



## **Time and Extent Application**

### **Bisotrizole**

**Prepared to support the Inclusion of Bisotrizole into FDA's Monograph for Sunscreen Drug Products for Over-the-Counter Human Use; (64 FR 27666-27693, as amended by 66 FR 67485-67487, Docket No. 78N-0038).**

**Submitted on:  
April 11<sup>th</sup>, 2005**

**Submitted by:**

**Ciba Specialty Chemicals Corporation  
Home and Personal Care Business Line  
4090 Premier Drive  
High Point, NC 27265**

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## INTRODUCTION

This Time and Extent Application ("TEA") is being submitted by Ciba Specialty Chemicals Corporation ("Ciba"), Home and Personal Care Business Line. It contains the information required to be submitted to the FDA for consideration of inclusion of a new ingredient into the OTC drug monograph system under the Agency's Final Rule on *"Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded"* (21 CFR Part 330, 67 FR 3060, January 23, 2002).

This TEA contains the most current and factual information on the ingredient: Bisotrizole being proposed for inclusion into FDA's Monograph for Sunscreen Drug Products for Over-the-Counter Human Use; (64 FR 27666-27693, as amended by 66 FR 67485-67487, Docket No. 78N-0038).

### Background

Ciba previously submitted this request to FDA on September 5, 2000 under the provisions of 21 CFR § 10.30 (i.e., Citizen Petition, Docket No. 78N-0038). Under this petition, Ciba stated that it would be appropriate for the FDA to consider our submission in concurrence with its plans to develop a comprehensive final monograph for UVB and UVA radiation protection as our petition primarily addresses the need for more photostable and UVA effective sunscreen ingredients.

FDA formally responded to our Citizen Petition (CP) on April 10, 2002 by stating that it had developed, and was now implementing, a new Time and Extent Application (TEA) process under which drugs without marketing experience in the United States could become eligible for consideration in the agency's Over-the-Counter (OTC) drug review (67 FR 3060, January 23, 2001). In this letter, FDA also stated that we would need to submit a TEA if we wished to pursue inclusion of our active ingredients in the OTC drug monograph system, as it did not intend to take further action on our CP. Moreover, it was also mentioned that FDA would give priority to those TEAs associated with pending CPs if those CPs were converted to TEAs and submitted within 120 days after publication of that final rule establishing the TEA program (i.e., January 23, 2002).

### Ciba's Position - New Photoprotection Ingredients are Needed to Combat Skin Cancer

Since the publication of the Sunscreen Tentative Final Monograph on May 12, 1993 (58 FR 28194), FDA medical groups and consumer interest groups have continued to document the significance of, and expressed increasing concern about, exposure to UVA radiation. Exposure to UVA radiation has been causally linked with the high incidence of skin cancer in the United States<sup>1</sup>.

UVA radiation has also been demonstrated to contribute to both acute and chronic skin damage such as erythema, melanogenesis, carcinogenesis, drug-induced photosensitivity, photoaging, and morphological alterations of Langerhans cells (58 FR 28233). Moreover, the large amount of UVA radiation present in the solar spectrum at the earth's surface also results in a significant contribution to the generation of erythema.

According to public health experts, skin carcinoma and melanoma rates have reached epidemic levels in the U.S. and are expected to rise. Estimates from the American Cancer Society suggest that 1.3 million new cases of basal cell and squamous cell carcinomas were seen in 2000<sup>2</sup>. In response to this threat, FDA has repeatedly stated that:

<sup>1</sup> Nelson, C.G. Photoprotection. In: Shaath N.A ed. Sunscreens, Regulations and Commercial Development, 3<sup>rd</sup> ed. Boca Raton, FL: Taylor and Francis, 2005: 19-43

<sup>2</sup> Idem



*"protection against UVA radiation is much more important than previously realized. Protection against UVA radiation may be as important to consumers' well-being as protection against UVB radiation"* (Baker, D.E., *FDA Response to CTFA Petition, Docket No. 78N-0038/CP11*, October 1, 1999).

Thus, it is clear that as the significance of UVA radiation in terms of public health concerns continues to mount, the need for more effective UVA filters that provide protection from the deleterious effects of UVA exposure also increases.

As far as the current OTC sunscreen monograph is concerned, Ciba's ultimate interest lies in the finalization of a comprehensive, scientifically sound final sunscreen monograph that addresses both UVB and UVA exposure. It is our firm belief that the availability of photostable and effective UVA absorbers is extremely limited under the existing FDA OTC Sunscreen Final Monograph. Thus, we are herein proposing that the FDA take action under the TEA to include Bisocetrizole in the final sunscreen monograph for UVB and UVA protection.

Ciba truly believes that its request for FDA to consider adding Bisocetrizole to the sunscreen monograph under this TEA is in the best interest of public health. This request, if implemented, will assure the availability of superior, state-of-the-art, photostable and safe UVA radiation protection products for the American public. Moreover, it will also provide American consumers with a more effective means for protecting themselves against the deleterious effects of overexposure to solar radiation.

#### **Ciba Applauds FDA for Creating the Time and Extent Application Process**

As stated in our previous comments relating to the Agency's approach to regulating OTC drug products on August 24, 2000 (*Docket No. 001N-1256*) and September 5, 2000 (*Docket No. 78N-0038/CP13*), Ciba believes that the process for adding new ingredients to OTC monographs needs to be flexible and dynamic in order to allow for the adoption of new active ingredients that are state-of-the-art, safe and efficacious.

Prior to the establishment of the TEA program, it was virtually impossible to add a new active ingredient to a finalized monograph unless the New Drug Application (NDA) route was utilized. This was problematic for non-pharmaceutical companies such as ours who are interested in offering more efficacious OTC active ingredients but cannot afford the prohibitively high costs associated with developing a formulation-specific NDA. This is especially the case with sunscreen actives, where amortization of the NDA costs for "second-generation" ingredients are economically unfeasible when compared to first-generation OTC-monographed ingredients.

Thus, Ciba would like to applaud the FDA for creating the new Time and Extent Application program, which essentially establishes a vehicle for including "foreign" ingredients that have been used for a material extent and time into FDA OTC monographs. With the establishment of this vehicle, new superior, photostable and safe UVA radiation protection ingredients may now become available for consumer use in the United States. Below is the information supporting our TEA for Bisocetrizole.



## 1. BASIC INFORMATION ABOUT THE ACTIVE INGREDIENT (Bisotrizole) AND ITS INTENDED USE

### 1.1. Description and Identity

The generic name of the active ingredient is Bisotrizole. Bisotrizole became the United States Adopted Name (USAN) for the drug substance in 2004<sup>3</sup>

The Ciba tradename for the commercial formulation of Bisotrizole is TINOSORB® M.

Chemically, Bisotrizole is known as 2,2'-methylene bis-[6-(2H-benzotriazol-2-yl), 4-(1,1,3,3-tetramethyl-butyl) phenol] (CASRN: 103597-45-1). The official International Nomenclature Cosmetic Ingredient (INCI) name for TINOSORB® M is: Methylene Bis-Benzotriazolyl Tetramethylbutylphenol ("MBBT").

*Note:* For clarification purposes, while Bisotrizole is the active ingredient, it is sold commercially as "TINOSORB® M" which is the micronized pre-formulation product (i.e., Bisotrizole with four inactive ingredients: Methylene bis-benzotriazolyl tetramethylbutylphenol (and) Aqua (and) Propylene glycol (and) Decyl glucoside (and) Xanthan Gum). Validated analytical studies submitted to USP demonstrate that Bisotrizole is distinctly identified in formulation and that there is no interaction between the active and inerts.

TINOSORB® M is currently under patent protection and Ciba is the sole manufacturer. A draft USP monograph for Bisotrizole was submitted to the United States Pharmacopoeia on July 23, 2004. It is currently under review by the USP.

### 1.2. Intended OTC Use

The intended use is as an active ingredient for human OTC sunscreen drug products as permitted under FDA's sunscreen monograph.

### 1.3. Pharmacological class

Sunscreens are considered as non pharmacological products in all of the countries where Bisotrizole is currently marketed. Hence, no pharmacological class is associated to Bisotrizole. However, UV filters fall under local legislation of countries where end products (sunscreens) containing Bisotrizole are sold. Details on these specific regulatory statuses are given below (Section 3.1.).

### 1.4. OTC Strength

Proposed maximum concentration in sunscreen formulations: 10% alone or in combination with any other registered UV filters.

Background: Bisotrizole was reviewed by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) of the European Commission and listed as safe as an ingredient for sunscreens at a concentration up to 10% in 2000<sup>4</sup>.

In addition to the European Union, Bisotrizole is also approved for use as a UV-filter in sunscreens in other countries at a maximum use concentration of 10% for the active ingredient.

<sup>3</sup> American Medical Association, 2001-04 published names: <http://www.ama-assn.org/ama/pub/category/7478.html>

<sup>4</sup> 24th Commission Directive 2000/6/EC of 29 February 2000, adaptation to technical progress of Annexes II, III, VI and VII to Council Directive 76/768/EEC



Further information related to all the countries of foreign use is presented below (in Section 3.1.).

### 1.5. Route of Administration, dosage forms and directions for use

Route of administration would be dermal via topical application of sunscreen formulations making SPF claims.

Dosage forms and directions for use are referred to in Section 3.3.1. and specified for each market sample presented in **Appendix III**.

### 1.6. Applicable OTC Monograph

FDA Monograph for Sunscreen Drug Products for Over-the-Counter (OTC) Human Use (64 FR 27666-27693, as amended by 66 FR 67485-67487, Docket No. 78N-0038).

*Note:* Ciba believes that it would be appropriate for the FDA to consider this application in concurrence with its plans to develop a comprehensive final monograph for UVB and UVA as stated in the Agency's Federal Register Notice of December 31, 2001 (66 FR 67485).

## 2. PHYSICAL-CHEMICAL CHARACTERISTICS OF ACTIVE INGREDIENT

### 2.1. Chemical Name

2,2'-Methylene bis-[6-(2H-benzotriazol-2-yl), 4-(1,1,3,3-tetramethyl-butyl) phenol]

### 2.2. Chemical Abstract Service Number

103597-45-1

### 2.3. Molecular Weight

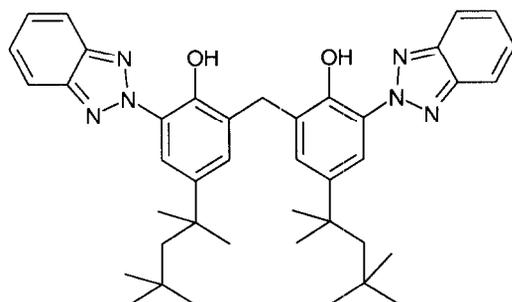
658.89

### 2.4. Molecular Formula

C<sub>41</sub>H<sub>50</sub>N<sub>6</sub>O<sub>2</sub>

### 2.5. Molecular Structure

Figure 1. Structure of Bisotrizole



### 2.6. Melting Point

195.7°C



**Ciba**

### 2.7. Method of Synthesis and Purification

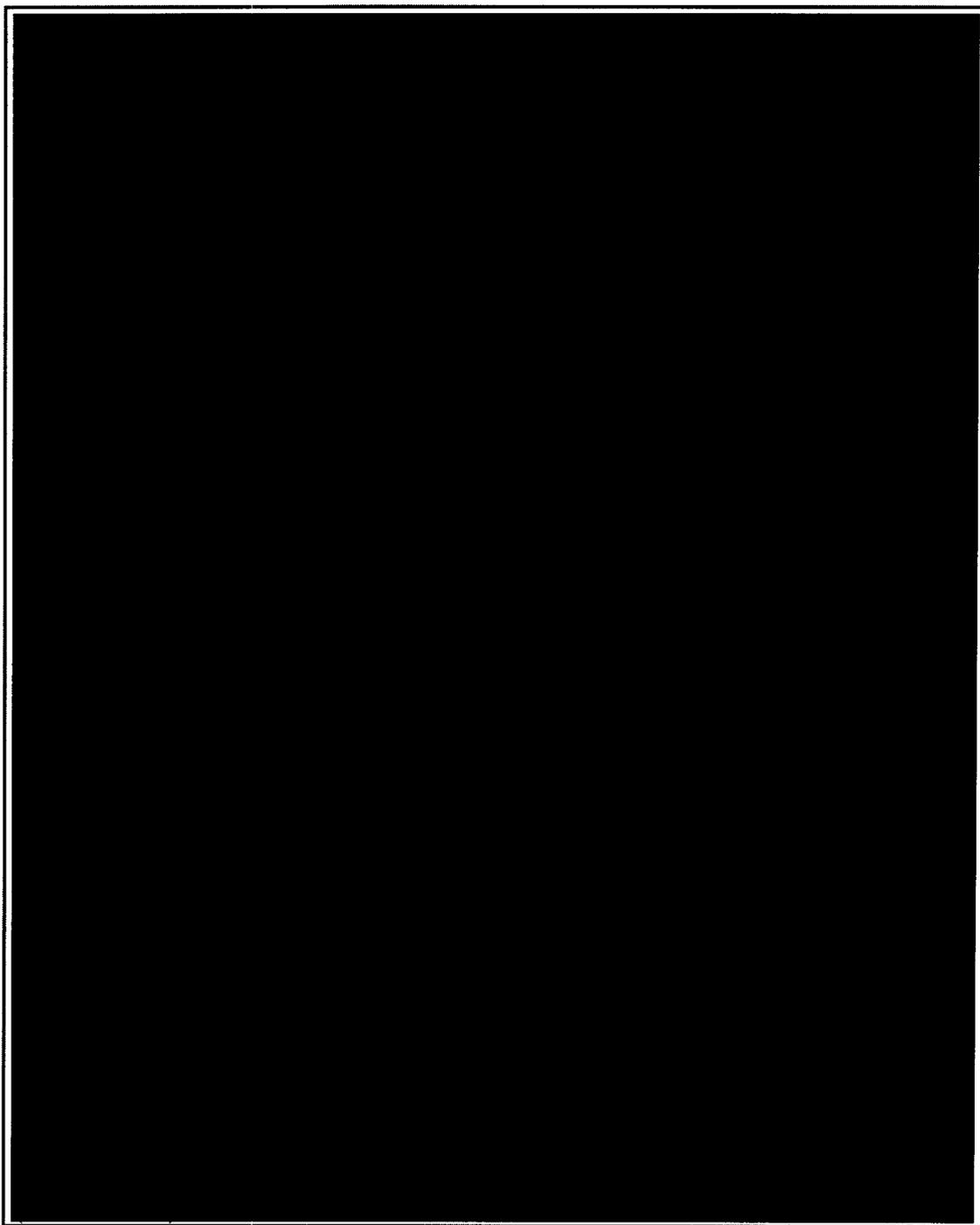






Table 1. - Product Specifications

Test Point	Test Method	Unit	Requirement
Appearance	Visual test		Yellowish fine to coarse powder
Identity	Infrared spectroscopy USP <197> <851> HPLC Spectroscopy CSL-IA-111/1E		Confirm
Assay	HPLC spectroscopy CSL-IA-111/1E	%	96 – 100
Assay isomer including individual compounds <0.1%	HPLC spectroscopy CSL-IA-111/1E	%	< 4
Assay starting material	HPLC spectroscopy CSL-IA-111/1E	%	≤ 0.5
Residual solvents	GC spectroscopy CSL-IA-110/1E	%	≤ 0.1 for each
Sum of heavy metals	USP <231> method II	mg/kg	≤ 20

### 3. FOREIGN USE DATA

Bisotrizole is currently sold in 39 countries worldwide. Nine of them have already reached 5 continuous years of market life (See Table 3).

#### 3.1. Global Regulatory Status of Bisotrizole<sup>5</sup>

End products containing Bisotrizole, sold as sunscreen or daycare products, are similar but are not sold as “over-the-counter” products like those marketed in the United States. Instead, all of these products are commercially available to consumers and are not regulated as drugs.

In Europe for example, they require no prescription because they are regulated as cosmetic ingredients. The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) concluded that Bisotrizole<sup>6</sup> is safe for use without restrictions as a UV absorber in cosmetic products, including sunscreen products, at concentrations up to 10%. The UV filter was listed in Europe as an ingredient for sunscreen use under the Twenty-Fourth Commission Directive 2000/6/EC of the Commission of the European Community on March 1, 2000<sup>7</sup>. This safety status is addressed in the Official Journal of the European Community adapting to technical progress a council directive<sup>8</sup> on the approximation of the laws of the Member States relating to cosmetic products. The information concerning Bisotrizole is included in paragraphs (10), (12) and Annex VII of the Directive.

In addition to the European Union, Bisotrizole has also been approved for use as a UV-filter in sunscreens in many other countries including key countries such as Australia, Japan, Taiwan, and China. Maximum use concentration of the active ingredient in all cases is 10%. These countries are considered key because they have regulatory review and approval systems similar to FDA's approval process (i.e., therapeutic goods, quasi drugs, etc.).

<sup>5</sup> Last update 24/11/2004

<sup>6</sup> Identified as 2,2'-methylene bis-[6-(2H-benzotriazol-2-yl), 4-(1,1,3,3-tetramethyl-butyl) phenol] in the SCCNFP documentation.

<sup>7</sup> 24th Commission Directive 2000/6/EC of 29 February 2000, adaptation to technical progress of Annexes II, III, VI and VII to Council Directive 76/768/EEC

<sup>8</sup> Official Journal, Council Directive 76/768/EEC, L 262, 27.9.1976, p. 169



Table 2 provides a summary of the registration status of Bisotrizole used as a UV filter in sunscreen products.

**Table 2. - Summary on the Registration Status in countries where Bisotrizole has been approved**

Country	Approval Status
<b>Europe</b>	
European Union <sup>9</sup>	Included in Part I of Annex VII of the European Cosmetic Directive 76/768/EEC
Switzerland	Included in Appendix 2 of Regulation on Cosmetic Products (Verordnung über kosmetische Mittel - VKos)
<b>Africa</b>	
South Africa	Included in South Africa's Foodstuff, Cosmetics and Disinfectants Act
<b>Asia</b>	
China	Hygienic Standard for Cosmetics
Hong-Kong	Sunscreen products are free to be placed on the market as long as no therapeutic claims are made and safe use is warranted. No registration of raw material or end product required.
India	Included in IS 4707 Standards
Japan	Included in Positive List under Japanese Pharmaceutical Affairs Law.
Malaysia	No special registration requirements for active ingredients. Customer formulations need to be registered with the Drug Control Authority.
Singapore	Sunscreen products are free to be placed on the market as long as no therapeutic claims are made. No registration of raw material or end product required.
Taiwan	Approved by Department of Health.
Thailand	No special registration requirements for active ingredients. Customer formulations need to be registered with the Ministry of Public Health.
<b>Australia</b>	
	Approved by Therapeutic Goods Agency (TGA) for use in dermal sunscreen products.
<b>South and Central America</b>	
Argentina	Included in Lista Positiva de Filtros Ultravioletas do Mercusol (Positive List of UV Filters, Mercosur)
Bolivia	
Brazil	
Paraguay	
Uruguay	
Mexico	Approved by the Ministry of Health
French Guyana	Included in Part I of Annex VII of the European Cosmetic Directive 76/768/EEC.
Bolivia	No registration of the raw material required. Finished sunscreen products are registered with Ministry of Health upon application by the manufacturer.
Colombia	
Ecuador	
Peru	
Chile	

<sup>9</sup> European Union Members: Austria; Belgium; Cyprus; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Luxembourg; Malta; Poland; Portugal; Slovakia; Slovenia; Spain; Sweden; The Netherlands; United Kingdom



In all of the above countries where registration is required, Bisotrizole has been approved for use up to a concentration of 10% in the final sunscreen products.

In Korea, Bisotrizole has not yet been included in the Positive List of Functional Actives, but several finished products containing Bisotrizole have been approved (Korean Food and Drug Administration) and are on the market.

### 3.2. Geographical presence

#### 3.2.1. All countries

Sunscreen products containing Bisotrizole are sold worldwide. Table 3 presents the list of the 39 countries in which Bisotrizole has been marketed and permits to identify the countries where it has been marketed for a minimum of 5 continuous years.

**Table 3. - Countries where Bisotrizole is marketed**

REGION	COUNTRY	YEARS OF CONTINUOUS SALES
Africa	South Africa	2
Asia	China	3
	Hong Kong	4
	India	4
	Indonesia	4
	Japan	<1
	Korea, Republic of	3
	Malaysia	5
	Philippines	3
	Singapore	<1
	Sri Lanka	<1
	Taiwan	<1
	Thailand	3
Australia	Australia	2
Europe	Austria	3
	Belarus	2
	Belgium	4
	Denmark	<1
	Finland	3
	France	5
	Germany	5
	Greece	5
	Italy	4
	Poland	3
	Slovenia	4
	Spain	5
	Switzerland	5
	Ukraine	1
United Kingdom	4	
Middle East	Iran	4
	Turkey	2
Latin America	Argentina	5
	Bolivia	1
	Brazil	5
	Colombia	5
	Ecuador	3
	Guatemala	1
	Mexico	4
	Peru	1



In 9 of the above countries, Bisotrizole-containing sunscreens have already been marketed for 5 consecutive years. The following 6 countries represent the largest volume of product used.

- Brazil
- France
- Germany
- Greece
- Spain
- Switzerland

These 6 countries, plus Australia, have been selected for the high volumes of sales they represent, but also for the breadth, and the variety of the product range their producers put on the market every year. Including Australia was considered as relevant because of the similarities between Australian and American legislation concerning UV filters.

Detailed data concerning these 7 countries is given below.

### 3.2.2. Selected countries

The seven countries selected present a large ethnic diversity<sup>10</sup> in their population and can be considered as reasonably representative for the diversity of USA inhabitants. Indeed, Australia, Brazil, France, Germany, Greece, Spain, and Switzerland bring together the Caucasian (white), black, Asian and other populations that also compose the US American highly diversified population.

More details on demographics are given in **Appendix I** for these selected countries and the United States.

Moreover, comparing the population pyramids<sup>11</sup> corresponding to the selected countries and the US population pyramid reveals that this combination of countries is very close, from a demographics standpoint, to the United States. "Middle-aged" layers of the population (baby-boomers) are the strongest. Younger layers show the declining birth-rates and older layers tend to decrease gradually. This "barrel" configuration is characteristic of industrialized countries. In these countries, market is led by the 30 to 50 year-old generation that consume not only for themselves but for their children as well. Sunscreen remains a convenience product that will be purchased by the parents for the whole family. On the other hand, older generations tend to expose themselves in the sun to a lesser extent and above all were less familiar with using sunscreen.

### 3.3. Use Pattern

The use patterns with global products utilizing Bisotrizole as an active ingredient for UV protection claims are consistent with those that appear in FDA's Monograph for Sunscreen Products for Over-the-Counter Human Use.

#### 3.3.1. Products

Bisotrizole-containing products can either be daywear or beachwear products.

- The former are used daily, are in general face specific (applied to the face only rather than the entire body) and aim to protect the skin on a daily basis from UV-induced damages. They do not always claim a precise SPF but general average UV protection.

<sup>10</sup> Source ethnic groups: CIA World Facts book 2004

<sup>11</sup> Source population: U.S. Census Bureau, International Data Base.

- The latter, commonly called sunscreens are seasonal products. They are extensively used during the summer (i.e. beachwear) or for winter sports. The protection they offer has to be adapted to the skin type (sensitive or not) and to the sun exposure conditions (from light to extreme).

Beachwear corresponds to sunscreens that aim to avoid sunburn whereas dailywear is more intended for daily protection against photoinduced skin aging. This distinction however loses its meaning in some countries such as Japan or India (and generally Asian countries) where sunscreen's first function is preventing suntan on a daily basis.

### Usual Claims

Sunscreens usually have certain characteristics that help to differentiate them such as the following:

- SPF (Sun Protection Factor)
- Target market (children; aging skin: anti-aging, firming; sensitive skin: sun allergic skin; cosmetic reactive skin; other: sport...etc.)
- Forms (lotion, spray, oil, mousse...etc.)

The most frequent specific product use directions or indications include the following:

- Low/ Medium/ High protection (+ SPF)
- Apply 20/ 30 minutes before sun exposure
- Reapply regularly, especially after bathing or toweling
- Avoid intensive midday sun
- For sensitive/ dry / children's skin

SPF (Sun Protection Factor) is generally used to convey the level of protection provided by sunscreens. In some cases, specific formulations may also include anti-aging, moisturizing, and skin firming claims. Some formulations may also be specifically targeted for children, or adapted for skin exposed to intense sweating due to sport practice, or extreme climatic conditions.

Beyond UVB protection claims conveyed by the SPF, specific UVA protection is also an important claim and is nowadays visible on most products.

Photostability claims are also put forward by some manufacturers as a quality warrant.

### Labeling

In all cases, directions for use and claims for these products appear on the product packaging and containers. In some cases, supplemental use information is also contained on a separate page (information leaflet) inserted into the product packaging. For the most part, product use information is similar between countries and the major differences are in packaging and language utilization.

*Note:* Package labeling complies with the applicable legislation in the country of sale

### Market examples

Representative examples of product labels and packaging for sunscreen products currently utilizing Bisotrizole as an active ingredient in sunscreen products are presented in **Appendix III**. In this appendix, a large number of marketed products, considered representative for the Bisotrizole-containing sunscreen market are listed.



Table 4. – Specified details for each market sample

<b>DOSAGE FORM</b>	The dosage form was referred to as the type of formulation or format utilized and its UV protection level. e.g.: High Protection Sun Spray
<b>Route of administration</b>	Dermal via topical application.
<b>Intended use</b>	In this section the SPF and, if applicable, the UVA protection level, as well as other specific claims (e.g.: “water resistant” or “for sensitive skin”) are specified.
<b>Directions for use</b>	Usually refer to an application, 20 to 30 min before sun exposure, and renewable.
<b>Pharmacological class of active ingredients</b>	No pharmacological class is referred to for a UV filter in any of the selected countries where Bisotrizole is in use. In this section the applicable legislation in the producer's country is specified.
<b>Applicable US FDA OTC Drug Monograph</b>	OTC Sunscreen Monograph

In addition, in Appendix III the following information on the products is provided:

- Active ingredients (UV filters) and their associated concentrations if available
- Other ingredients
- Photographs of the labels (product, box and information leaflet if applicable)
- Translation for labels if not originally in English.

Ciba can provide FDA with further information upon request.

### 3.3.2. Distribution of sunscreen products

Sunscreens are sold all over the world through different channels such as supermarkets and pharmacies. In all countries where Bisotrizole-containing products are sold, the choice for a given channel is often based on marketing considerations and is not related to any safety or health concerns due to active ingredients. No constraints, other than branding preferences, determines whether or not a sunscreen should be sold in a pharmacy and that its purchase should imply a pharmacist's approval.

### 3.3.3. Combinations with other sunscreen actives

Bisotrizole belongs to a new class of UV filters that acts both as a micropigment and organic UV absorber and is a highly efficient sunscreen due to its triple action: UV absorption by a photostable organic molecule, light scattering and light reflection by its microfine structure.

Beyond being an inherently photostable broadspectrum filter absorbing both UVA and UVB rays, Bisotrizole is an efficient SPF booster and has a stabilizing effect on other UV filters (eg: Octyl Methoxycinnamate → after irradiation with 10 MED, 27% of the OMC alone is lost; in the presence of Bisotrizole this loss is only 8%)<sup>12</sup>.

Bisotrizole, beyond its own efficiency, is also an enhancer for the properties of other filters and is thus used in combination with numerous other UV filters. Table 5 lists these filters.

In Table 6 the filter combinations observed in Bisotrizole-containing market samples, provided in **Appendix III** as indicated above, are summarized.

<sup>12</sup> Brochure TINOSORB® M: Microfine UV-A Absorber with Triple Action (available on [www.cibasc.com](http://www.cibasc.com))



Table 5. - Filters used in combination with Bisotrizole

Abbr.	USAN	US Registration Status
BEMT	Bemotrizinol	In the TEA process
BMBM	Avobenzene	US registered
BP3	Oxybenzone	US registered
DBT	Diethylhexyl Butamido Triazone	Not applicable
EHMC	Octinoxate	US registered
EHS	Octisalate	US registered
EHT	Ethylhexyl Triazone (a.k.a Octyl Triazone)	In the TEA process
IMC	Amiloxate	In the TEA process
MBC	Enzacamene	In the TEA process
OCR	Octocrylene	US registered
TiO2	Titanium Dioxide	US registered
ZnO	Zinc Oxide	US registered



Table 6. - Summary of filter combinations with Bisoctrizole<sup>13</sup>

Country	Brand	Product type	SPF	BEMT	BMBM	BP3	DBT	EHMC	EHS	EHT	IMC	MBBT	MBC	OCR	TiO2	ZnO
<b>Europe</b>																
France	Avène	Lotion	20					X				X			X	X
France	Avène	Lotion	60	X				X				X			X	X
France	Photoderm Max	Lotion	100		X					X		X	X			
France	Ducray (Photoscreen)	Cream-gel	30					X				X		X	X	
France	Ducray (Photoscreen)	Cream	60					X				X		X	X	
Spain	E. Carreras	Lotion	50	X											X	
Spain	E. Carreras	Lotion	70	X							X				X	
France	Galenic	Spray	25					X				X		X		
France	Galenic	Cream	60					X				X		X	X	
Spain	Fotoprotector Extreme Isdin	Lotion	Total					X				X	X		X	
Spain	Fotoprotector Extreme Isdin	Cream	Total				X	X				X	X		X	
Switzerland	Piz Buin	Lotion	30	X				X				X	X		X	
Switzerland	Piz Buin	Duo Lotion	15	X				X				X	X			
Switzerland	Piz Buin	Mountain Cream	15	X				X				X	X			
Switzerland	Piz Buin	Mountain Cream	30	X				X				X	X		X	
France	ROC (Minesol)	Spray	20	X				X				X	X			
France	ROC (Minesol)	Cream	30	X				X				X	X		X	
France	ROC (Minesol)	Lotion	40	X				X				X	X		X	
France	ROC (Minesol)	Cream	60	X				X				X	X		X	
Switzerland	Sun Look	Spray/kids	30		X			X	X			X	X	X		
Switzerland	Sun Look	Spray	30		X			X	X	X		X	X	X		
Switzerland	Sun Look	Milk	30		X			X	X	X		X	X	X		
<b>Asia</b>																
Malaysia	Eversoft White	Cream	35					X			X	X			X	
Malaysia	Safar White	Cream	25			X		X				X			X	
Malaysia	Tracia	Cream	40			X		X	X			X			X	
<b>South America</b>																
Colombia	Tanga	Cream	24	X				X		X	X	X			X	
Colombia	Tanga	Spray	50	X		X		X		X		X			X	
Ecuador	Suncare	Cream	60					X		X		X				
Ecuador	Suncare	Gel	60	X				X		X		X				
<b>Australia</b>																
Australia	Every Day Plus	Cream	30+					X				X	X			X

<sup>13</sup> Reference: see Appendix III



**3.4. Estimation of population exposure to Bisotrizole**

**3.4.1. Amount of Active Ingredient Sold**

Table 7 shows the volume (Kg) of Bisotrizole sold over the past 5 years, by country, for sun care applications (claiming sun protection benefits). The figures presented in this table correspond to sales figures of Bisotrizole to customers located in the selected countries quoted in Section 3.2.2. Bisotrizole-containing formulations have been documented as being used in personal care products in several countries around the world since 2000.

**Table 7. - Summary of volume of Bisotrizole (Kg) sold for sunscreen products per selected country over 2000-2004, and Estimate for 2005**

Confidential Business Information: Ciba Specialty Chemicals	
	Total Volume 2000-2004 (KGS.)
TOTAL (7 countries)	287748

**3.4.2. Calculation of Number of Units Sold and of Exposed Populations**

Package size for sunscreen typically ranges from 50 ml to 200 ml (this is roughly equivalent to 50 to 200 g for all dosage units). The typical amount of Bisotrizole incorporated to sunscreen is 2.5%. Table 8 provides an estimate of the total number of units of Bisotrizole-containing sunscreens sold by the most representative countries over the last five years. Although sun care products are available in different commercial forms (e.g. gel, cream, lotion, spray, etc) they are all topically applied formulas. Therefore the cumulative total number of dosages is best represented using the assumption of a single dosage form. Hence, this estimate considers an average product in terms of size and concentration.

Total number of units was derived using the following calculation:

$$(0.025 \text{ Kg of Bisotrizole} / \text{Kg of sunscreen}) * (0.2 \text{ Kg of sunscreen} / \text{Unit}) = 0.005 \text{ Kg Bisotrizole} / \text{Units}$$

$$\text{Volume of Bisotrizole sold (Kg)} / 0.005 \text{ Kg of Bisotrizole} / \text{units} = \text{Number of units}$$

*Note:* An average of 6 months is generally observed between the time that the active is purchased and the time that the end product containing this active is actually put on the shelves by the sunscreen manufacturer.



**Table 8. - Calculated number (x1000) of Bisotrizole-containing product units sold per selected country over 2000-2004, and Estimate for 2005**

Confidential Business Information: Ciba Specialty Chemicals	
	Total Number of Units (x1000) 2000-2004
TOTAL (7 countries)	57551

Then, considering these calculated numbers of Bisotrizole-containing sunscreen units sold over 2000-2004, corresponding numbers of applications have been estimated. The calculation was based on the assumption that a standard sunscreen application is of 1 mg of sunscreen per cm<sup>2</sup> of skin. This leads to approximately 14 applications per unit of sunscreen.

*Note:* In a study run by B. Diffey<sup>14</sup>, it is reported, "[...] volunteers were asked to apply sunscreen to one forearm "as if you were on the beach" using a quantity of sunscreen sufficient to produce an average thickness of 1 mg/cm<sup>2</sup> over the forearm." This amount corresponds to half the amount used in SPF testing

**Table 9. - Calculated number (in millions) of applications of Bisotrizole-containing sunscreen per selected country over 2000-2004, and Estimate for 2005**

Confidential Business Information: Ciba Specialty Chemicals	
	Total Application Number (Million) 2000-2004
TOTAL (7 countries)	805.7

<sup>14</sup>B. Diffey, Sunscreen isn't enough, Journal of Photochemistry and Photobiology, 64 (2001) 105-108

**Conclusion:**  
Over 1 billion applications of Bisotrizole-containing sunscreen over the first five years of marketing

*Note:* These calculated numbers are not customer (sunscreen manufacturers) data. This approximation allows an interesting overview of the quantities of Bisotrizole consumed worldwide but resulting exposure estimates are to be considered as indicative only.

We globally observe that products manufactured in one country by a given producer, may be sold worldwide; the only limitation being the applicable regulations in the area where the end product (sunscreen) is to be sold. We can observe indeed that consumer exposure to Bisotrizole-containing products goes far beyond the boundaries of the primary country of manufacture. In some cases, a product made in one country may be distributed to many other countries. Thus, although only seven major countries are specifically represented above, the distribution process actually extends the global presence of this product to even broader demographics.

Further illustration can be given on consumer exposure to Bisotrizole by considering the example of the French producer BIODERMA (DIPTA), with its specific high protection factor sunscreen range, Photoderm MAX. Details on BIODERMA's sales of this range are given in **Appendix II**.

*Note:* The example presented here is documented in Appendix II. Other producers/brands will address information directly to the FDA to protect confidential information.

### 3.5. Description of Method for Collecting Adverse Drug Experience Data

Below, the regulatory situation in the 7 selected countries is described in more detail:

In the **European Union** (comprising 25 member states including France, Germany, Greece, and Spain out of the 7 selected countries, as well as Austria, Belgium, Denmark, Finland, Italy, Poland Slovenia and the United Kingdom among the other sales countries) the monitoring of adverse effect data is regulated by the EU Cosmetics Directive in its most recent version. Article 7a 1. says:

"The manufacturer or his agent or the person to whose order a cosmetic product is manufactured or the person responsible for placing an imported cosmetic product on the Community market shall for control purposes keep the following information readily accessible to the competent authorities of the Member State concerned at the address on the label in accordance with Article 6(1) (a):

(f) existing data on undesirable effects on human health resulting from use of the cosmetic product."

In **Switzerland** to date there are no specific regulatory requirements regarding collection of adverse effects apart from the good practice applied by the industry on a voluntary basis. However, it is expected that later in 2005 a new regulation similar to the EU Cosmetics Directive described above will also be introduced in Switzerland.

In **Brazil**, a so-called Consumer Code exists that requires suppliers to print at least a contact address on the product packages. Usually Personal Care companies have a consumer hotline that can answer simple questions and passes on more difficult issues to the experts in charge.

In **Australia**, the Therapeutic Goods Agency is responsible for regulating sunscreen actives and has set up the Adverse Drug Reactions Unit (ADRU). Together with the Adverse Drug Reactions Advisory Committee they run a system for collecting and assessing reports on adverse effects.

Reports can be submitted by anybody. ADRU also publishes an electronically available bulletin. On top of this the TGA conducts post marketing surveillance of marketed products and subject samples to analysis and regulatory scrutiny. Also notifiers of marketed products are required to carry out on going stability testing on each product as well as assurance that any adverse trend will be reported. If adverse effects are not appropriately reported, the TGA will take action which may include cancellation of the products registration status.

Other countries:

In general, the larger companies selling sunscreen products with Bisotrizole employ a "customer attendance service" type system for collecting adverse drug experience data. In general, the system works as follows. This is part of their obligation under the applicable product liability legislation.

- Information regarding customer (end consumer) adverse drug experience or information address/telephone number is provided on the product label;
- Sunscreen product company receives a complaint via phone call or mail.
- Company investigates incident and requests that a sample be sent by consumer.
- Sample is analyzed and compared to standard.
- If the sample is ok without any external interference they write a letter to the customer indicating test results with technical information regarding product safety, etc.
- If medical emergency exists, company provides relevant toxicity information to doctor and pays for doctor to treat the problem. Quality Assurance Department and Customer Attendance Service Department have all the data related to these complaints in their files to be checked and audited as per GMP.
- Active ingredient manufacturer is advised of serious incidents and follows up accordingly.

To our knowledge, as of the date of submission of this document, there have been no serious or adverse experiences filed for any sunscreen products containing Bisotrizole.

### 3.6. Prescription Drug information

All sunscreen products containing Bisotrizole are sold to consumers (e.g., in commercial retail establishments) and not via prescription or OTC drug.

### 3.7. Marketing Withdrawals

We are not aware of any withdrawals of Bisotrizole-containing products due to adverse health claims in any of the countries where it is used as an active ingredient in sunscreen formulations. Applications for Bisotrizole-containing products have been established in each geographic region sought; this product has not been denied by any regulatory authority.