Module 2.6.1 Nonclinical Summary

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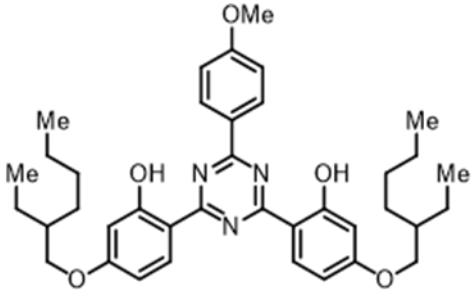
MGF 400105
Bemotrizinol (BEMT)

1. BEMT Description and Structure:

Bemotrizinol (BEMT) is a broad-spectrum UV filter used in sunscreens, protecting against both UVB and UVA radiation. DSM is sponsoring its inclusion at 6% in the FDA's OTC Sunscreen Monograph as a GRASE active ingredient. BEMT offers photostable protection, helping to prevent sunburn and skin damage by absorbing UV rays and releasing the energy as heat. Its approval would address the need for a reliable sunscreen filter in the U.S. market, enhancing public health protection against harmful UV radiation. Below is a summary of its P-chem properties.

Established Name (USAN):	Bemotrizinol (BEMT)
Brand/Proprietary Name/Tradename:	PARSOL® Shield
CAS Name:	Phenol,2,2'-[6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis(5-((2-ethylhexyl)oxy)
IUPAC Names:	6,6'-(6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diyl) bis(3-((2-ethylhexyl)oxy)phenol) 2,2′-[6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl] bis{5-[(2-ethylhexyl)oxy]phenol} 2,4-bis{[4-(2-ethyl-hexyloxy-2-hydroxy]-phenyl}-6-(4-methoxyphenyl)-(1,3,5)-triazine 5-[(2-ethylhexloxy)]-2-[4-[4-(2-ethylhexoxy)-2-hydroxyphenyl]-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl] phenol
CAS Registration Number:	187393-00-6
Unique ingredient identifier code:	UNII-PWZ1720CBH
Molecular Formula:	$C_{38}H_{49}N_3O_5$
Molar volume:	565.7 cm3
Molecular Weight:	627.81 g/mol
Polar surface area:	107 Å
Structural (graphic) Formula	
UV Absorption Spectrum:	

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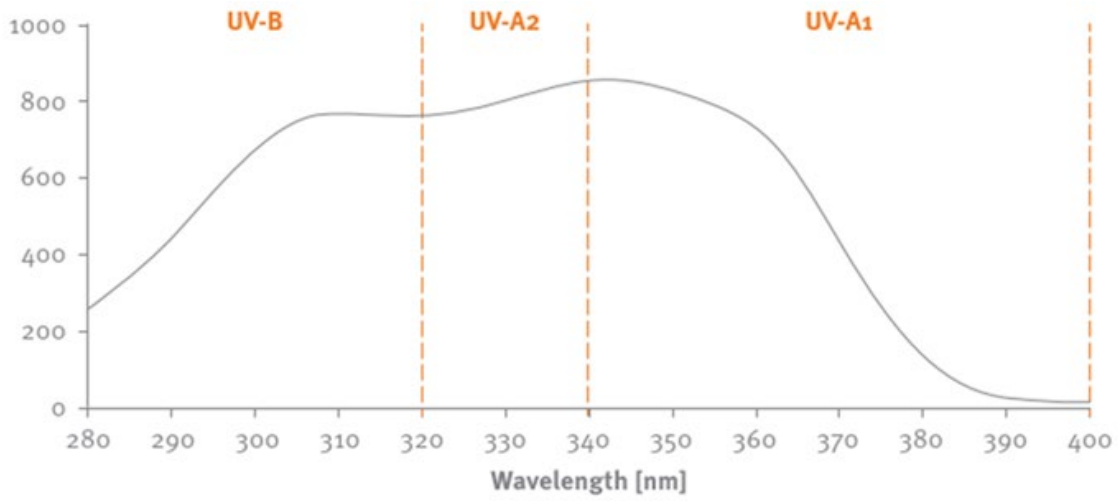

2. Pharmacological Class and Indication

Bemotrizinol is a UV filter active ingredient intended for use in topical products applied for sunburn protection.

Indication: helps prevent sunburn and others allowed per 21 CFR § 352.52 - Labelling of sunscreen drug products (Module 1.14)

3. Pharmacological Properties

As a UV protective molecule used topically to prevent sunburn, BEMT is not intended to have significant pharmaceutical or pharmacological effects. Specific tests for pharmacological effects or indications were not conducted with BEMT and such effects were not observed in any of the results for an extensive set of non-clinical and clinical studies with Bemotrizinol.

4. Proposed Clinical Indication, Dose and Duration of Use

As a topically applied drug substance, BEMT (Bemotrizinol) at 6% is designed to prevent sunburn. It is intended to be formulated at concentrations of up to 6% in sunscreen formulations and applied regularly to the skin. The nonclinical safety of BEMT as a drug substance was tested and evaluated in accordance with the FDA's 2016 Guidance for Industry on Nonprescription Sunscreen Drug Products - Safety and Effectiveness Data. Efficacy and clinical safety tests for BEMT 6% in sunburn protection were completed following discussions with the FDA.

5. Nonclinical Studies of Pharmacokinetics

The pharmacokinetic studies of BEMT include two legacy in vivo tests in rats, using a single oral gavage and a comparative single dermal dose of 14C-BEMT, followed by observations of absorption, distribution, and elimination of the parent molecule. Results showed no significant differences between dermal and oral dosing routes, with both demonstrating very low systemic exposure to BEMT, not exceeding 1% of the applied doses, and over 98% elimination recovered as the radiolabeled parent material.

Recent pharmacokinetic studies with BEMT include bioanalytical methods for BEMT analysis in the plasma of mice and rats, establishing a lower limit of quantitation at 0.5 ng BEMT/mL for both species. Two legacy plasma methods using reverse-phase chromatography and mass spectrometry with a quantitation limit of 2 ng/mL were developed and validated for two legacy toxicology studies: a 39-week dermal dosing in minipigs and a lifetime dermal dosing in rats.

In vitro percutaneous penetration tests (IVPT) of 6% BEMT in market-image complete sunscreen formulations were conducted to support drug product formulation selection for the human clinical pharmacokinetic maximum usage test (MUsT). IVPT results with human skin membranes dosed with 14C-BEMT showed no meaningful differences in skin absorption among the five formulations. No penetration into the receptor fluid occurred, and the absorbed dose was below 0.6% of the applied dose. An IVPT using rat skin membranes dosed with one market-image formulation indicated that rat skin is about 6–10 times more permeable to BEMT than human skin membranes.

In vitro metabolism testing using well-established models of human liver enzymes in hepatocyte suspensions and liver S9 fractions co-incubated with radiolabeled 14C-BEMT did not produce any phase I or phase II metabolites. This suggests no disproportionate drug metabolites specific to humans, and additional clinical testing or plasma measurements for such metabolites are not required during the MUsT clinical phase. The nonclinical safety of any BEMT metabolites occurring in test species was adequately evaluated in previous studies.

Two parallel pharmacokinetic studies in rats, involving single and repeated dosing for 21 days by oral gavage or dermal application of unlabeled BEMT, provide key evidence for low systemic exposure to BEMT at NOAEL doses of 1000 mg/kg body weight/day. After 21 days, dermal dosing resulted in a modestly higher plasma concentration (AUCtlast 748 (271 SD) hng/mL) compared to oral gavage dosing (AUCtlast 1460 (676 SD) hng/mL). These results, which align with the low systemic exposure observed in the clinical MUsT, are crucial to supporting a waiver request for a systemic oral carcinogenicity study required by the FDA.

Overall, BEMT demonstrates low systemic availability, as reflected in plasma concentrations. The key conclusions from these findings are that BEMT is stable within biological systems, not readily absorbed after high oral or dermal dosages, and safe for repeated and prolonged topical applications in humans when used at 6% in OTC sunscreen products.