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| **CONDITIONS** | Bemotrizinol, at a maximum concentration of 10 percent, as a single active ingredient and in combination with other sunscreen active ingredients | |
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| **PHARMACOLOGICAL CLASS** | UVA and UVB sunscreen | |
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| **MONOGRAPH** | | OTC Sunscreen Drug Products (21 CFR part 352) |
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| **APPLICANT** | | Ciba Specialty Chemicals Corporation  Home and Personal Care Business Line |
|  | | 4090 Premier Drive |
|  | | High Point, NC 27265 |
|  | |  |
| **SUBMISSION DATE** | | April 11, 2005 |
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| **RECEIVED DATE** | | April 12, 2005 |
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| **REVIEW DATE** | | April 17, 2005 |
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| **REVIEWER** | | Michael L. Koenig, Ph.D. |
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| **TEAM LEADER** | | Matthew R. Holman, Ph.D. |
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as a single active ingredient and in combination with other sunscreen active ingredients, to the monograph for OTC sunscreen drug products (21 CFR part 352). This TEA does not request any changes (e.g., labeling or testing) to the sunscreen monograph other than the addition of bemotrizinol. It is important to note that the applicant claims bemotrizinol protects against both UVA and UVB radiation.

Before submitting the TEA, the applicant submitted a citizen petition (CP13 in Docket Number 1978N-0038) in September 2000. The petition requested the addition of TINOSORB® S (bemotrizinol) to the sunscreen monograph. The petition also requested the addition of another sunscreen ingredient, TINOSORB® M (bisoctrizole and 4 inactive ingredients), to the sunscreen monograph. In our April 2002 response letter, FDA stated that the applicant should use the newly developed TEA format (67 FR 3060, January 23, 2002) rather than a petition to add these ingredients to the monograph. As directed by the FDA, the applicant submitted a TEA for both TINOSORB® M and TINOSORB® S on May 21, 2002. On July 15, 2002, FDA informed the applicant that we could not find either ingredient eligible for the OTC drug review, because neither ingredient had been “marketed for a minimum of five continuous years,” as required in 21 CFR 330.14(b)(2). Both ingredients had only been marketed for 2.5 years at that time. The applicant submitted the current TEAs on April 11, 2005, because bemotrizinol (and bisoctrizole) have now been marketed for 5 continuous years.

**REVIEWER’S COMMENTS**

The applicant has provided basic information about bemotrizinol including a detailed chemical description as required in 21 CFR 330.14(c)(1)(i). Although bemotrizinol is not included in the U.S. Pharmacopeia (USP)-National Formulary (NF), the applicant submitted a draft monograph to the USP on July 23, 2004. According to the applicant, USP is currently reviewing the draft monograph.

Bemotrizinol has been marketed for varying lengths of time in 31 countries on every continent except Antarctica and for at least 5 continuous years in 5 of these countries. The applicant has selected 7 countries to serve as the basis of the TEA, because these 7 countries represent the greatest volume of sales: Brazil, France, Germany, Greece, Italy, Spain, and Switzerland (bold print in Table 1). Bemotrizinol has been marketed for 5 continuous years in Brazil, France, Germany, Greece, and Switzerland. One of the selected countries (Switzerland) is listed in section 802(b)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act (the act) and 5 others (France, Germany, Greece, Italy, and Spain which are part of the European Union) are listed in section 802(b)(1)(A)(ii) of the act. The applicant states that, in all 31 countries, sunscreen products containing bemotrizinol are sold directly to consumers without a prescription and are “not regulated as drugs.” However, FDA notes that sunscreens are regulated as OTC medicines by the Therapeutic Goods Administration in Australia.

**TABLE 1.** **Countries in which bemotrizinol has been marketed (7selected countries appear in bold print)**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  | | --- | --- | | **Continent** | **Countries** | | Africa | South Africa | | Asia | China, Hong Kong, India, Indonesia, Korea, Malaysia, Philippines, Taiwan, Thailand | | Australia | Australia | | Europe | Austria, Belgium, **France1**, **Germany1**, **Greece1**, Israel, **Italy**, Poland, Slovenia, **Spain**, Sweden, **Switzerland1**, United Kingdom | | North America | Mexico | | South America | Argentina, Bolivia, **Brazil1**, Chile, Columbia, Ecuador | |

1 Bemotrizinol has been marketed for 5 continuous years in these countries.

The applicant indicates that bemotrizinol is most commonly marketed in combination with other sunscreen active ingredients. Formulations marketed in different countries include bemotrizinol and other monograph active ingredients (e.g. avobenzone, titanium dioxide) and/or other active ingredients under consideration for inclusion in the sunscreen monograph (e.g. amiloxate, enzacamene).

Detailed information about the population demographics in each of the 7 selected countries is provided in Appendix 1 of the TEA. Considering these 7 countries together with the other countries listed in Table 1, the population demographics appears to reflect the diversity of the U.S. population.

The applicant reports that it is unaware of any adverse drug experiences (ADEs) in any of the countries in which bemotrizinol-containing sunscreens have been marketed. The applicant also states that sunscreen products containing bemotrizinol have not been withdrawn from the market in any country.

Examples of labeling are provided for product sold in Europe (23 labels), South America (7 labels), and Asia (1 label). The indications, warnings, and directions included in the labeling from these countries are comparable to those outlined in 21 CFR 352.52(b), (c), and (d) respectively.

The applicant calculated the total number of dosage units sold in the 7 selected countries according to 21 CFR 330.14(c)(ii)(B). This paragraph stipulates that applicants can estimate the total number of dosage units sold for each dosage form by dividing the total weight of the active ingredient sold by the total weight of the active ingredient in the largest package size marketed. The sponsor used the average concentration (2.5%), rather than the highest concentration (10%), of bemotrizinol contained in the marketed products. Use of the average concentration seems appropriate, because it is reflective of the concentrations listed in the submitted labeling. By this method, the applicant estimates that approximately 120.1 million dosage units of sunscreen containing bemotrizinol were sold in the 7 selected countries between 2000 and 2004 (Table 2). Moreover, approximately 127 million dosage units were sold worldwide during this period. If the highest concentration of bemotrizinol were used in the calculation, an estimated 30 million dosage units of bemotrizinol-containing sunscreens were sold in the 7 selected countries and approximately 32 million dosage units were sold worldwide.

**TABLE 2.** **Estimated regional sales of bemotrizinol in sunscreen products (2000 - 2004).**

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| --- | --- |
| **Region** | **Estimated total sales**  **(million dosage units)** |
| Europe (6 countries) | 99.8 |
| South America (1 country) | 20.3 |
| **Total** (7 countries) | **120.1** |

**RECOMMENDATION**

I recommend that bemotrizinol, up to a maximum concentration of 10 percent, be considered eligible for the OTC drug review. Bemotrizinol should be eligible as a single active ingredient and in combination with other active ingredients in the OTC sunscreen monograph (21 CFR Part 352). Bemotrizinol has been marketed, primarily in combination, “for a material time” and “to a material extent” in 1 South American and 4 European countries. The demographics of these countries, especially when considered in combination with other countries in which this ingredient has been marketed as a component in sunscreens, adequately reflects the diversity of the U.S. population. At least 30 million dosage units of sunscreens containing bemotrizinol have been sold in 7 selected countries on 2 continents during 2000-2004. Furthermore, over 32 million dosage units have been sold in 31 countries on every continent except Antarctica. The applicant states that no serious adverse drug experiences have been reported for sunscreen products containing bemotrizinol. The sponsor should be advised of the following:

an official or proposed USP monograph must be included with data and information demonstrating the safety and effectiveness of this ingredient, in accordance with 21 CFR 330.14(i)

safety and effectiveness data are required for bemotrizinol as a single active ingredient and bemotrizinol in combination with GRASE active ingredients