

2.7.4 Summary of Clinical Safety

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2.7.4.1 Exposure to the Drug

2.7.4.1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

Legacy Clinical Testing Completed and Reviewed by FDA

In our initial IND 146892 Serial 0000 (Section 2.5; April 2020), was included a summary of the legacy clinical controlled and uncontrolled studies with Bemotrizinol that are available on the FDA OTC public Docket (<https://www.regulations.gov/document?D=FDA-2005-N-0453-0003>). The FDA has reviewed and commented on the adequacy of the studies and identified the data gaps for completing the scientific record of BEMT to meet requirements for GRASE classification (FDA 2014 1)

Brief Summary of Previous Clinical Experience

A summary of the legacy clinical controlled and uncontrolled studies with Bemotrizinol was included in our initial IND 146892 Serial 0000 (Section 2.5; April 2020). The positive outcomes from these controlled clinical tests, the absence of documented customer and consumer complaints regarding BEMT, and its continued regulatory classification as safe for use in consumer products worldwide have supported its ongoing safe use over more than 20 years. From its first regulatory approval in 2000 until March 2023, only two fully relevant adverse event case reports have been published: one in 2019 (Luna-Bastante et al.) and another in 2022 (Suzuki et al.). These 2 reports are summarized in section 2.7.4.2.2 below.

Considered together, the clinical experience with Bemotrizinol presents a safety profile that does not raise any concerns, providing clear support for BEMT's safety in topical use.

Clinical Development Program

The product development process for BEMT adhered to FDA guidelines outlined in "Nonprescription Sunscreen Drug Products - Safety and Effectiveness Data" (FDA 2016), Guidance on Maximal Usage Trials for Topically Applied Active Ingredients (FDA 2019), and several relevant ICH guidelines referenced in this submission. This approach also incorporated the agreed upon tests and recommendations and advice received from the FDA at a BEMT pre-IND meeting in June 2019 and as part of our IND 146892 general investigational plan and subsequent updates to our testing program communicated to FDA in IND 146892.

Completed studies include an assessment of the human systemic absorption of sunscreen ingredients be made via the conduct of a pivotal Maximum Usage Trial (MUsT) in humans as well as skin irritation, sensitization and phototoxicity and photosensitization determinations. SPF efficacy studies for sunburn protection to human skin was also completed under standard clinical protocols to meet each of the FDA requirements supporting the BEMT determination as GRASE. Each of the completed controlled clinical studies followed standard, FDA recommended protocol designs using healthy subjects with intact skin to show clinical safety and effectiveness for the intended skin protective intervention.

1 FDA 2014. Determination and Feedback Letter from FDA CDER to Ciba Specialty Chemicals Corporation and Morgan Lewis and Bockius LLP re Time and Extent Application (TEA) Bemotrizinol for use in Over the Counter OTC Sunscreen. Available at <https://www.regulations.gov/document/FDA-2005-N-0453-0035>

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Table 1 presents a summary of the studies conducted under our clinical development program (IND 146892) to support the safety and efficacy of BEMT 6% as an OTC sunscreen active ingredient.

Table 1 Studies Conducted Under Clinical Development Program for BEMT

Study Type	Test Design and Objectives	Status
Clinical Studies		
Human Repeated Insult Patch Test (HRIPT) - Dermal Irritation, Sensitization, and Cumulative Irritation Study # CRLNJ2020-0493	Primary objective: determine the potential of 6% BEMT (PARSOL® Shield) either in a basic sunscreen oil formulation or as dispersion in petrolatum to elicit dermal irritation and/or induce sensitization following repeated patch application. Secondary objective: determine the cumulative irritation potential of 6% BEMT (PARSOL® Shield) either in a basic sunscreen oil formulation or as dispersion in petrolatum topically applied to the skin of human subjects over a 21-day period. Study Summary submitted under IND 146892 Serial 0010, section 1.13.8.1.2.3.	Completed
Phototoxicity Study # CRLNJ2020-0494	The objective of this study was to evaluate the potential of 6% BEMT (PARSOL® Shield) in a suitable vehicle (i.e., sunscreen oil or petrolatum) to produce a phototoxic response after application to the skin of human subjects followed by exposure to UV radiation. Study summary submitted under IND 146892 Serial 0010, section 1.13.8.1.2.2.	Completed
Photoallergenicity Study # CRLNJ2020-0495	The objective of this study was to evaluate the potential of investigational product, 6% BEMT (PARSOL® Shield) in a suitable vehicle (i.e., sunscreen oil or petrolatum) to produce a photoallergic response after application to the skin of human subjects followed by exposure to UV radiation. Study summary submitted under IND 146892 Serial 0010, section 1.13.8.1.2.1.	Completed
BEMT Pilot Maximum Usage Trial (MUsT) Spaulding Study # BEMT-001 Part 1	This was Part 1 of a single clinical MUsT study conducted in 2 parts (Part 1: pilot study and Part 2: pivotal study). Part 1 was an open-label, 1-arm study that had the following objectives: Primary: To explore whether Bemotrizinol (PARSOL® Shield), is absorbed into the systemic circulation from a high-penetrating sunscreen formulation including 6% BEMT when applied under maximal-use conditions. Secondary: To obtain information needed for a successful pivotal study such as preliminary pharmacokinetic (PK) data, validation of study and analytical procedures, and the number of subjects needed. Study summary submitted under IND 146892 Serial 0008, section 1.13.8.2.1.	Completed
BEMT Pivotal Maximum Usage Trial (MUsT) Spaulding Study # BEMT-001 Part 2	This was Part 2 of a single clinical MUsT study conducted in 2 parts (Part 1: pilot study and Part 2: pivotal study). Part 2 was an open-label, randomized, 3-arm study with the following objective: Primary: To assess the systemic absorption and pharmacokinetics of 6% BEMT from 3 market image sunscreen formulations under maximal-use conditions. Study summary and report submitted under IND 146892 Serial 0011, section 5.3.3.1.	Completed

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2.7.4.1.2. Overall Extent of Exposure

In the pivotal phase participants remained in-clinic for four days receiving 4 daily applications at 0, 2, 4, and 6 hours to 75% of body surface area each with 2 mg formulation/cm² of skin; 27.75 grams mean weight of study drug was applied per subject and application, which contained 1.66 grams BEMT for 6.66 g BEMT per day (111 mg/kg b.wt./day). Specific times of study drug applications and the blood sample times after first daily dose are shown in [Table 2](#).

Table 2 Pivotal phase dose application and blood sample times

Study Drug Application: hours after 1 st Dose		Blood Sample Times: hours after 1 st Dose
Day1	0, 2, 4, 6	-0.5, 2, 4, 8, 12
2	24, 26, 28, 30	23.5, 28, 32
3	48, 50, 52, 54	47.5, 52, 56
4	72, 74, 76, 78 (last dose)	71.5, 74, 76, 78, 80, 82, 84, 86
5	None	96

Clinical Pharmacokinetics of Maximal Dermal Exposures (MU_sT) to BEMT 6%

Clinical evidence for the very low bioavailability of BEMT was demonstrated in a clinical pilot and pivotal human maximal use pharmacokinetic study.

Overall, in plasma samples BEMT concentrations were above LLOQ in 31% (1169) of the 3722 plasma samples collected and analyzed from the 54 individuals in each of the three study arms; only 3% (113) of all samples had BEMT concentrations at or above a 0.5ng/mL threshold. Five of 162 subjects did not have any quantifiable BEMT concentrations in any of their 22 plasma samples.

Evidence was sparse, and due to the limited number of quantifiable plasma results, estimations for BEMT accumulation or steady-state concentrations above the FDA's plasma threshold of 0.5 ng/mL, or the LLOQ of 0.1 ng/mL, were poorly substantiated. Nonetheless, the data provide pivotal indications of the extremely low bioavailability of BEMT 6% when applied at unreasonably high maximum topical doses (6.66 g/d; 111 mg/kg b.wt./d). These findings support the absence of concern regarding the human topical use of BEMT 6% in sunscreens.

Additional information regarding the pharmacokinetic data can be found in [2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES](#) and 5.3.2 Reports for Biomaterials Pharmacokinetics.

Additionally, the low level of BEMT absorption into systemic circulation supports its sustained sun protection efficacy following topical application, ensuring that the active ingredient remains primarily on the skin where it can effectively provide UV protection without raising concerns about systemic exposure.

- In Part, overall, topical applications of BEMT 6% sunscreen oil with 10% ethanol as penetration enhancer, applied 4 times per day for 4 days, were safe and well tolerated by the healthy adult male and female subjects in this study.
- In Part 2, overall, topical applications of BEMT 6% sunscreen oil with 10% ethanol as penetration enhancer, BEMT 6% O/W emulsion, and BEMT 6% W/O cream emulsion applied 4 times per day for 4 days were safe and generally well tolerated by the healthy adult male and female subjects in this study.

2.7.4.1.3. Demographic and Other Characteristics of Study Population

Pilot phase 1 study (BEMT-001 Part 1):

Test participants demographics were as follows: of the 14 participants enrolled, 9 (64.3%) were White, and 5 (35.7%) were Black or African American, and most participants were not Hispanic or Latino (85.7%). The Fitzpatrick skin type assessments on Day –1 were IV (8 participants, 57%), III (5, 36%), and V (1, 7%).

Pivotal Phase 3 Study (BEMT-001 Part 2):

The pivotal clinical MUSt was conducted with a diverse American population-representative panel of 162 human participants exposed to maximal topical applications of 3 different market-like sunscreen formulations. These were identified after an exhaustive global market survey yielding over 68,000 finished products, among which were over 5400 targeted sunscreen products containing BEMT and were the foundation for selecting and formulating the study drug products for the MUSt. To ensure balanced and diverse representation of all subpopulations most likely to use products with BEMT in the future, a statistical factorial approach was used with respect to the following factors and subgroups: sex (female, male), age (18-40, 41-60, and 60+ years), and race (Group 1: Black or African Americans; Group 2: Hispanic or Latin Americans, Asians, Native Hawaiians, American Indians, Alaska Natives; and Group 3: White Americans).

2.7.4.2 Adverse Events

2.7.4.2.1. Analysis of Adverse Events

Part 1:

In Part 1, overall, 8 of 14 subjects (57.1%) reported a total of 36 TEAEs. The SOC within which the greatest number of subjects reported TEAEs was skin and subcutaneous tissue disorders (5 subjects [35.7%] Overall). The TEAE reported by the most subjects was skin irritation (4 subjects [28.6%]) followed by dry skin, increased lacrimation, and skin laceration (2 subjects [14.3%] each). All other TEAEs were reported by 1 subject (7.1%) each. Five subjects (35.7%) reported 26 TEAEs that were considered related to study drug. The TEAEs considered related to study drug were skin irritation (4 subjects [28.6%]) and dry skin, erythema, pruritus, erythematous rash, urticaria, increased lacrimation, constipation, and rhinorrhea (1 subject [7.1%] each).

Seven subjects (50.0%) reported 30 TEAEs that were considered mild in severity, and 1 subject (7.1%) reported 6 TEAEs that were considered moderate in severity. The TEAEs

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considered moderate in severity were erythema and urticaria and led to the subject's discontinuation from the study (section 2.7.4.2.1).

No severe TEAEs, SAEs, or deaths were reported. All TEAEs resolved by the end of the study.

Part 2:

In Part 2, overall, 62 of 162 subjects (38.3%) reported 143 TEAEs. Treatment-emergent AEs were reported by 24 subjects (44.4%) after receiving BEMT 6% oil, 24 subjects (44.4%) after receiving BEMT 6% W/O, and 14 subjects (25.9%) after receiving BEMT 6% O/W. The SOC within which the greatest number of subjects reported TEAEs was skin and subcutaneous tissue disorders (42 subjects [25.9%] Overall); TEAEs within this SOC were reported by 19 subjects (35.2%) after receiving BEMT 6% W/O, 13 subjects (24.1%) after receiving BEMT 6% oil, and 10 subjects (18.5%) after receiving BEMT 6% O/W. The TEAE reported by the most subjects Overall was pruritus (17 subjects [10.5%]) followed by maculopapular rash (14 subjects [8.6%]), erythematous rash (12 subjects [7.4%]), papular rash (11 subjects [6.8%]), and eye irritation (8 subjects [4.9%]). All other TEAEs were reported by less than 5 subjects (3.1%) each.

A total of 49 subjects (30.2%) reported 111 TEAEs that were considered related to study drug. Related TEAEs were reported by 20 subjects (37.0%) after receiving BEMT 6% W/O, 19 subjects (35.2%) after receiving BEMT 6% oil, and 10 subjects (18.5%) after receiving BEMT 6% O/W. The related TEAE reported by the most subjects Overall was pruritus (17 subjects [10.5%]) followed by maculopapular rash (13 subjects [8.0%]), erythematous rash (11 subjects [6.8%]), papular rash (11 subjects [6.8%]), and eye irritation (8 subjects [4.9%]). All other related TEAEs were reported by less than 5 subjects (3.1%) each.

All TEAEs were considered mild in severity. No severe TEAEs, SAEs, deaths, or TEAEs leading to study discontinuation were reported.

2.7.4.2.1.1 Common Adverse Events

Data on the frequency of adverse events by subject is listed in [Module 5.3, CSR Appendix 16-2-7](#).

2.7.4.2.1.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

In Parts 1 and 2, no SAEs or deaths were reported ([Listing Module 5, CSR 14.3.2.1](#)).

In Part 1, 1 subject (7.1%) experienced 6 TEAEs (erythema and urticaria, 3 events each) that led to study discontinuation ([Module 5.3, CSR Section 12.3.2, Table 14.3.1.5.1, and Appendix 16.2.7.2](#)).

In Part 2, no TEAEs leading to study discontinuation were reported ([Module 5.3, CSR Table 14.3.1.5.2 and Appendix 16.2.7.2](#)).

2.7.4.2.2. Narratives of Deaths, Serious Adverse Events, and Certain Other Significant Adverse Events

Part 1:

Subject 1010 (58-year-old White female) received BEMT 6% oil topical application 4 times per day on Days 1 through 3. On Day 3, approximately 1 hour after the third application, the subject reported TEAEs of skin irritation of the lower back and abdomen that were considered mild in severity, probably related to study drug, and resolved within approximately 18 hours of onset. On Day 4, approximately 17 hours after the fourth application on Day 3, on physical examination, the subject was observed to have erythema and welts confluent on the abdomen and all 4 extremities, and approximately 2 hours later, the subject was observed to have skin irritation of the abdomen and lower back that were considered clinically significant. The events were documented as TEAEs of erythema of the upper arms, abdomen, and lower back and TEAEs of urticaria of the upper arms, abdomen, and lower back that were considered moderate in severity and probably related to study drug. The TEAEs led to study drug withdrawal and study discontinuation on Day 4. The TEAE of erythema of the upper arms and the TEAE of urticaria of the upper arms resolved within 9 hours of onset. The TEAEs of erythema of the abdomen and lower back and TEAEs of urticaria of the abdomen and lower back resolved within 7 days of onset. Also on Day 4, approximately 1 day after the last study drug application, the subject reported a TEAE of dry skin of the upper arms that was considered mild in severity, probably related to study drug, and resolved within approximately 8 days of onset. The subject did not receive any treatment for the TEAEs of erythema, urticaria, or dry skin. In addition, the subject did not report any relevant medical history.

Part 2:

Not applicable.

2.7.4.3 Clinical Laboratory Evaluations

Clinical laboratory reference ranges are listed in [CSR Module 5.3, Appendix 16.1.10.1](#). Individual hematology, serum chemistry, and urinalysis results are listed in [CSR Module 5.3, Appendices 16.2.8.1, 16.2.8.2, and 16.2.8.3](#), respectively.

*Laboratory Values Over Time*Part 1:

There were no clinically meaningful changes in hematology, serum chemistry, or urinalysis test results over time.

Hematology results and changes from Baseline for Part 1 are summarized in [CSR module 5.3, Table 14.3.5.3.1](#). Serum chemistry results and changes from Baseline for Part 1 are summarized in [CSR Module 5.3, Table 14.3.5.4.1](#). Urinalysis results and changes from Baseline for Part 1 are summarized in [CSR Module 5.3, Table 14.3.5.5.1](#).

Part 2:

There were no clinically meaningful changes in hematology, serum chemistry, or urinalysis test results over time. Hematology results and changes from Baseline for Part 2 are summarized in [CSR Module 5.3, Table 14.3.5.3.2](#). Serum chemistry results and changes from Baseline for Part 2 are summarized in [CSR Module 5.3, Table 14.3.5.4.2](#). Urinalysis results and changes from Baseline for Part 2 are summarized in [CSR Module 5.3, Table 14.3.5.5.2](#).

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Individual Subject Changes

Individual subject shifts from Baseline in clinical laboratory values were not assessed.

Individual Clinically Significant Abnormalities

Part 1:

No individual clinical laboratory abnormality was considered clinically significant or reported as a TEAE.

Part 2:

Subject 1-1097 (female, BEMT 6% oil [without BOS]) had clinically significant abnormal urinalysis results on Day 5, which included positive urine leukocyte esterase (reference range: negative), 3+ urine occult blood (reference range: negative), many urine erythrocytes (reference range: none), and many urine leukocytes (reference range: none). A TEAE of urinary tract infection, considered not related to study drug and mild in severity, was reported on Day 5. The subject received oral nitrofurantoin 500 mg twice per day for this TEAE from Days 6 through 10. The TEAE of urinary tract infection was considered resolved on Day 10, 5.6 days after onset.

No other individual clinical laboratory abnormality was considered clinically significant or reported as a TEAE.

Clinically significant clinical laboratory results are provided in [CSR Module 5.3 Listing 14.3.4.1](#).

2.7.4.4 Vital Sign Measurements, Physical Findings, and Other Observations Related to Safety

Part 1:

There were no clinically meaningful changes in vital sign measurements. No individual abnormal vital sign measurement was reported as a TEAE.

Part 2:

There were no clinically meaningful changes in vital sign measurements. No individual abnormal vital sign measurement was reported as a TEAE.

Vital sign measurements and changes from Baseline for Parts 1 and 2 are summarized in [CSR Module 5.3, Tables 14.3.5.2.1 and 14.3.5.2.2](#), respectively. Vital sign measurements are listed in [CSR Module 5.3, Appendix 16.2.7.3](#).

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Physical and Skin Examinations

Part 1:

As discussed in [Section 2.7.4.2](#), Subject 1010 (BEMT 6% oil) had abnormal physical examination findings of the skin (skin irritation of the abdomen and lower back and erythema with welts that were confluent on the abdomen and all 4 extremities) that were considered clinically significant, documented as TEAEs, and led to study drug withdrawal and discontinuation from the study.

All physical examination findings observed after study drug application were documented as TEAEs. Treatment-emergent AEs in the SOC of skin and subcutaneous tissue disorders for Part 1 are provided in [CSR Module 5.3, Table 12-3](#). Skin examination findings for Part 1 are summarized in [Table 3](#).

Table 3 Skin Examination Results – Part 1 (Safety Population)

Prompt Visit Result	BEMT 6% Oil (N = 14)
Are there any signs of skin irritation at the sites of topical application? (n, %)	
Day 1	
Yes	0
No	14 (100.0)
Day 2	
Yes	0
No	14 (100.0)
Day 3	
Yes	3 (21.4)
No	11 (78.6)
Day 4	
Yes	4 (30.8)
No	9 (69.2)
Day 5	
Yes	4 (30.8)
No	9 (69.2)
Day 8	
Yes	3 (23.1)
No	10 (76.9)
Day 12	
Yes	0
No	13 (100.0)
Early Termination	
Yes	1 (100.0)
No	0

Abbreviation: BEMT, Bemotrizinol.

The denominator for percentages was based on the number of subjects in the safety population with data for the given characteristic.

Treatment was BEMT 6% oil, applied 4 times per day for 4 days.

Source: [CSR module 5.3, Table 14.3.5.7.1](#).

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Signs of skin irritation at the sites of study drug application were observed in a maximum of 4 subjects (30.8%; on Days 4 and 5).

Part 2:

No subjects had abnormal physical or skin examination findings that were considered clinically significant. All physical examination findings observed after study drug application were documented as TEAEs. Treatment-emergent AEs in the SOC of skin and subcutaneous tissue disorders for Part 2 are provided in [CSR module 5.3, Table 12-4](#). Skin examination findings for Part 2 are summarized in [Table 5](#).

Table 4 Skin Examination Results – Part 2 (Safety Population)

Prompt Visit Result	BEMT 6% Oil (Without BOS) (N = 54)	BEMT 6% O/W (N = 54)	BEMT 6% W/O (N = 54)
Are there any signs of skin irritation at the sites of topical application? (n, %)			
Day 1			
Yes	0	1 (1.9)	1 (1.9)
No	54 (100.0)	53 (98.1)	53 (98.1)
Day 2			
Yes	2 (3.7)	1 (1.9)	4 (7.4)
No	52 (96.3)	53 (98.1)	50 (92.6)
Day 3			
Yes	4 (7.4)	6 (11.1)	9 (16.7)
No	50 (92.6)	48 (88.9)	45 (83.3)
Day 4			
Yes	7 (13.2)	6 (11.1)	15 (27.8)
No	46 (86.8)	48 (88.9)	39 (72.2)
Day 5			
Yes	4 (7.4)	4 (7.4)	15 (27.8)
No	50 (92.6)	50 (92.6)	39 (72.2)

Abbreviations: BEMT, Bemotrizinol; BOS, butyloctyl salicylate; O/W, oil-in-water; W/O, water-in-oil.

The denominator for percentages was based on the number of subjects in the safety population in each treatment and Overall with data for the given characteristic.

Treatment was BEMT 6%, applied 4 times per day for 4 days, as either an oil (BEMT 6% oil [without BOS]), an O/W emulsion (BEMT 6% O/W), or a W/O cream emulsion (BEMT 6% W/O).

Source: [Table 14.3.5.7.2](#).

Signs of skin irritation at the sites of study drug application were observed in a maximum of 15 subjects (27.8%) after receiving BEMT 6% W/O (on Days 4 and 5), 7 subjects (13.2%) after receiving BEMT 6% oil (on Day 4), and 6 subjects (11.1%) after receiving BEMT 6% O/W (on Days 3 and 4).

Physical examination findings are listed in [Appendix 16.2.7.5](#). Skin examination results for Parts 1 and 2 are summarized in [Tables 14.3.5.7.1](#) and [14.3.5.7.2](#), respectively, and listed in [Appendix 16.2.7.7](#).

2.7.4.5 Dermal Clinical Safety Testing

According to our OTC Docket review, FDA has concluded that the data submitted are not sufficient to assess the dermal safety of BEMT and specifically its potential to cause irritation, sensitization, photoirritation or photoallergenicity. The Clinical Safety tests requested by FDA in their initial determination and restated in their Memorandum of Meeting Minutes to the TEA Sponsor, are intended to demonstrate the dermal safety of BEMT as used in sunscreens.

All clinical trials sponsored by DSM under this OMOR abided by the Protection of Human Subject and Institutional Review Board (IRB) requirements set forth under 21 CFR Parts 50 and 56, followed FDA guidelines for Good Clinical Practice and were registered under *ClinicalTrials.gov*. DSM conducted each of the required clinical safety tests following standard test design protocols as outlined in [Table 6-7](#), [Table 6-8](#), [Table 6-9](#), and [Table 6-10](#) below.

Table 6-5. Proposed Clinical Skin Irritation Test

	Design and Description	Comments
Parameter	Use a “standard” patch-testing study design; GCP Compliant	“Skin irritation studies should generally include at least 30 evaluable subjects and should evaluate the test formulation (i.e., Bemotrizinol in an appropriate test vehicle), the vehicle alone, and both negative and positive controls. The test site applications should be randomized, and the test observer blinded to the identities of the test formulations.” (FDA, 2014).
Topical dosing formulations	One formulation vehicle and BEMT at up to 10% will be used; Vehicle Control: Formulation without BEMT Positive Control: a reference skin irritant to be selected. Negative Control: patch only	Select one from among the series of different sunscreen type formulations being screened for reliable preparation, physical stability, and representativeness.
Number of subjects	Minimum of 30 evaluable Subjects at completion	BEMT has been tested in animals and smaller panels of humans and does not cause skin irritation.
Selection, Exclusion Criteria	Age: 20-60 years of age Any Skin Type may be used Healthy, intact skin Sex: Males and Females; equal numbers	A more complete set of criteria will be provided by the clinical test laboratory.
Topical applications	One application site on back with a standard patch, without occlusion, applied for 24 hours.	Applied patches should be blinded to observer. All patches assigned randomly by application site.
Duration of treatments	24-hour patch	Persistent reactions should be observed daily up to 3 days after patch removal.
Grading skin reactions	Evaluate just <u>after patch removal & then at 24h after removal</u> . A standardized but detailed grading scale should be used.	Scores should be averaged for all subjects for each material used.

**Clinical
observations**

Test Observer should be blinded to the identity of the test formulations locations. Unblinding only at study results interpretation and evaluation phase.

Record and assess any signs and symptoms indicating potential adverse events.

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Table 6-6. Proposed Clinical Skin Sensitization Test

Design and Description		Comments
Parameter	Human Repeat Insult Patch Test GCP Compliant	"Skin sensitization studies generally should include at least 200 subjects and should evaluate the test formulation containing Bemotrizinol, the vehicle, and a negative control. The test site applications should be randomized, and the test observer blinded to the identities of the test formulations." (FDA, 2014).
Topical dosing formulations	Formulation as used in skin irritation test; BEMT at up to 10% Vehicle Control: Formulation without BEMT Negative control: patch only	
Number of subjects	Minimum of 200 evaluable subjects at conclusion	BEMT has been tested in animals and small panels of humans and does not cause allergic contact dermatitis.
Selection, Exclusion Criteria	Age: 20-60 years of age Any Skin Type Healthy, intact skin Sex: Males and Females, equal numbers	Exclusion criteria: avoid subjects known to be allergic to formulation ingredients; subjects screened by dermatological diseases & allergies. A more complete set of criteria will be provided by the clinical test laboratory.
Topical applications	Occlusive chamber; sites on upper arm or back; Induction patches on same sites; Challenge dose applied to new site (in same area)	Applied patches should be blinded to observer. All patches to be assigned randomly by application site.
Duration of treatments	Induction phase: 10 patches, 3/week, 24h each Rest phase: 14 days Challenge phase: 1 patch for 24h	
Grading skin reactions	Use a standardized, detailed grading scale. Evaluate at patch removals in induction phase; Challenge site scored at removal & at 24h	Induction phase evaluations should consider signs of fatiguing & cumulative irritation. Scores should be averaged for all subjects for each material used.
Clinical observations	Test Observer should be blinded to the identity of the test formulations locations. Unblinding only at study results interpretation, evaluation phase.	Record and assess any signs and symptoms indicating potential adverse events.

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Table 6-7. Proposed Clinical Photo-Toxicity Test (Irritation)

	Design and Description	Comments
Parameter	A patch-testing study design including UV-B & UV-A irradiation. GCP Compliant	"Skin irritation studies should generally include at least 30 evaluable subjects and should evaluate the test formulation (i.e., Bemotrizinol in an appropriate test vehicle), the vehicle alone, and a negative control. The test site applications should be randomized, and the test observer blinded to the identities of the test formulations." (FDA, 2014).
Topical dosing formulations	Formulation as used in skin irritation test; BEMT at up to 10% Vehicle Control: Formulation without BEMT Negative control UV + patch; patch only	Formulation and concentration as determined for patch test.
Number of subjects	Minimum of 30 evaluable Subjects at completion	BEMT has been tested in animals and smaller panels of humans and does not cause skin photo-irritation.
Selection, Exclusion Criteria	Age: 20-60 years of age Any Skin Type may be used Healthy, intact skin Sex: Males and Females; equal numbers	A more complete set of criteria will be provided by the clinical test laboratory.
Topical applications	One application on back with a standard patch, without occlusion, applied for 24 hours.	Applied patches should be blinded to observer. All patches to be assigned randomly by application site.
UV Radiation exposures	Based on individual's minimal erythema dose (MED)	irradiated with 16 J/cm ² UVA and UVB at 0.7 times an individual's MED
Duration of treatments	24-hour patch, after UV Irradiation	Persistent reactions should be observed daily up to 3 days after patch removal.
Grading skin reactions	Evaluate just after patch removal & then at 24h after removal. A standardized detailed grading scale to be used.	Scores should be averaged for all subjects for each material used.
Clinical observations	Test Observer should be blinded to the identity of the test formulations locations. Unblinding only at study results interpretation, evaluation phase.	Record and assess any signs and symptoms indicating potential adverse events.

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Table 6-8. Proposed Clinical Photoallergenicity (Skin) Test

Design and Description		Comments
Parameter	Human Repeat Insult Patch Test with UV-A & UV-B irradiation. GCP Compliant	"Photoallergenicity studies generally should include at least 45 evaluable subjects and should evaluate the test formulation containing Bemotrizinol in a vehicle, the vehicle, and a negative control. The test site applications should be randomized, and the test observer blinded to the identities of the test formulations." (FDA, 2014).
Topical dosing formulations	Formulation as used in skin irritation test. BEMT at up to 10% in a formulation; Vehicle Control: Formulation without BEMT Negative control: patch only; UV irradiated	
Number of subjects	Minimum of 45 evaluable subjects at conclusion	BEMT has been tested in animals and small panels of humans and does not cause photoallergic responses
Selection, Exclusion Criteria	Age: 20-60 years of age Any Skin Type Healthy, intact skin Sex: Males and Females, equal numbers	A more complete set of criteria will be provided by the clinical test laboratory.
Topical applications	Occlusive chamber; sites on upper arm or back; Induction patches on same sites; Challenge dose applied to new site (in same area)	Applied patches should be blinded to observer. All patches to be assigned randomly by application site.
UV Radiation exposures	Induction phase: Rest phase: Challenge:	Induction by repeated applications of test & controls formulations, then irradiated at 2x the volunteer's MED for UVA & UVB; Challenge phase: applications then irradiated at 16 J/cm ² UVA and UVB at 0.7 times an individual's MED
Duration of treatments	Induction phase: 10 patches, 3/week, 24h each Rest phase: 14 days Challenge phase: 1 patch for 24h	
Grading skin reactions	Use a standardized, detailed grading scale. Evaluate at patch removals in induction phase; Challenge site scored at removal & at 24h	Dosed site evaluations should consider signs of fatiguing & cumulative irritation. Scores should be averaged for all subjects for each material used.
Clinical observations	Test Observer should be blinded to the identity of the test formulations' locations. Unblinding only at study results interpretation, evaluation phase.	Record and assess any signs and symptoms indicating potential adverse events.

2.7.4.6 Safety in Special Groups and Situations

2.7.4.6.1. A Pediatric Survey

As discussed during the Type Y meeting between DSM and the FDA on February 5, 2024 (refer to the official meeting minutes from March 6, 2024, in [Module 1.6.3](#)), DSM confirmed its intent to market Bemotrizinol (BEMT) at a 6% concentration for use in sunscreen products intended for adults and children aged six months and older. Consequently, DSM has updated the Drug Facts Label to include the statement “*Children under 6 months: Ask a doctor*” and align with FDA's sunscreen labeling requirements as outlined in the Over-the-Counter Sunscreen Monograph M020 ([Module 1.14](#)).

Furthermore, as indicated by the FDA in the official minutes from the March 6, 2024, Type Y meeting, there are no Pediatric Research Equity Act (PREA) requirements for monograph products. In alignment with the 2019 Sunscreen Proposed Rule and the 2021 Sunscreen Proposed Order, the FDA has indicated that as long as a wide margin of safety exists, it is unlikely to request additional pediatric information beyond the required clinical data. The FDA also recommended that DSM include any available pediatric data from the European market in its OMOR submission, including postmarketing safety reports, while noting that no specific pediatric studies are being requested.

In follow-up, DSM conducted a market analysis using data from the 2000 -2023 Global New Product Database (GNPD) for data EU Countries including: Austria; Belgium; Czech Republic; Denmark; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Poland; Portugal; Spain; Sweden; Switzerland; UK; Latvia; Lithuania; Estonia; Bulgaria; Romania; Croatia; Slovakia; Slovenia (excluding Cyprus, Luxembourg and Malta).

This database, operated by Mintel, tracks new product launches, formulations, packaging, and claims across a wide range of industries, including beauty, personal care, food, and beverages. The GNPD is widely used by companies, marketers, and researchers to understand market trends, innovations, and consumer preferences. The GNPD-based market survey includes information on European market usage trends, market size, and examples of pediatric sunscreen products and labels containing BEMT (INCI: Bis-ethylhexyloxyphenol Methoxyphenyl Triazine). The relevant product age demographics searched were:

- Babies & Toddlers (age 0-4 years) and includes products intended for newborns, babies, toddlers, or infants.
- Children (age 5-12 years).
- Teenagers (age 13-17 years).

The results of this survey along with examples of various EU pediatric product labels for the years 2010, 2016 and 2023 are presented in and attached to [section 1.3.6 \(Appendix 1, 2, 3, respectively\)](#). Additional information supporting the margin of safety for pediatric use can be found in [section 2.4.5](#).

There are no widely documented case reports or clinical data that specifically highlight adverse events related to the use of Bemotrizinol in children. Post-market surveillance of the public literature, case reports, and adverse event databases such as the European Medicines

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Agency (EMA) pharmacovigilance reporting EudraVigilance system, the Australian Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications reporting systems, and the Canada Vigilance Adverse Reaction Online Database available in countries where Bemotrizinol is already approved do not indicate any safety concerns in pediatric populations.

2.7.4.7 Postmarketing Data

2.7.4.7.1. Published Adverse Event Case Report (Global Post Marketing Experience)

Being sold in global markets since 2000 has brought BEMT into regular use in topically applied consumer cosmetics and other related sunscreen and skin care products. Only 2 case reports of Bemotrizinol-related clinical adverse events have been published, one for a female in 2019 (Luna-Bastante et al. 2019. Allergic contact dermatitis to Tinosorb S, Scutellaria baicalensis, and other emerging allergens in cosmetics. *Contact Dermatitis*. 2020;82(5):307-309. doi.org/10.1111/cod.13460), and most recently in 2022 for one female (Suzuki et al. 2022. Allergic contact dermatitis caused by dimethicodiethylbenzalmalonate (polysilicone-15, PARSOL® SLX) and bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S) in sunscreen cream. *Contact Dermatitis*. 2022 Jul;87(1):108-110. doi: 10.1111/cod.14112. Epub 2022 Apr 11. PMID: 35306675.). Considering the 23 years since BEMT approval and continuous use in globally available commercial topical products, this number of reported adverse effects in case reports is very low.

Australia's Therapeutic Goods Administration (TGA) has available an online accessible Database of Adverse Event Notifications (DAEN) for medicines on the market in Australia (<https://daen.tga.gov.au/medicines-search/>). In our IND serial 0000 submission (section 5.3.6; June 2020) was included a summary of results for our search of that database for the years 1999-2020 completed on May 24, 2020. Using Bemotrizinol as the key search phrase showed that 16 sunscreen medicines, all being commercially sold sunscreen products containing BEMT and at least 3 additional UV filters, were associated with about 40 identified adverse events.

Another search of this TGA database was completed on 14 March 2023, and covered the time from June 2020 through 28 February 2023. This search revealed 36 sunscreen-containing medicines that were cited in 38 case reports of adverse events identified, wherein the case reporter considered (suspected) there to be an association of the medicine to the adverse event. The number of cases reported by year are summarized in the following [Figure 1](#). The detailed tables and listings of the reported adverse events are included in section [2.7.4.7 Additional Tables and Figures](#). Presented are the case reports with their specific MEDRA system organ class and reaction terms and a second table listing medicines reported to have been used and their case-related information (<https://daen.tga.gov.au/medicines-terms-condition> :Reported 10-Jun-2020 thru 14-Mar-2023 232906)

As noted in the additional tables, each of the adverse effects or complaints are categorized as “suspected to be related to the medicine”, which is in all cases a complete sunscreen product and not BEMT specifically. Each of the medicines listed in the reports contain at least three other UV filter active ingredients in addition to Bemotrizinol, plus any included but not listed, inactive formulation excipients.

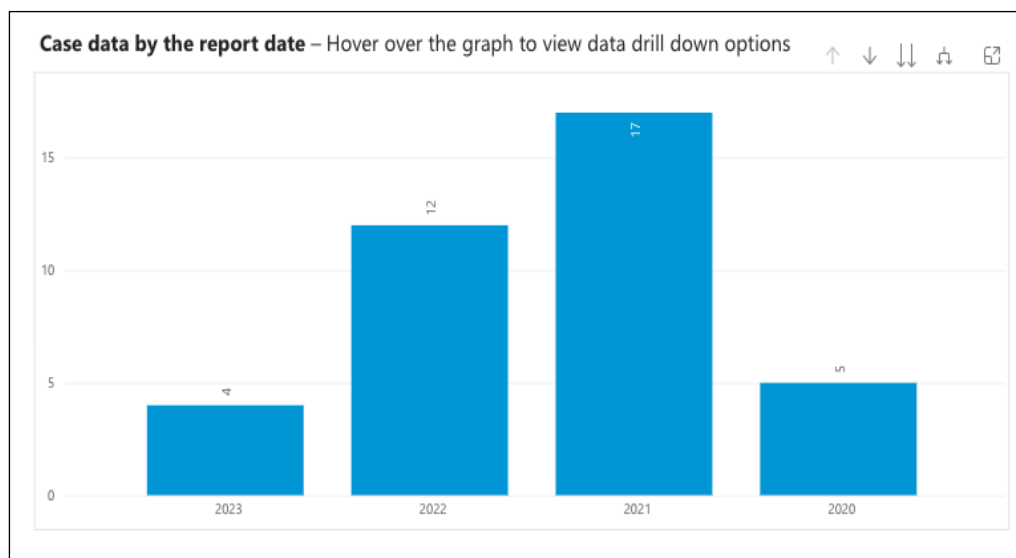


Figure 1 Summary by year of 38 Case reports for 36 single medicines also containing BEMT (June 2020- February 2023). Source: Australia Therapeutic Goods Administration Database of Adverse Event Notifications; accessed on 14 March 2023.

To clarify and put these data into context, the TGA database interpretation guide cautions that the presence of an adverse event report does not mean that the medicine is the cause of the adverse event. Further, it should be noted that each patient presented in a case report may have experienced or demonstrated more than one MEDRA reaction term that is included in the total number of adverse events reported; also, the same medicine may have elicited adverse events in more than one person.

Because systematic diagnostic patch testing of the specific UV filters or ingredients in these 36 suspected medicines was not disclosed to have been done or results reported, none of these adverse event reports implicate Bemotrizinol as the direct causative agent. Such finding or association would be inconsistent with all other available testing results with BEMT, including our recent clinical safety tests, and contrary to the safe use concentrations for the selected excipients used in our market image formulations for the MUSt, which are also commonly used in commercial sunscreen products in the United States.

2.7.4.7.2. Post-Marketing experience- Case reports.

In 2020 one case report of adverse reactions on human skin related to BEMT was published (Luna-Bastante et al. 2020). In this event, a 39-year old non-atopic female presented with eyelid eczema and two-years history of pruritic erythematous scaly plaques in both periorbital skin regions. Patch testing in the subject with the Spanish Contact Dermatitis Standard Baseline series, the two suspect cosmetic formulations, and then their individual ingredients tested separately revealed positive skin reactions to two ingredients in the sunscreen: *Scutellaria baicalensis* root extract and Tinosorb S®. In their systematic approach the authors also used the ingredients found positive in the subject to patch test 16 healthy controls, none of which showed positive reactions to the ingredients. The subject was treated with topical medications that resolved the lesions and advised to avoid cosmetics containing the two ingredients.

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Another search (17 March 2023) of the literature indexed by PubMed revealed only one additional adverse event case report published since 2020 (Suzuki et al. 2022). In this report, a 51-year-old female presented with unresolved facial signs (scales and erythema) unresponsive to topical medication. Diagnostic patch testing was conducted with the woman's personal cosmetics, including her sunscreen, and a standard allergen baseline series (Japan) and cosmetic series ingredients, applied in Finn chambers to the upper back for 48h then evaluated on days 2, 3 and 7. A score of + or higher on D3 or D7 was considered a positive reaction. A UV-irradiation exposure was not used.

The sunscreen product showed a positive (+) reaction on each day and subsequent testing with its ingredients indicated Bemotrizinol and dimethyldiethylbenzalmalonate (INCI: polysilicone-15; CAS: 207574-74-1; trade name: Parsol SLX) 10% pet., were confirmed positive in a second set of patch testing. Testing of each UV filter alone without the application of the other filter was not done, so a combined effect from the UV filters could not be excluded.

While we cannot exclude a rare event of contact dermatitis associated with BEMT, in both published case reports a second ingredient was present in the tested-positive cosmetic product. A clear implication of BEMT in the observed clinical event has not been established and would not be expected in view of results from all of the controlled clinical safety tests with BEMT that provide clear conclusions that it is not a contact dermal allergen, with or without concomitant UV irradiation.

DSM Post Marketing experience and customers' feedback has not documented complaints or adverse experiences with BEMT.

2.7.4.7.3. Clinical Safety of Drug Substance

Completion of the clinical safety profile was the objective for discussion with FDA on protocol designs for the required controlled studies. The agreed safety studies used BEMT 6% in the Sunscreen Oil with ethanol as a skin penetration enhancer (formulation no. SU-E-101413-85). The following four studies were conducted:

- Evaluation of Bemotrizinol in Human Repeated Insult Patch Test (HRIPT) and Cumulative Irritation Test -Protocol Identification Number: DSM RIPT 2020 ([5.3.5.1 CRLNJ2020-0493_RIPT](#))
- Evaluation of Topically Applied Bemotrizinol for Human Phototoxic Potential -Protocol Identification Number: DSM PT 2020 ([5.3.5.1_CRLNJ2020-0494_PhotoTox](#))
- Evaluation of Topically Applied Bemotrizinol for Human Photoallergic Potential –Protocol Identification Number: DSM PA 2020 ([5.3.5.1 CRLNJ2020-0495_PhotoAllergy](#)).

A brief overview of the study results follows.

1. In the clinical repeat insult patch test phase, none of the 185 subjects (18 to 74 years of age; 5 of 190 were lost to follow) completing the RIPT phase showed evidence of dermal irritation or sensitization after 9 induction and the challenge applications of 6% BEMT in a sunscreen oil with skin penetration enhancer formulation (SU E 101413 85). The cumulative skin irritation phase was completed by 30 subjects aged 22 to 74 years and none of them showed evidence of cumulative skin irritation after 21 daily

patch applications of the drug formulation (SU E 101413 85). The respective control formulations and applications without BEMT gave their expected responses in each study phase (CRLNJ2020-0493).

2. The evaluation of 6% BEMT in a sunscreen oil with skin penetration enhancer formulation (SU E 101413 85) was used in this test for phototoxic responses after application to the skin of human subjects followed by exposure to UV radiation. Vehicle and negative control formulations and an empty patch control were used in parallel on individual skin sites. Among the 34 male and female subjects aged 21 to 72 years none of them showed evidence of a phototoxic response to the 6% BEMT formulation (CRLNJ2020-0494).
3. A test for photoallergenicity responses to 6% BEMT in a sunscreen oil with skin penetration enhancer formulation (SU E 101413 85) enrolled 50 male and female subjects (two discontinued) with ages of 21 to 72 years; over 20 days of clinic visits for 4 weeks in a 6-week period the six induction applications and skin response gradings were completed. Two weeks thereafter subjects returned for patch applications and 24h later UVA irradiation; sites were graded for skin responses at 24, 48 and 72h after UVA exposure. Evidence of photoallergic responses did not occur in any of the subjects at any time point; the negative and vehicle control formulations gave their expected responses (CRLNJ2020-0495).

In each of these clinical tests, BEMT 6% did not elicit signs or reactions indicating skin irritation, allergenicity, phototoxicity or photoallergenicity in any of the subjects completing the studies; non-completers were lost to follow-up or discontinued for reasons not related to the BEMT test formulation. Other adverse events or effects did not occur in any volunteers in any of these studies.

2.7.4.7.4. Clinical Safety of Excipients in Market-image Drug Product Formulations

The clinical safety of each of the excipients used in the several market image sunscreen formulations was considered acceptable if it is included on the FDA inactive drug ingredients database and had the best safety profile supporting the concentrations to be used in a formulation. The results of the four clinical safety tests did not reveal any adverse effects in any of the study participants at any of their completed dose site scoring visits, which is further support for the topical safety of BEMT and the selected drug product excipients.

2.7.4.8 Conclusions

Overall conclusions from the completed clinical dermal safety tests are that the drug substance and the drug product as used in these clinical topical safety tests do not elicit dermal reactions of irritation, sensitization, phototoxicity or photoallergenicity.

A search of the Australia Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications (June 2020 through February 2023) returned 38 case reports for 36 individual medicines containing Bemotrizinol among the medicines' finished ingredients lists; diagnostic causative confirmation of BEMT association with the reported adverse events was not found.

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There are no reported adverse events related to Bemotrizinol use in children. Post-market surveillance from systems like EMA's EudraVigilance, Australia's TGA, and Canada's Vigilance Database shows no safety concerns in pediatric populations where Bemotrizinol is approved.

In over 23 years of consumer global use of BEMT in commercial products, only two published case reports related to BEMT clinical adverse events were found, one published in 2019 (Luna-Bastante et al.) and a second in 2022 (Suzuki et al. 2022). In both case reports the subjects' personal products contained BEMT and a second ingredient shown by diagnostic patch testing to be associated with the adverse events. However, although BEMT was present and showed positive skin responses, a clear implication of BEMT as the only positive ingredient was not found for either case.

Further evidence to justify safety of BEMT and in particular a waiver of the systemic oral carcinogenicity test requirement, can be found in [Module 1.12.5.1](#) and references such as in [Module 2.6.2](#).

2.7.4.9 Appendix

Two additional tables are included in this section to provide further details on the Adverse Events discussed in [section 2.7.4.3](#) Global experience with BEMT. Most of these adverse events are mild, not serious or life threatening, and similar to the common reactions associated with sunscreens in general, typically involving skin sensitivities or irritations, which can range from mild to severe.

Table 1. Occurrence of Adverse Events Suspected Associated with Medicines Containing BEMT and Other UV Filters: Number of Case Reports (38 Total), TGA Database of Adverse Event Notifications (<https://daen.tga.gov.au/medicines-terms-condition> :Reported 10-Jun-2020 thru 14-Mar-2023 232906)

MedDRA system organ class	MedDRA reaction term	Number of cases	Cases with a single suspected medicine	Cases where death was a reported outcome
Injury, poisoning and procedural complications	Sunburn	16	16	0
Skin and subcutaneous tissue disorders	Erythema	9	8	0
Immune system disorders	Hypersensitivity	7	6	0
General disorders and administration site conditions	Drug ineffective	7	6	0
Skin and subcutaneous tissue disorders	Blister	6	6	0
General disorders and administration site conditions	Pain	6	6	0
Skin and subcutaneous tissue disorders	Rash	3	3	0
Skin and subcutaneous tissue disorders	Skin irritation	3	3	0
Product issues	Product quality issue	3	3	0
Nervous system disorders	Burning sensation	3	3	0
Eye disorders	Eye swelling	3	2	0
Skin and subcutaneous tissue disorders	Pruritus	2	2	0
Skin and subcutaneous tissue disorders	Skin exfoliation	2	2	0
Product issues	Product complaint	2	2	0

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Injury, poisoning and procedural complications	Burns third degree	2	2	0
Injury, poisoning and procedural complications	Recalled product administered	2	2	0
Injury, poisoning and procedural complications	Thermal burn	2	2	0
General disorders and administration site conditions	Swelling face	2	1	0
General disorders and administration site conditions	Therapeutic product ineffective	2	2	0
Skin and subcutaneous tissue disorders	Dermatitis allergic	1	1	0
Skin and subcutaneous tissue disorders	Dermatitis contact	1	1	0
Skin and subcutaneous tissue disorders	Pain of skin	1	0	0
Skin and subcutaneous tissue disorders	Rash erythematous	1	1	0
Skin and subcutaneous tissue disorders	Rash macular	1	1	0
Skin and subcutaneous tissue disorders	Rosacea	1	1	0
Skin and subcutaneous tissue disorders	Skin erosion	1	1	0
Skin and subcutaneous tissue disorders	Skin lesion	1	1	0
Skin and subcutaneous tissue disorders	Urticaria	1	1	0
Product issues	Product physical consistency issue	1	1	0
Nervous system disorders	Paraesthesia	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer	1	0	0
Metabolism and nutrition disorders	Dehydration	1	1	0
Injury, poisoning and procedural complications	Burns second degree	1	1	0
Injury, poisoning and procedural complications	Chemical burn of skin	1	1	0

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Injury, poisoning and procedural complications	Third degree chemical burn of skin	1	1	0
Infections and infestations	Burn infection	1	1	0
Immune system disorders	Allergy to chemicals	1	1	0
General disorders and administration site conditions	Application site hypersensitivity	1	1	0
General disorders and administration site conditions	Concomitant disease aggravated	1	1	0
General disorders and administration site conditions	Condition aggravated	1	0	0
General disorders and administration site conditions	Face oedema	1	1	0
General disorders and administration site conditions	Peripheral swelling	1	1	0
Gastrointestinal disorders	Nausea	1	1	0

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Table 2. Products (Medicines) in List of Reports of Adverse Events, TGA Database of Adverse Event Notifications (<https://daen.tga.gov.au/medicines-terms-condition> :Reported 10-Jun-2020 thru 14-Mar-2023 232906)

Case number	Report entry date	Age (years)	Gender	Medicines reported being taken	MedDRA reaction terms
511312	2020-11-05 00:00:00	69	Female	• Ultra UV Protective Daily Moisturiser SPF50+ - AUST L 237094 (Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene; octyl methoxycinnamate; phenylbenzimidazole sulfonic acid) - Suspected	• Hypersensitivity
512609	2020-11-20 00:00:00	54	Female	• EGO SUNSENSE ANTI-AGEING FACE (193124) (octyl methoxycinnamate; diethylamino hydroxybenzoyl hexyl benzoate; Bemotrizinol) - Suspected	• Erythema
512811	2020-11-23 00:00:00	69	Female	• Ultra UV Protective Daily Moisturiser SPF50+ - AUST L 237094 (Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene; octyl methoxycinnamate; phenylbenzimidazole sulfonic acid) - Suspected	• Erythema
513195	2020-11-27 00:00:00	46	Female	• Banana Boat Ultra SPF50+ (octocrylene; 4-methylbenzylidene camphor; butyl methoxydibenzoylmethane; Bemotrizinol) - Suspected	• Drug ineffective • Sunburn
514912	2020-12-18 00:00:00	18	Female	• LA ROCHE-POSAY LABORATOIRE DERMATOLOGIQUE ANTHELIOS XL DRY TOUCH GEL-CREAM AUST L 308621 (octyl salicylate; homosalate; octocrylene; titanium dioxide; ethylhexyl triazone; butyl methoxydibenzoylmethane; Bemotrizinol; Ecamsule; Drometrizole trisiloxane) - Suspected	• Face oedema • Paraesthesia • Sunburn
516049	2021-01-07 00:00:00	4	Male	• Banana Boat Ultra SPF50+ (octocrylene; 4-methylbenzylidene camphor; butyl methoxydibenzoylmethane; Bemotrizinol) - Suspected	• Blister • Burns third degree • Pain • Sunburn
516900	2021-01-18 00:00:00	1	Male	• NIVEA Sun Ultra Sport Cooling SPF50+ AUST L 234675 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Product quality issue • Sunburn
517076	2021-01-20 00:00:00	48	Female	• LA ROCHE-POSAY LABORATOIRE DERMATOLOGIQUE ANTHELIOS XL ULTRA LIGHT TINTED FLUID (AUST L 268394) (octocrylene; titanium dioxide; ethylhexyl triazone;	• Burning sensation • Erythema • Skin exfoliation

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				butyl methoxydibenzoylmethane; Bemotrizinol; Ecamsule; Drometrizole trisiloxane) - Suspected	
517224	2021-01-22 00:00:00	'	Female	• Nivea Sun Protect & Moisture Moisturising Sunscreen Lotion SPF50 - AUST L 270877 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Sunburn
517351	2021-01-25 00:00:00	'	Not Specified	• NIVEA Sun Ultra Beach Sunscreen Spray SPF50+ AUST L 234687 (octyl salicylate; homosalate; octocrylene; butyl methoxydibenzoylmethane; Bemotrizinol) - Suspected	• Drug ineffective • Product quality issue • Sunburn
517892	2021-01-31 00:00:00	53	Male	• Nivea Sun Protect & Moisture Moisturising Sunscreen Lotion SPF50 - AUST L 270877 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Sunburn
518532	2021-02-08 00:00:00	29	Female	• Ultra UV Protective Daily Moisturiser SPF30 Hydrating - AUST L 236265 (octyl methoxycinnamate; octocrylene; phenylbenzimidazole sulfonic acid; butyl methoxydibenzoylmethane; Bemotrizinol) - Suspected	• Skin irritation
519256	2021-02-15 00:00:00	3	Male	• BANANA BOAT KIDS SPF50+ ROLL ON SUNSCREEN AUST L 196672 (4-methylbenzylidene camphor; Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene) - Suspected	• Erythema • Eye swelling • Hypersensitivity • Pruritus • Rash
519480	2021-02-17 00:00:00	17	Female	• Banana Boat Ultra SPF50+ (octocrylene; 4-methylbenzylidene camphor; butyl methoxydibenzoylmethane; Bemotrizinol) - Suspected	• Hypersensitivity • Urticaria
519606	2021-02-18 00:00:00	'	Female	• Nivea Sun Protect & Moisture Moisturising Sunscreen Lotion SPF50 - AUST L 270877 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Product quality issue • Sunburn
531700	2021-04-06 00:00:00	62	Female	• LA ROCHE-POSAY LABORATOIRE DERMATOLOGIQUE ANTHELIOS XL ULTRA LIGHT TINTED FLUID (AUST L 268394) (octocrylene; titanium dioxide; ethylhexyl triazone; butyl methoxydibenzoylmethane; Bemotrizinol; Ecamsule; Drometrizole trisiloxane) - Suspected	• Rosacea

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546766	2021-05-03 00:00:00	46	Male	• Ultra UV Protective Daily Moisturiser SPF 30 Mattifying - AUSTL 251012 (Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene; octyl methoxycinnamate; phenylbenzimidazole sulfonic acid) - Suspected	• Application site hypersensitivity
615027	2021-08-31 00:00:00	3	Female	• NIVEA Sun Kids Protect & Play Caring Roll-On SPF 50 (4-methylbenzylidene camphor; Bemotrizinol; methylene bis-benzotriazolyl tetramethylbutylphenol; zinc oxide) - Suspected	• Burning sensation • Rash erythematous • Skin irritation
624871	2021-09-15 00:00:00	46	Male	• Ultra UV Protective Daily Moisturiser SPF50+ - AUST L 237094 (Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene; octyl methoxycinnamate; phenylbenzimidazole sulfonic acid) - Suspected	• Allergy to chemicals • Erythema • Pruritus • Skin exfoliation
638629	2021-10-06 00:00:00	<1	Female	• Banana Boat Baby SPF50+ Roll On Sunscreen (4-methylbenzylidene camphor; Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene) - Suspected	• Blister • Erythema • Eye swelling • Skin erosion • Swelling face • Third degree chemical burn of skin
648959	2021-10-22 00:00:00	'-	Male	• LA ROCHE-POSAY LABORATOIRE DERMATOLOGIQUE ANTHELIOS XL WET SKIN KIDS GEL CREAM SPF50+ (Bemotrizinol; butyl methoxydibenzoylmethane; drometrisole trisiloxane; ethylhexyl triazone; homosalate; octyl salicylate) - Suspected	• Burning sensation • Rash
688705	2021-12-31 00:00:00	36	Female	• Nivea Sun Protect & Moisture Moisturising Sunscreen Lotion SPF50 - AUST L 270877 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Sunburn
690195	2022-01-06 00:00:00	'-	Female	• NIVEA Sun Ultra Sport Cooling SPF50+ AUST L 234675 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Blister • Erythema • Pain • Product complaint • Product physical consistency issue • Sunburn
696947	2022-01-19 00:00:00	29	Female	• Ultimate UV Protective Daily Moisturiser SPF 50 Mattifying AUSTL 343257 (Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene; octyl methoxycinnamate; phenylbenzimidazole sulfonic acid) - Suspected	• Dermatitis contact

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709696	2022-02-14 00:00:00	10	Female	• Banana Boat Sport Very High Protection Sunscreen Lotion SPF 50+ AUST L 196376 (4-methylbenzylidene camphor; Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene) - Suspected	• Burns third degree • Drug ineffective • Pain • Recalled product administered
715479	2022-03-01 00:00:00	33	Female	• Banana Boat Sport Very High Protection Sunscreen Lotion SPF 50+ AUST L 196376 (4-methylbenzylidene camphor; Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene) - Suspected	• Blister • Burn infection • Burns second degree • Dehydration • Drug ineffective • Erythema • Nausea • Pain • Peripheral swelling • Sunburn
717793	2022-03-06 00:00:00	2	Male	• BANANA BOAT KIDS VERY HIGH PROTECTION SUNSCREEN LOTION SPF 50+ AUST L 205791 (4-methylbenzylidene camphor; Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene) - Suspected	• Drug ineffective • Hypersensitivity • Pain • Rash • Rash macular • Skin lesion • Sunburn
720327	2022-03-15 00:00:00	'-	Female	• NIVEA Sun Ultra Sport Cooling SPF50+ AUST L 234675 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Product complaint • Sunburn
732056	2022-04-28 00:00:00	2	Not Specified	• BANANA BOAT KIDS VERY HIGH PROTECTION SUNSCREEN LOTION SPF 50+ AUST L 205791 (4-methylbenzylidene camphor; Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene) - Suspected	• Recalled product administered • Thermal burn
733636	2022-05-06 00:00:00	'-	Female	• Ultra UV Protective Daily Moisturiser SPF50+ - AUST L 237094 (Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene; octyl methoxycinnamate; phenylbenzimidazole sulfonic acid) - Suspected	• Blister • Hypersensitivity
737399	2022-05-26 00:00:00	'-	Female	• LA ROCHE POSAY LABORATOIRE DERMATOLOGIQUE ANTHELIOS ULTRA COMFORT NON PERFUMED CREAM SPF50+ AUST L 307004 (Bemotrizinol; drometrizole trisiloxane; ecamsule; ethylhexyl triazone; octyl salicylate) - Suspected	• Hypersensitivity • Skin irritation

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Bemotrizinol (BEMT)

744193	2022-07-11 00:00:00	25	Female	• DermaVeen Regenerating Night Cream - Not on ARTG (alkyl (C12-15) benzoate; Avena sativa; cetareth-20; Cetearyl Alcohol; cetyl alcohol; coco-caprylate; Cocos nucifera; Dimethicone; ethylhexylglycerin; glycerol; glyceryl monostearate; Hydroxypropyl methacrylate; medium chain triglycerides; phenoxyethanol; polysorbate 60; propanediol; Shea butter; sodium gluconate; sodium hyaluronate; squalene; stearic acid; Tocopheryl acetate; xanthan gum) - Suspected • DermaVeen Ultra Light Day Lotion SPF50+ (AUST L 380592) (Bemotrizinol; butyl methoxydibenzoylmethane; ethylhexyl triazone; homosalate; octyl salicylate; phenylbenzimidazole sulfonic acid) - Suspected	• Condition aggravated • Drug ineffective • Erythema • Eye swelling • Hypersensitivity • Pain of skin • Swelling face
757596	2022-11-09 00:00:00	19	Female	• Ultimate UV Protective Daily Moisturiser SPF 50 Mattifying AUSTL 343257 (Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene; octyl methoxycinnamate; phenylbenzimidazole sulfonic acid) - Suspected	• Dermatitis allergic
759091	2022-11-24 00:00:00	1	Female	• Neutrogena Ultra Sheer Body Mist SPF30+ AUST L 157580 (butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate; oxybenzone) - Suspected • Neutrogena Ultra Sheer Body Mist Sunscreen Spray - AUST L Unknown (Bemotrizinol; butyl methoxydibenzoylmethane; ethylhexyl triazone; homosalate; octocrylene) - Suspected	• Skin cancer
764567	2023-01-17 00:00:00	28	Female	• Nivea Sun Protect & Moisture Moisturising Sunscreen Lotion SPF50 - AUST L 270877 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Sunburn • Therapeutic product ineffective
765500	2023-01-30 00:00:00	73	Female	• Ultra UV Protective Daily Moisturiser SPF 50 Mattifying - AUSTL 343242 (Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene; octyl methoxycinnamate; phenylbenzimidazole sulfonic acid) - Suspected	• Concomitant disease aggravated
766401	2023-02-10 00:00:00	5	Female	• BANANA BOAT KIDS VERY HIGH PROTECTION SUNSCREEN LOTION SPF 50+ AUST L 205791 (4-methylbenzylidene camphor; Bemotrizinol; butyl methoxydibenzoylmethane; octocrylene) - Suspected	• Blister • Chemical burn of skin • Drug ineffective • Pain • Sunburn • Thermal burn

MGF 400105

Bemotrizinol (BEMT)

767287	2023-02-22 00:00:00	-	Female	• Nivea Sun Protect & Moisture Moisturising Sunscreen Lotion SPF50 - AUST L 270877 (Bemotrizinol; butyl methoxydibenzoylmethane; homosalate; octocrylene; octyl salicylate) - Suspected	• Sunburn • Therapeutic product ineffective
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