicity Studies

The mutagenicity studies<sup>40</sup> provided did not demonstrate that amiloxate is mutagenic. However, the test articles in these studies were only identified by code numbers, so the identity of the test article is not clear. There are also questions about the doses used in many of the studies. A micronucleus study in mice<sup>41</sup> was also negative. A limited photogenotoxicity study conducted in *Salmonella*<sup>42</sup> was negative, as was a chromosomal aberration study<sup>43</sup> in Chinese hamster ovary cells conducted with and without UV light. While these studies ease concerns about potential genotoxicity and mutagenicity, they are not definitive evaluations of potential toxic effects from long term systemic or dermal exposure.

### Data Available for Amiloxate: Carcinogenicity Studies

We did not receive dermal and systemic carcinogenicity studies. Assessments of both dermal

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<sup>37</sup> International Conference on Harmonization (ICH), ICH Harmonized Tripartite Guideline. Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals S1A”, 1995, available on the Internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074911.pdf>.

<sup>38</sup> ICH, “ICH Harmonized Tripartite Guideline: Testing for Carcinogenicity of Pharmaceuticals S1B,” 1997, available on the Internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM74916.pdf>.

<sup>39</sup> ICH, “ICH Harmonized Tripartite Guideline: Dose Selection for Carcinogenicity Studies of Pharmaceuticals SIC(R2),” 2008, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM074919.pdf>.

<sup>40</sup> SUP3, Vols 1&2, H&R Tests No. 1980096, 1988065, 1987025, 1989139, 1997041, 1991002, 1986016, 1994018, and 1994263.

<sup>41</sup> SUP3, Vol. 1, H&R Test No. 1986016.

<sup>42</sup> SUP3, Vol. 1, H&R Test No. 1994018.

<sup>43</sup> SUP3, Vol. 1, H&R Test No. 1994263.

and systemic carcinogenicity are recommended because sunscreen products containing amiloxate are expected to be applied over large portions of the body with multiple daily applications. In addition, as discussed above, adding this ingredient to the OTC sunscreen monograph would permit its formulation in a variety of as-yet-unknown vehicles that might enhance systemic absorption.

## 2. Developmental and Reproductive Toxicity (DART) Studies<sup>44</sup>

FDA recommends conducting DART studies to evaluate the potential effects that exposure to amiloxate may have on developing offspring throughout gestation and postnatally until sexual maturation, as well as on the reproductive competence of sexually mature male and female animals. Gestational and neonatal stages of development may also be particularly sensitive to active ingredients with hormonal activity. For this reason, we recommend that such studies include assessments of endpoints such as vaginal patency, preputial separation, anogenital distance, and nipple retention, which can be incorporated into traditional DART study designs to assess potential hormonal effects of amiloxate on the developing offspring. We also recommend performing behavioral assessments (e.g., mating behavior) of offspring, which may also detect neuroendocrine effects.

### Data Available for Amiloxate: DART Studies

The embryo-fetal (teratogenicity) data in the rat indicated that amiloxate was maternally toxic at a dose of 2.25 mL/kg.<sup>45</sup> This dose was also associated with death of some fetuses and growth retardation in those that survived. No teratogenic effects (structural anomalies) were noted at the lower doses. An HET-embryotoxicity test<sup>46</sup> conducted in fertilized chicken eggs also found no increase in malformations. Retardation of hatching weight, skull diameter and bone length were noted after amiloxate injection. The LD<sub>50</sub> (dose that was lethal in 50% of the eggs) was 5.8 (microliters)  $\mu$ L/egg or about 120 parts per million (ppm) on day 1 and 1.15  $\mu$ L/egg or about 25 ppm on day 5. Data from avian reproductive toxicity studies are of limited utility in assessing human risk. However, the embryo-fetal data in the rat suggested that, under the conditions of the test, amiloxate is not a teratogen. FDA therefore does not request an additional embryo-fetal toxicity test.

Amiloxate did not exhibit significant rat androgen receptor or human estrogen receptor binding in vitro.<sup>47</sup> No evidence of estrogenic activity was observed for amiloxate in a juvenile rat study; this conclusion was based on the lack of change in uterine weight.<sup>48</sup> These preliminary studies suggest that amiloxate does not have any hormonal activity. However, these findings need to be corroborated by adequate DART studies (fertility and pre/postnatal studies) using hormonally sensitive endpoints as described above.

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<sup>44</sup> ICH, "ICH Harmonized Tripartite Guideline: Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2)," 2005, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074954.pdf>

<sup>45</sup> SUP3, Vol. 2, H&R Test No. 1988034.

<sup>46</sup> SUP3, Vol. 2, H&R Test No. 1987126.

<sup>47</sup> SUP3, Vol. 2, H&R Tests No. 2002031 and 2002077.

<sup>48</sup> SUP3, Vol. 2, H&R Test No. 2001155.

### 3. Toxicokinetics<sup>49</sup>

We recommend conducting animal toxicokinetic studies because they provide an important bridge between toxic levels seen in animal studies and potential human exposure. Data from these studies can be correlated to potential human exposure via clinical dermal pharmacokinetic study findings. Toxicokinetic data could be collected as part of animal studies conducted to assess one or more of the safety parameters described above.

#### Data Available for Amiloxate: Toxicokinetics

No toxicokinetic data were submitted as part of any of the studies, thus it is difficult to bridge from animal findings to potential human exposure. Toxicokinetic data should be collected as part of the animal studies to allow exposure comparisons between animals and humans.

## II. Effectiveness Data Considerations for OTC Sunscreen Products Containing Amiloxate

FDA's evaluation of the effectiveness of active ingredients under consideration for inclusion in an OTC drug monograph is governed by the following regulatory standard:

Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of efficacy shall consist of controlled clinical investigations as defined in § 314.126(b) of this chapter [...] . . . Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.<sup>50</sup>

To evaluate the efficacy of amiloxate for use in OTC sunscreen products, FDA requests evidence from at least two adequate and well-controlled SPF studies showing that amiloxate effectively prevents sunburn. In order to support finding amiloxate to be generally recognized as effective (GRAE) for use in OTC sunscreens at concentrations in a range with the proposed maximum strength of 10%, as requested, two adequate and well-controlled SPF studies of amiloxate at a lower concentration should be conducted according to established standards.<sup>51</sup> These SPF

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<sup>49</sup> ICH, "ICH Harmonized Tripartite Guideline: The Assessment of Systemic Exposure in Toxicity Studies S3A," 1995,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074937.pdf>

<sup>50</sup> 21 CFR 330.1(a)(4)(ii).

<sup>51</sup> The upper bound of any concentration ultimately established in the OTC sunscreen monograph will be governed by the safety data, as well as by efficacy.

studies should demonstrate that the selected concentration (below 10%) provides an SPF of 2 or more.

The current standard procedure for SPF testing is described in FDA's regulations at 21 CFR 201.327(i).<sup>52</sup> Future SPF tests for amiloxate should be performed as described in these regulations, using a test formulation containing amiloxate in isolation in order to identify its contribution to the overall SPF test results. (But see below for further discussion of existing SPF tests of amiloxate, submitted to the docket.) The study should also include a vehicle control arm in order to rule out any contribution the vehicle may have on the SPF test results. Finally, as described in 21 CFR 201.327(i), an SPF standard formulation comparator arm should be another component of the study design.

While current sunscreen testing and labeling regulations also specify a "broad spectrum" testing procedure to support certain additional labeling claims for monograph products, the indications that are tied to broad spectrum testing are permitted, but not required, for monograph products.<sup>53</sup> To be added to the OTC sunscreen monograph, a sunscreen containing amiloxate need only be effective for the labeled indication of sunburn prevention, for which the SPF test can provide sufficient evidence. Broad spectrum protection is often, although not always, the result of the combined contribution of multiple active ingredients in a final sunscreen formulation. Thus, if amiloxate is established to be GRASE for use in sunscreens (based in part on the efficacy data requested here), the determination of whether an individual sunscreen product containing amiloxate may be labeled as broad spectrum and bear the related additional claims will be made on a product-specific basis, by following the requirements of existing regulations. A finished product containing amiloxate would be potentially eligible to make "broad spectrum"-related claims if it satisfies those regulations.

#### Data Available for Amiloxate: Effectiveness

The amiloxate data submissions included 39 SPF studies.<sup>54</sup> Thirty-five of these studies evaluated formulations containing amiloxate in combination with one or more other sunscreen active ingredients. While these studies demonstrate that products that combine amiloxate with other sunscreen active ingredients are effective to prevent sunburn, they were not designed to confirm that amiloxate at the concentrations studied, on its own, provides an SPF value of at least 2. Testing should be designed to demonstrate that amiloxate itself provides an SPF value of at least 2 to demonstrate that the results shown reflect amiloxate's effectiveness and are not attributable to the other components of the tested products.<sup>55</sup> Thus, these thirty-five studies are not sufficient

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<sup>52</sup> Although the SPF testing procedure is used primarily for final formulation testing of finished products marketed without approved new drug applications, under the sunscreen monograph, it is equally applicable for determining whether or not a sunscreen active ingredient is GRAE.

<sup>53</sup> 21 CFR 201.327(c)(2), 201.327(j).

<sup>54</sup> SUP3 Vols. 3-4 and RPT 1.

<sup>55</sup> 21 CFR 330.10(a)(4)(iv); See also 21 CFR 352.10, 352.20 (currently stayed indefinitely). These monograph provisions establish that each finished sunscreen product must have an SPF value of at least 2, and that each active ingredient in a sunscreen product that combines active ingredients must contribute a minimum SPF of not less than 2 to the final formulated product.

to demonstrate that amiloxate is GRAE in OTC sunscreen products for use as labeled to prevent sunburn.

Four SPF studies evaluated formulations in which amiloxate (at various strengths) was the only active ingredient. Three of those studies could not be evaluated because only summary data were supplied.<sup>56</sup> However, one study showed that a test formulation containing 10% amiloxate had an SPF value of 13.6.<sup>57</sup> This study was conducted according to the then-current U.S. SPF test method and provided raw data for 20 evaluable subjects.<sup>58</sup> The study used a standard reference sunscreen control that produced the expected SPF value, indicating that the test results were accurate. Therefore, this study provides evidence that amiloxate at a concentration of 10% is effective for use in sunscreen. To support a finding that amiloxate is generally recognized as effective for this use at a lower concentration, we request two adequate and well-controlled SPF studies be conducted according to established standards to demonstrate that the lower concentration provides an SPF of 2 or more.

In addition to SPF studies, the amiloxate submissions included broad spectrum protection studies of specific sunscreen product formulations that included amiloxate in combination with other sunscreen active ingredients.<sup>59</sup> Broad spectrum studies are not necessary to establish that a sunscreen containing amiloxate would be generally recognized as effective to prevent sunburn. As explained above, other regulations for OTC sunscreens establish the testing required to support "broad-spectrum" labeling and related claims for sunscreen products (final formulations).<sup>60</sup> The agency does not intend to require a separate demonstration that amiloxate alone is sufficient to provide broad spectrum protection in order to establish that the ingredient may be included in the sunscreen monograph. If amiloxate is determined to be GRASE for the prevention of sunburn, and included in the monograph, the eligibility of specific sunscreen products for the "broad spectrum"-related labeling claims would be determined on a product-specific basis by applying contemporary testing and labeling requirements to that product. Thus, we do not request any further broad spectrum testing data for amiloxate as part of our evaluation of effectiveness of amiloxate for use in OTC sunscreen products.

Nonetheless, the agency did evaluate the broad spectrum protection studies submitted for amiloxate. These studies provided evidence to indicate that formulations containing amiloxate in combination with other sunscreen active ingredients provide broad spectrum protection.

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<sup>56</sup> COLIPA Sun Protection Test of formulation K 18/1-21504 C/E, and Sun Protection test of formulations K 18/1-51090/E and K 18/1-51090 D/E, using a German DIN protocol (SUP3 vol. 3). These studies tested the effectiveness of 3.5 and 4 percent amiloxate using non-U.S. SPF methods.

<sup>57</sup> Sun Protection Factor Determination Examination of the Product Emulsion U 53390A According to FDA Guidelines, SUP3, vol. 3.

<sup>58</sup> The method used in the study is described at 21 CFR 352.70-352.73 (currently stayed indefinitely) and has since been superseded by the current method described in 21 CFR 201.327(i). Although the two methods differ in some respects, we accept studies that were made using the earlier method before the current regulation took effect as adequate evidence of efficacy for purposes of sunscreen efficacy evaluation.

<sup>59</sup> RPT 1, appendices 5-8.

<sup>60</sup> 21 CFR 201.32.

However, they are not adequately controlled to demonstrate the contribution made by amiloxate, and do not demonstrate whether amiloxate as a single ingredient contributes to broad spectrum protection.

### **III. Summary of Current Data Gaps for Amiloxate**

Based on our review of the available safety and efficacy data discussed above, we request the types of data listed below, at minimum, in order for the Agency to reverse our initial determination that amiloxate has not been shown to be GRASE. For additional information about the purpose and design of studies recommended to address these data gaps, please refer to the earlier sections of this letter referenced in parentheses. Note that, in some cases, the submissions provided the results of studies of the type requested below, but only in summary form. Were complete study data provided to the docket, allowing the agency to verify the validity and accuracy of the summaries, these studies might be sufficient. If data from these previously conducted studies are not made publically available, further studies should be added to the public record to support a finding that amiloxate is GRASE for use in sunscreens. We welcome discussions on the design of any of the studies you intend to perform prior to their commencement.

#### Safety Data (see Section I)

##### A. Human Clinical Studies

1. Skin irritation/sensitization and photosafety (see Section I.A.1)
2. Human dermal pharmacokinetics (bioavailability) (see Section I.A.2)

##### B. Human Safety Data to Establish Adverse Event Profile (I.A.3)

1. A summary of all available reported adverse events potentially associated with amiloxate
2. All available documented case reports of serious side effects
3. Any available safety information from studies of the safety and effectiveness of sunscreen products containing amiloxate in humans
4. Relevant medical literature describing adverse events associated with amiloxate

Alternatively, the results of a literature search that found no reports of adverse events may be provided. In that case, detailed information on how the search was conducted should be provided.

##### C. Nonclinical (Animal) Studies

1. Dermal and systemic carcinogenicity (see Section I.B.1)
2. Fertility (see Section I.B.2)
3. Prenatal/postnatal development (see Section I.B.2)
4. Toxicokinetics (see Section I.B.3)

Effectiveness Data (see Section II)

If concentrations of amiloxate below 10% are to be included in the monograph requested, two SPF studies showing effectiveness of a selected concentration lower than 10%.

**IV. Administrative Procedures**

A copy of this letter will be filed in the Division of Dockets Management in Docket No. 2003N-0233. We encourage you and other interested parties to submit additional data regarding the safety and effectiveness of amiloxate for use in an OTC sunscreen product, to inform FDA's evaluation of whether this ingredient can be included in the sunscreen monograph. We also encourage interested parties to notify us in writing of their intent to submit additional data, and to request meetings with FDA to discuss protocol and data development. However, as noted previously, because the data submitted to date are not sufficient to support a determination that amiloxate is GRASE for use as an active ingredient in OTC sunscreen drug products, at this time OTC sunscreen products containing amiloxate may not be marketed without approval of a new drug application.<sup>61</sup>

Data submissions and other communications relating to this letter should be submitted to Docket No. 2003N-0233 at the Division of Dockets Management, 5360 Fishers Lane, Room 1601, Rockville, MD, 20852. In addition, you can submit the data through the Federal eRulemaking Portal at: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Sincerely,



Sandra L. Kweder, M.D., F.A.C.P.  
RADM (Ret.) U.S. Public Health Service  
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<sup>61</sup> See 21 CFR 330.14(h); see also 21 CFR 314.105.