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To: Avinash Clarke,		

THERAPEUTIC GOODS (PERMISSIBLE INGREDIENTS) DETERMINATION

Purpose

To seek your approval to register the Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025 (Attachment 1) and the accompanying Explanatory Statement (Attachment 2).

Timing

The final date for your approval is sought on or before 13 June 2025 as the Determination needs to be registered on the Federal Register of Legislation for commencement on 20 June 2025.

Issues/Sensitivities

The proposed Determination includes changes relating to 25 ingredients, summarised below. Links are provided to overviews justifying changes, which have been accepted by the A/g Director of the Complementary Medicines Evaluation Section.

The new Determination includes the following changes to the former Determination:

Addition of new ingredients

- the addition of the following two new ingredients for use in listed and assessed listed medicines, and specific requirements for the use of the ingredients in medicines:
  - *methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate* (D25-225063); and
  - *citicoline* (D25-626449).

Changes to existing ingredients

- amendments to the requirements for the following 21 ingredients (D25-1413027) to align with the update to the Poisons Standard (which principally revises the concentration limit of specific components of the stated ingredients), as indicated in the *Notice of final decision to amend (or not amend) the current Poisons Standard – amygdalin, hydrocyanic acid and Wild Cherry Bark, Joint ACMS ACCS #34* (www.tga.gov.au/resources/publication/scheduling-decisions-final/notice-final-decision-amend-or-not-amend-current-poisons-standard-amygdalin-hydrocyanic-acid-and-wild-cherry-bark-joint-acms-accs-34) with an implementation date of 1 June 2025, as well as minor formatting changes and correction of minor typographical errors for the purpose of improving the internal consistency of the Determination:
  - *Almond oil;*
  - *Bitter almond oil;*
  - *Eriobotrya japonica;*
  - *Persic oil;*
  - *Prunus Africana;*
  - *Prunus armeniaca*

Commented s22 We suggest including a statement of what changes were made to update the Poisons Standard - were these just formatting changes, changes to requirements, or more substantive changes?

Commented s22 Hyperlink removed as hyperlinks are not included in instruments or ESs.

Commented s22 s22 - for consideration, are these formatting changes and corrections of typographical errors only in relation to the 21 ingredients listed below, or is it more broadly across the Determination?

Commented s22 This is in relation to the 21 ingredients

- *Prunus avium;*
- *Prunus cerasifera;*
- *Prunus cerasus;*
- *Prunus domestica;*
- *Prunus dulcis;*
- *Prunus humilis;*
- *Prunus japonica;*
- *Prunus laurocerasus;*
- *Prunus mume;*
- *Prunus persica;*
- *Prunus salicina;*
- *Prunus serotina;*
- *Prunus spinosa;*
- *Wild cherry bark dry;* and
- *Wild cherry bark powder.*

- the removal of requirements for the following two ingredients to reflect the expiry of the periods of exclusive use for the applicant, and minor formatting changes for the purpose of improving the internal consistency of the Determination (D25-1529445):
  - *Calanus finmarchicus oil*; and
  - *Galactooligosaccharides*.

Other issues relating to the preparation of the instrument:

- The Office of Impact Analysis (OIA) has issued a standing exemption from a RIS for all quarterly updates to the Determination where the updates are minor or machinery in nature (OIA ref no. 21645). This exemption applies to the addition of new ingredients, correction of errors, clarification of requirements, changes to ingredient requirements or availability to reflect scheduling decisions contained in the Poisons Standard, or the outcomes of TGA safety evaluations.
- Where future updates to the Determination are suspected to have more than a minor regulatory impact, further OIA advice will be sought.
- We will publish an update on the TGA website and provide a list of the changes in the proposed Determination to CHP Australia, CMA, Accord, and the Association of Therapeutic Goods Consultants (ATGC) shortly after your decision.
- The Determination and Explanatory Statement have been drafted based on the previous Determination and reviewed by the Regulatory Legal Services Branch.

Consultation

- Consultation has been outlined in the explanatory statement at Attachment 2.

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Recommendation

1. That you MAKE the Determination by signing and dating the front page (**Attachment 1**)	☒
2. That you APPROVE the accompanying Explanatory Statement (without signature) (**Attachment 2**)	☒
3. That you NOTE the proposed changes to the ingredients list (**Attachment 3**)	☒
4. That you APPROVE the web publication for the TGA website (**Attachment 4**). We will submit a web publishing request following your approval.	☒
5. That you NOTE the email to peak industry bodies will be sent out shortly after your approval of the instrument (**Attachment 5**)	☒

Avinash Clarke
Assistant Secretary
Complementary Medicines and Over the Counter Branch
Date: 12 June 2025

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Attachments:
The following documents are attached:

1. The Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025:

Volume	TRIM	FRL Description
1	D25-1778984	A-A
2	D25-1787274	B-E
3	D25-1788020	F-J
4	D25-1788166	K-O
5	D25-1788645	P-T
6	D25-1788780	U-Z

2. Explanatory statement for the Permissible Ingredients Determination: D25-2090525
3. List of amendments to Permissible Ingredients Determination: D25-1741318
4. TGA Web updates: D25-1291677
5. Email to peak industry bodies (CHP, CMA, ACCORD, & ATGC): D25-1291544

Contact officer:	s22 A/g Director – Complementary Medicines Evaluation Section
Phone:	s22
TRIM ref:	D25-1291629
Cleared by:	s22

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Safety Evaluation of New Sunscreen Active

Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate [UVINUL® LR]

Submission No: OM-2022-GL-01046-1/OM-2022-00102-1
Sponsor: BASF Australia Ltd
October 2024

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type: New chemical entity
Sponsor: BASF Australia Ltd
Generic name: **Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)**
Drug class: Sunscreen active
Submission No: OM-2022-GL-01046-1/OM-2022-00102-1
Tox file No: 2011/002522
TRIM reference: D23-2275436
Evaluator: s22 [redacted]
Date authorised: October 2024
(updated February 2025)

The main body of this evaluation report was based on the SCCS (Scientific Committee on Consumer Safety) opinion on Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)- Submission II (SCCS/1605/19) - (submitted to the TGA) contained in Appendix 1. Wherever possible, efforts were made to verify the accuracy of statements made therein.

Note: This evaluation report has been peer-reviewed. This version of the document contains confidential information (this page and page 11) and is not authorised for release to the sponsor.

TABLE OF CONTENTS

SUMMARY

- BASF Australia Ltd has applied to register a new chemical entity, methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate (UVINUL® LR; S87) as a new active ingredient in sunscreen products at concentration of up to 3% w/w.
- The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were GLP compliant.
- The *in vivo* pharmacokinetic parameters were not determined. *In vitro* assay in human skin samples indicates low percutaneous absorption of methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate.
- Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate had a low order of acute oral toxicity in rats. Acute toxicity in other species was not assessed. Studies following dermal administration route were not available for evaluation.
- Repeat-dose toxicity studies by the oral route were conducted in rats (up to 3 months). Major target organ for toxicity was the liver (increased weight with minimal centrilobular hepatocellular hypertrophy at 1000 mg/kg/day; relative exposure of~24, based on body surface area -BSA-) with a NOAEL of 300mg/kg/day (relative exposure of ~7). Recovery was not investigated. Studies in non-rodent species or following dermal administration route were not available for evaluation.
- Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate was clastogenic *in vitro* in human lymphocytes with and without metabolic activation, but at concentrations giving moderate levels of cytotoxicity. Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate was not mutagenic in the bacterial mutation assay or clastogenic *in vivo* in the rat micronucleus test. No carcinogenicity studies were conducted, which is considered acceptable based on minimal human exposure to percutaneous methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate, an absence of alert features for the substance, absence of *in vivo* genotoxicity, absence of sensitisation, photosensitisation or phototoxicity activities, and the absence of neoplastic or pre-neoplastic changes in the repeat dose toxicity study.
- Fertility was unaffected in male and female rats treated with methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate up to 250 mg/kg/day (relative exposures of ~6, based on BSA). Decreased fetal weight and impaired ossification (rats), were seen in embryofetal development studies, but only in the context of significant maternotoxicity (at relative exposures of ~17). Studies in juvenile animals were not available for evaluation. Studies in non-rodent species were not available for evaluation.
- Local tolerance studies indicated no irritancy or sensitisation potential of methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate.
- The proposed specifications for impurities/degradants in the drug substance/product have been adequately qualified.

CONCLUSIONS AND RECOMMENDATION

- Module 4 contained no secondary pharmacodynamics, safety pharmacology studies, nor information on the toxicity following dermal administration route, which is acceptable considering the proposed indications and negative dermal and ocular irritancy tests *in vitro*.
- Primary pharmacology studies were not available. UVINUL® LR is intended as an active ingredient in sunscreens and absorbs UV at 228, 385 and 460 nm, supporting the proposed indication.
- Pharmacokinetics parameters were not measured in animals or human subjects. Estimated exposure margins were moderate (based on BSA).
- In the repeat-dose toxicity studies, the liver was identified as the major target organ. Effects on the liver are not expected for the proposed indication.
- UVINUL® LR was clastogenic in human lymphocytes *in vitro*, but was not genotoxic nor clastogenic in animal models *in vivo*. The weight of evidence supports the conclusion that methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate is not carcinogenic *per se*.
- Since methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate is a secondary amine, and thus is prone to nitrosation and formation of nitrosamines, and the interaction potential with other ingredients of sunscreen products was not specifically addressed, approval will be subject to methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate not being used in combination with nitrosating substances, and the nitrosamine content of the final formulation must be below 50 parts per billion (ppb).
- Reproductive toxicity is unlikely for the proposed indication.

Based on the nonclinical data provided for methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate and evaluated in this report, approval of UVINUL® LR as a new active ingredient in sunscreen products at a concentration of up to 3% is supported on nonclinical grounds, with the following conditions:

- ***Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate must not be used in combination with nitrosating substances.***
- ***The nitrosamine content of the final formulation must be below 50 parts per billion (ppb).***
- ***The Sponsor should completely eliminate 2-ethoxyethanol and diethyl sulphate from UVINUL® LR.***
- ***The Sponsor should declare limits for 3-methoxypropylamine (update 10/04/2024: Sponsor's declared limits are <500 ppm; issue resolved).***
- ***The sponsor should conduct genotoxic potential analysis (by in silico analyses, with two complementary methodologies used — expert-rule based & statistical-based) for methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate impurities identified at levels of ≥0.1% (update 26/09/2024: Sponsor provided the data requested [D24-3722957]. Update 9/10/2024: the Sponsor confirmed via email that the impurities identified at levels ≥0.1% will be kept at ≤0.15%).***
- ***There are no nonclinical objections for the registration of methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate.***

Comments following ASEM adoption

On January 24, 2025, the TGA adopted the Australian Sunscreen Exposure Model (ASEM) for evaluating sunscreen ingredient safety. As a result, the Systemic Exposure Dose (SED) of UVINUL® LR has been updated using ASEM method 2, with a new SED of 0.588 mg/kg/day (CMES - 16GA Evaluation - Delegate Overview - Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate - Sunscreen Active - BASF Australia; D25-225063). The updated relative safety exposure margins recalculated using the new SED (see Addendum), are increased . The substantive conclusions of the Nonclinical Evaluation Report (NER) remain unchanged.

ASSESSMENT

BASF Australia Ltd has applied to register a new chemical entity, methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate (UVINUL® LR) as a new active ingredient in sunscreen products. Approval is sought to use this active in sunscreen products at concentration of up to 3%.

Pharmacokinetics

No in *vivo* ADME studies were conducted. Instead, percutaneous absorption of UVINUL® LR (3.23% w/w) in a commercial suncare formulation was determined *in vitro* in human skin samples after 24h long exposure. The assay was performed adequately and according to OECD 428 and OECD 28 guidelines. At 24h post dose, mean maximum absorbed level of the active ingredient was 1.08 µg/cm^2 ± 0.67 (SD) corresponding to the mean 1.63% ± 1.02 (SD) of the applied dose, indicating low dermal absorption under the assay condition. The skin absorption of the active ingredient was calculated as the sum of the mean and 1SD (1.08 + 0.67 µg/cm^2) and estimated at 1.75 µg/cm^2 (17.5 mg/m^2), which corresponds to 2.65% of "neat" UVINUL® LR or 0.086% of the total sunscreen formulation containing 3.23% (w/w) of UVINUL® LR.

Based on an absorption rate of 17.5 mg/m^2 and 7 applications per day (for details see section 1.6, Plasma kinetics in human subjects), estimated daily systemic exposure of UVINUL® LR is 122.5 mg/m^2.

Toxicity

Acute toxicity

A single dose, non-GLP compliant acute toxicity study was conducted in SD female rats (300, 2000 mg/kg; PO). The study did not contain a histopathological panel or necropsy evaluation. The observation period was shorter than 14 days and only animals of one sex were used. Therefore, the acute toxicity of orally administered UVINUL® LR cannot be assessed based on the study. However, adequate information can be inferred from the GLP compliant, short term (14 days), range-finding repeat dose toxicity study in Han rats as stated in the Australian regulatory guidelines for sunscreens[1]. Orally administered UVINUL® LR displayed a low order of acute toxicity in rats. Since no mortality was observed in the 14-day study, the estimated LD_{50} is above 1000mg/kg/day. Data on acute dermal toxicity *in vivo* was not available.

Repeat-dose toxicity

Two GLP compliant studies, short and medium term (14- and 90- day respectively) were conducted in rats of both sexes following oral (gavage) administration of UVINUL® LR. Studies in non-rodent species were not conducted. Group sizes, study duration, frequency of dosing and dose levels (up to 1000 mg/kg/day) were acceptable. The proposed route of administration (dermal application) was not used. The reversibility of effects was not examined. An evaluation of potential inhalation toxicity was not conducted. No toxicokinetic parameters were measured and ECG analysis was not conducted. Body weight, clinical signs, food intake, haematology, clinical chemistry, and urinalysis (females) were evaluated. Necropsy and histopathology examinations were performed on all animals. No mortality was reported in the 14-day study. In the 90-day study, the deaths of two females (one in 100 mg/kg/day and one in 300 mg/kg/day group) were not compound related.

[1] Australian regulatory guidelines for sunscreens (tga.gov.au)

Relative exposure

Toxicokinetic parameters in animals were not measured. The relative exposures were estimated using animal:human doses adjusted for body surface, and assuming 50% bioavailability following the oral administration in rats. The results are presented in the table below.

Table 11111. Estimated relative exposure of UVINUL® LR in human subjects

Species/Study	Route	Dose (mg/kg/day)	Dose (mg/m^2)*	Relative exposure
Rat (SD) 11X221 (14-days) 11X497 (90-days)	PO	100	300	2.4
		300	900	7.3
		1000	3000	24.5
Human, *In vitro* percutaneous absorption 792670	Dermal	-	122.5	-

* Rats dose based on body surface area (BSA) was calculated by multiplying the mg/kg dose by a conversion factor of 6 and dividing by 2 to assume 50% bioavailability; humans BSA dose calculated by multiplying absorption rate of 17.5 mg/m^2 by 7 daily applications.

Major toxicities

The major target organ for methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetat was the liver. Increased liver weight in males at 1000mg/kg/day and in females from 300mg/kg/day, but without macroscopical or histopathological correlates were observed in the 14-day study. In the 90-day study, relative liver weights were increased in both sexes from 300 mg/kg/day. In addition, at 1000 mg/kg/day, minimal centrilobular hepatocellular hypertrophy was observed in 50% of males and 80% of females. Since no histopathological correlate, nor AST or ALT induction were observed, the increased liver weight at 300 mg/kg/day is likely an effect related to the test-item adaptive response and is not considered adverse.

Bilirubin

Urinalysis was not performed in male rats, but 50% of females in each group tested positive for markedly elevated bilirubin in urine from 100 mg/kg/day, although the exact levels were not specified. The outcomes were not stochastically distributed; in all UVINUL® LR treated groups, the first 5 females always tested positive, suggesting a methodological error. While urine bilirubin may be falsely decreased if the urine sample undergoes prolonged exposure to ultraviolet light or stands at room temperature exposed to air (bilirubin oxidizes into biliverdin, which is not detected), the total bilirubin levels were comparable between vehicle, 100 and 300 mg/kg/day groups, strongly suggesting that the signal was a false positive, likely related to the presence of methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate or its metabolite in urine. Notwithstanding, increased total bilirubin levels were observed in both sexes at 1000 mg/kg/day and at this dose bilirubin induction is considered compound related.

Other toxicities

At 1000 mg/kg/day in the 90-day study a slight decrease in body weight gains was observed in males. Slightly lower spermatid count and spermatid density was noted at the same dose, but without reduction in absolute testicular weight or microscopic correlations and thus not considered adverse. Slightly decreased haemoglobin levels were observed from 100 mg/kg/day in males, and a slight reduction in MCH and MCV levels was observed in females starting at 300 mg/kg/day. At 1000 mg/kg/day, there were reductions of haematocrit and MCV, and increased platelets counts in males; in females, MCHC was decreased, and leukocytes and lymphocytes were increased. Reticulocytes were increased in both sexes at 1000mg/kg/day. In both sexes, starting at 300 mg/kg/day, an increased incidence of dehydration and urine-stained abdominal fur was observed

Recovery was not investigated. The *in vivo* data indicate a low systemic toxicity of UVINUL® LR. A NOAEL of 300 mg/kg/day has been established in rats.

Genotoxicity

The mutagenic potential of UVINUL® LR was investigated *in vitro* using a bacterial reverse mutation test, a micronucleus induction study with human reconstructed skin EpiDerm™ assay, a HPRT locus assay in CHO cells, and a micronucleus test in human lymphocytes. An *in vivo* micronucleus test in SD rats was also conducted (with 500, 1000, 2000 mg/kg, PO).

All studies were GLP compliant and conducted with OECD guidelines 471, 487 and 474, except EpiDerm™ study, for which OECD guideline is not available. Assays were appropriately validated; adequate bacterial strains and concentrations were used in the Ames tests and sufficient test item concentrations were used in the *in vitro* chromosome aberration assay in CHO cells. There was no evidence of mutagenicity or clastogenicity in the submitted studies, except for an increase in the number of micronucleated cells in human lymphocytes *in vitro* (with and without metabolic activation). Since this effect was observed at cytotoxic levels, it can be interpreted as a false positive result. In a subsequent *in vivo* study in rats, the number of micronucleated polychromatic erythrocytes did not increase up to the highest dose tested (2000 mg/kg) in the mammalian erythrocytes micronucleus test in rats. The weight of evidence suggests UVINUL® LR is not genotoxic.

Photomutagenicity

The effect of UVA radiation on the mutagenic potential of UVINUL® LR was assessed in the GLP compliant bacterial reverse mutation test without metabolic activation. Adequate bacterial strains and test item concentrations were used; assay was appropriately validated. UVINUL® LR did not display mutagenic potential in bacterial strains exposed to irradiation. Photomutagenicity is not expected.

Carcinogenicity

The Sponsor stated that methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate lacks similarity to other molecules with known carcinogenic activity and the chemical structure lacks structural alerts for carcinogenicity. The lack of carcinogenicity studies is considered acceptable based on minimal human exposure to percutaneous methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate, an absence of alert features for the substance, absence of *in vivo* genotoxicity, absence of sensitisation, photosensitisation or phototoxicity activities, and the absence of neoplastic or pre-neoplastic changes in the repeat dose toxicity study.

Reproductive and developmental toxicity

One *in vivo*, GLP compliant study investigated the effect of orally administered (gavage) UVINUL® LR on fertility and embryofetal development in Wistar rats. The study duration, frequency of dosing and dose levels (up to 700 mg/kg/day) were appropriate. Attenuated body weight gains in the 700 mg/kg/day group indicate that the toxic end point was reached, but the number of litters (8 to10 per dose) was lower than recommended by ICH S5(R3) [2] guideline (16 to 20 per dose). Studies in non-rodent species were not conducted.

Administration of UVINUL® LR (100, 250, 700 mg/kg/day PO) was initiated 2 weeks prior to cohabitation. Fertility and reproductive performance in males and females were not affected up to the highest dose tested. Mean pup weight was significantly reduced (by 24% *c.f.* controls) in the 700

[2] https://database.ich.org/sites/default/files/S5-R3_Step4_Guideline_2020_0218_1.pdf

mg/kg/day group and concurrent with lower mean body weight gains in dams during gestation period at the same dose. Maternal and reproductive NOAEL was 250 mg/kg/day.

Decreased fetal weight and impaired ossification were seen in the embryofetal development study in rats, but only in the context of significant maternotoxicity at 700 mg/kg/dose. There are no concerns regarding embryotoxicity or teratogenicity for methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate.

Relative exposure and placental transfer

Placental transfer and excretion in milk were not investigated in animals. Toxicokinetic parameters in animals were not measured. The relative exposures were estimated using animal:human doses adjusted for body surface, and assuming 50% bioavailability following the oral administration in rats. The results are presented in the table below.

Table 2. Estimated relative exposure of UVINUL® LR in the reproductive study

Species/Study	Route	Dose (mg/kg/day)	Dose (mg/m^2)*	Relative exposure
Rat (SD) 11X498	PO	100	300	2.4
		250	750	6.1
		700	2100	17.1
Human, *In vitro* percutaneous absorption 792670	Dermal	-	122.5	-

* Rats dose based on body surface area (BSA) was calculated by multiplying the mg/kg dose by a conversion factor of 6 and dividing by 2 to assume 50% bioavailability; humans BSA dose calculated by multiplying absorption rate of 17.5 mg/m^2 by 7 daily applications.

Skin sensitisation and irritation

Undiluted UVINUL® LR (25 mg/0.6 cm^2) did not display irritation potential *in vitro* in the EpiDerm™ human skin model. Furthermore, the compound did not display skin sensitisation potential when applied dermally (up to 50% [w/v]) for 6 days in the murine local lymph node assay. Skin irritation and sensitisation effects are not expected.

Ocular irritation

UVINUL® LR did not display irritancy potential *in vitro* in either a bovine corneal opacity and permeability test at 3% (w/v) or in a human cornea model when administered in undiluted form or in 3% (w/v) solution. Eye irritation effects are not expected.

Phototoxicity

UVINUL® LR absorbs UV light in the 290 to 700 nm range (3 absorbance maxima were observed at 228, 385 and 460 nm, respectively). The extinction coefficients (MEC) were not established, but phototoxicity potential was tested in the GLP-compliant, neutral red uptake assay in 3T3 Balb/c cells [3]. An EC_{50} of 958.1 µg/mL was reported without irradiation, whereas the EC_{50} under irradiation ranged from 758.4 to 998.7 µg/mL, and the maximum PIF value was below 2 (1.3). UVINUL® LR related phototoxicity is not expected [4].

Photosensitisation

The photosensitisation potential of UVINUL® LR was tested up to 48h after application in a GPL compliant study in male guinea pigs (Hartley) exposed to UVA (1500s, ~5.7 mW/cm^2) and UBV

[3] ICH Guidance S10 on Photosafety Evaluation of Pharmaceuticals.

[4] OECD Test Guideline No. 432 In Vitro 3T3 NRU Phototoxicity Test

(100s, ~9.6 mW/cm^2) irradiation. The compound was administered dermally at 50% (w/v) in N,N-dimetyhylformamide (DMF). Group sizes were adequate. Neither mortality nor clinical signs were observed in any animal in the test item or vehicle control group. Body weight gains were unaffected. Positive controls confirmed the validity of the assay. UVINUL® LR did not display dermal photoirritancy potential when tested up to 50% (w/v) in DMF. A photosensitisation effect is unlikely.

Immunotoxicity

No studies were conducted.

Impurities

Impurities 2-ethoxyethanol (up to 120 ppm), 3-methoxypropylamine (< 500 ppm) and diethyl sulphate (< 1 ppm) impurities were detected in three tested batches of UVINUL® LR.

- Diethyl sulphate (classified as a carcinogen and mutagen[5]) and 2-ethoxyethanol (classified as a substance that poses a health risk when used in cosmetic products[6]) are listed in the Cosmetic Products Regulation Annex II[7] and are banned from use in any cosmetic product marketed for sale or use in the European Union. Since it is a condition for a substance to be used in sunscreens that the substance is not listed in the Cosmetic Products Regulation Annex II, **impurities 2-ethoxyethanol and diethyl sulphate must be absent from methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate and UVINUL® LR**.

- Impurity 3-methoxypropylamine is not listed in the Cosmetic Products Regulation Annex II, but is not listed in the Therapeutic Goods (Permissible Ingredients) Determination repository[Error! Bookmark not defined.Error! Bookmark not defined.8]. While the compound was demonstrated to be sensitising to the skin and can be regarded as causing serious eye damage, 3-methoxypropylamine is it is unlikely to have adverse dermal or ocular effects given the consistently negative outcomes of eye irritation and skin sensitisation studies with UVINUL® LR. 3-methoxypropylamine had no effect on fertility in rats (up to 1000 mg/kg bw/day, PO), nor did it display genotoxic potential *in vitro* in bacterial reverse mutation assay or *in vivo* in mice (75 mg/kg bw)[8]. **The exact content and limits for 3-methoxypropylamine in the UVINUL® LR product should be declared.**

- Five other impurities were identified in UVINUL® LR product at levels above 0.1% (page 10 of the SCCS opinion on Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate - Submission II). **The Sponsor is asked to provide the analysis of their mutagenic potential e.g., by *in silico* analyses (with two complementary methodologies used — expert-rule based & statistical-based) and state their exact limits.**

Interactions

Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate is a secondary amine, prone to nitrosation and formation of nitrosamines.

[5] https://www.ncbi.nlm.nih.gov/books/NBK424638/

[6] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out_199.pdf

[7] EU. Prohibited Substances: Annex II, Regulation 1223/2009/EC on Cosmetic Products, as amended by Regulation (EU) 2021/1902, OJ L 387 of 3 November 2021

[8] Registration dossier of European Chemicals Agency; 3-methoxypropylamine (https://echa.europa.eu/registration-dossier/-/registered-dossier/13449)

Since the interaction potential with other ingredients of sunscreen products was not specifically addressed, approval will be subject to methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate not being used in combination with nitrosating substances,.

In consensus with the European Scientific Committee on Consumer Safety, the nitrosamine content of the final formulation must be below 50 parts per billion (ppb).

TGA INTERNAL/CONFIDENTIAL INFORMATION

The TRIM file below is confidential and internal to the TGA. It must not be released outside of the TGA.

The proposed limit for the nitrosated form of S87 is not expected to raise a safety concern in the context of the proposed use of the sunscreen. The evaluation is located here: D23-2255179 .

Paediatric use

No specific studies in juvenile animals were available for evaluation.

1. PRODUCT DETAILS

1.1. BACKGROUND

BASF Australia Ltd has applied to register a new chemical entity, methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate (UVINUL® LR). UVINUL® LR is proposed to be used in sunscreen products at concentration of up to 3%.

1.2. CHEMISTRY AND FORMULATION

Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate (S87, CAS Number 1419401-88-9) is an active ingredient in sunscreen products. The chemical name of methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate is 2-ethoxyethyl (2Z)-2-cyano-2-[3-(3-methoxypropylamino) cyclohex-2-en-1-ylidene]acetate. It has the molecular formula C17H26N2O4 and a molecular weight of 322.41 g. The chemical is a yellow solid in form of a powder or small chunks.

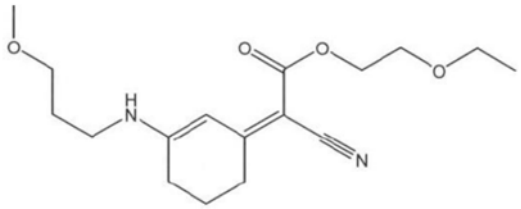


Figure 11111: Chemical structure of methoxypropylamino cyclohexenylidene ethoxyethylcyanoaceta

1.3. OVERSEAS REGULATORY STATUS

The substance was approved to be used in the European Union in cosmetic sunscreen products, with the exception of applications that may lead to exposure of the end-user's lungs by inhalation, on 12 November 2020 under conditions that it is not to be used with nitrosating agents (maximum nitrosamine content: 50 ppb) and it is kept in nitrite-free containers.

1.4. STABILITY

"The characterisation of the batches used for toxicological studies showed the homogeneity of test items. Batch C-1701 B_C_3 Lot 0009511412 was stable after being stored for 1 year at 40 °C. Neither active ingredient content nor the content and identity of impurities changed over the considered time interval."[9] The TGA nonclinical evaluator agrees.

1.5. APPROACH TO NONCLINICAL EVALUATION

Many of the Module 4 studies are summarised in the Scientific Committee on Consumer Safety (SCCS) opinion on Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)- Submission II (SCCS/1605/19) (excerpted in Appendix 1). The main findings are summarised in the Assessment. Additional studies are evaluated in Section 2 below.

[9] Scientific Committee on Consumer Safety opinion on Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)- Submission II (SCCS/1605/19), Page 12

1.6. PLASMA KINETICS IN HUMAN SUBJECTS

Based on the *in vitro* study, the skin absorption of the active ingredient was estimated at 1.75 µg/cm² (17.5 mg/m²) (see Assessment; *Pharmacokinetics*). Cancer Council Australia recommends applying the sunscreen product every 2 h if spending time outdoors, which equals to ~7 doses a day (~35 mL each). Based on an absorption rate of 17.5 mg/m² and 7 applications per day, estimated daily systemic exposure of UVINUL® LR is 122.5 mg/m².

2. TOXICOLOGICAL DATA NOT EVALUATED IN THE OVERSEAS ASSESSMENT REPORT

Genotoxicity

Study details	Test system & conditions	Results	Validity/comments
In vitro HPRT locus assay			
11M219 29 November 2012 GLP	X-linked hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus assay in Chinese hamster ovary (CHO) cells *Experiment 1 and 2:* *7 concentrations over 53.1 – 3400 µg/mL (± S9, 4 h)* *Experiment 3:* *8 concentrations over 7.8 – 1000 µg/mL (±S9, 24h)* *6 concentrations over 31.3 – 1000 ug/ml (-S9, 4h)*	**Negative/ Equivocal**	Yes: highest concentration tested was 3400 µg/ml Precipitation in culture medium at the end of treatment was observed at 1700 µg/mL and above in the 1st and 2nd experiment. Cytotoxicity was observed in the experiment 2 from ≥ 850 µg/mL (± S9) and the experiment 3 at 1000 µg/mL (+S9, 4h) and from ≥ 500 µg/mL(-S9, 24h). No increased mutation frequency was observed in the 1st and 2nd experiment. In the 3rd experiment (-S9, 4h) a statistically significant dose-related increase in the mutant frequency was found (MFcorr.: 0.84 - 2.48 per 10^6 cells). The values were within laboratory historical negative control data range (MFcorr.: 0.00 – 15.83 per 10^6 cells). Positive controls confirmed sensitivity of the assay.

Acute Toxicity

Study	Findings
s47G 05 February 2008 s47G	***Mortality:*** s47 ***Body weight gain:*** s47G ***Clinical signs:*** s47G s47G

APPENDIX 1 – OVERSEAS ASSESSMENT REPORT

5A SCCS Opinion
Submission II EWAQ2

3. ADDENDUM

On January 24, 2025, the TGA adopted the Australian Sunscreen Exposure Model (ASEM) for evaluating sunscreen ingredient safety. As a result, the Systemic Exposure Dose (SED) of UVINUL LR has been updated using ASEM method 2, with a new SED of 0.588 mg/kg/day (CMES - 16GA Evaluation - Delegate Overview - Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate - Sunscreen Active - BASF Australia; D25-225063). Updated estimated relative exposure in animal studies are presented in the tables below.

Table 11111. Estimated relative exposure of UVINUL® LR in human subjects using based on ASEM Systemic Exposure Dose (SED)

Species/Study	Route	Dose (mg/kg/day)	Relative exposure
Repeat dose toxicity			
Rat (SD) 11X221 (14-days) 11X497 (90-days)	PO	100	170
		300	510
		1000	1701
Reproductive toxicity			
Rat (SD) 11X498	PO	100	170
		250	425
		700	1190
SED based on human *in vitro* percutaneous absorption (Study 792670) and ASEM method 2	Dermal	0.588	-

ASEM = Australian Sunscreen Exposure Model

From: s22
To: TGA Toxicology
Cc: s22
Subject: FW: New Substance application received (16GA) - OM-2022-00102-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE - BASF [SEC=OFFICIAL]
Date: Wednesday, 1 February 2023 1:28:00 PM
Attachments: image001.png

Dear Tox team,

We have received an enquiry from the applicant regarding the status of this application (OM-2022-00102-1). May I get an update please? Thanks.

Kind regards,

s22

s22


s22

From: s22
To: s22
Cc: s22
Subject: RE: New Substance application received (16GA) - OM-2022-00102-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE - BASF [SEC=OFFICIAL]
Date: Monday, 24 July 2023 11:19:57 AM
Attachments: image001.gif
image002.png

Hi s22

The decision to limit the nitrosamine content was based on the fact the European Commission set that level. As the guidance states, 'Applicants of all human medicinal products should ensure that the presence of nitrosamines is controlled and kept as low as possible, irrespective of marketing status or the type of product'. If the Sponsor has the capability to keep nitrosamines below 50 ppb for products for the European market, Australian consumers should be offered the same protection from nitrosamines.

The Carcinogenic Potency Categorisation Approach (CPCA) for N-nitrosamines from the EMA guidance (dated 7 July) was indeed taken into account to conclude that with a concentration of 50 ppb nitrosamines, the maximum daily dose of the nitrosamine (394 ng/day) would be below the acceptable intake of 1.5 µg/day (D23-2255179; this document should not be disclosed outside of the TGA unless authorised in writing by the Toxicology section).

Kind regards

s22

From: s22 @health.gov.au>
Sent: Thursday, 20 July 2023 3:32 PM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 l@Health.gov.au>
Subject: RE: New Substance application received (16GA) - OM-2022-00102-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE - BASF [SEC=OFFICIAL]

Good afternoon s22

Thank you for your expedited response. Much appreciated.

May I have a follow up question on nitrosamine content? On 7 July, the EMA updated its guidance on nitrosamine impurities in human medicinal products, amending Q&A 10 and adding three appendices. Can you please confirm the proposed condition '[t]he nitrosamine content of the final formulation must be below 50 parts per billion (ppb)' is in compliance with the limits apply for nitrosamines as included in the updated EMA guideline?

Kind regards,

s22

From: s22 @health.gov.au>
Sent: Thursday, 20 July 2023 2:56 PM
To: s22 @health.gov.au>; s22 @health.gov.au>
Cc: s22 @Health.gov.au>; s22 @health.gov.au>
Subject: RE: New Substance application received (16GA) - OM-2022-00102-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE - BASF [SEC=OFFICIAL]

Hi s22

- For bullet point 1: the meaning of 'completely eliminate' diethyl sulphate and 2-ethoxyethanol is that it should not be found in the final product. I am happy for you guys to use your standard wording, such as reduced to below the level of detection, etcetera (and I guess the chemistry/quality area can say if their lowest level of detection is appropriate).
- For bullet point 2: as above, I don't have expertise in what level of detection/quantification is appropriate for the substance.
- For bullet point 3: batches 1442/3+4, C 1701/8, and 0009511412, used in the nonclinical studies provided, had a specification for 3-methoxypropylamine of <500 ppm (but not exact values). Since these studies were used to demonstrate the safety of the active including this impurity, the exact 3-methoxypropylamine levels in these 3 batches should be known and may be used to determine an appropriate level which gives us confidence of the safety of the presence of 3-methoxypropylamine. So I guess what I should have written is 'the Sponsor should declare exact levels of 3-methoxypropylamine in batches 1442/3+4, C 1701/8, and 0009511412'.
- For bullet point 4: the analysis of genotoxic potential should be considered mandatory, but the Sponsor could provide it as a post-approval condition (within a certain amount of time post-approval; e.g. 6-12 months).

Kind regards
s22

From: s22 @health.gov.au>
Sent: Monday, 17 July 2023 4:23 PM
To: s22 @health.gov.au>
Cc: s22 @Health.gov.au>
Subject: RE: New Substance application received (16GA) - OM-2022-00102-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE - BASF [SEC=OFFICIAL]

Dear Tox,

Thanks again for Tox's help evaluating this active ingredient. We are preparing the evaluation outcomes/questions that will be sent to the applicant. Can you please help us to have a better understating of some of the conditions summarised in the report?

Based on the nonclinical data provided for methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate and evaluated in this report, approval of UVINUL® LR as a new active ingredient in sunscreen products at a concentration of up to 3% is supported on nonclinical grounds, with the following conditions:

1. ***Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate must not be used in combination with nitrosating substances.***
2. ***The nitrosamine content of the final formulation must be below 50 parts per billion (ppb).***
3. ***The Sponsor should completely eliminate 2-ethoxyethanol and diethyl sulphate from UVINUL® LR.***
4. ***The Sponsor should declare limits for 3-methoxypropylamine.***
5. ***The sponsor should conduct genotoxic potential analysis (by in silico analyses, with two complementary methodologies used — expert-rule based & statistical-based) for methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate impurities identified at levels of ≥0.1%.***

We have the following questions:

- For condition 3, we understand diethyl sulphate and 2-ethoxyethanol are listed in the Cosmetic Products Regulation Annex II, thus cannot be used in sunscreen. From the perspective of imposing a restriction/specification for a permissible ingredient, 'completely eliminate' is not normally used. Can you please inform us the intended meaning of 'completely eliminate'?
- Follow up question on condition 3, can you please advise if specification of 'Not detectable with a detection limit of X ppm' (or words of similar meaning) for these two impurities is acceptable from safety perspective? If it is acceptable, can you please advise us the acceptable detection limit for each impurities? i.e. detection limit ≤ X ppm is acceptable for diethyl sulphate.
- For condition 4, can you please advise if we need to specify the upper limit for impurity 3-methoxypropylamine? If we do, can you please advise this limit (3-methoxypropylamine ≤ X ppm can be considered as safe)?
- For condition 5, can you please advise us if you consider these genotoxic potential analyses requested are mandatory data to establish the safety of the methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate? In other words, the safety of this UV filter cannot be established if the applicant fail to provide these analyses?

Please feel free to reach back to us if you need any clarification.

Kind regards,
s22

From: s22 @health.gov.au>
Sent: Thursday, 13 July 2023 5:23 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: New Substance application received (16GA) - OM-2022-00102-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE - BASF [SEC=OFFICIAL]

Dear s22

The evaluation for the UV filter METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE (3%) has finished.

The evaluation report is here: D23-2275436.

Kind regards,

s22

Senior Toxicologist
Toxicology Section
Scientific Evaluation Branch

Therapeutic Goods Administration
Australian Government, Department of Health and Aged Care
Location: 27 Scherger drive, Fairbairn ACT
PO Box 100
Woden ACT 2606
www.tga.gov.au

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community.

From: s22 @health.gov.au>
Sent: Thursday, 2 March 2023 2:52 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>
Subject: RE: New Substance application received (16GA) - OM-2022-00102-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE - BASF [SEC=OFFICIAL]

Hi s22

Thank you for your email with that info.

We'll take the information into account during the evaluation, and will be in touch if we require extra information.

Thank you

s22

From: s22 @health.gov.au>
Sent: Thursday, 23 February 2023 12:30 PM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22

s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>

Subject: FW: New Substance application received (16GA) - OM-2022-00102-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE - BASF [SEC=OFFICIAL]

Hi Tox team,

I have identified some issues during my quality evaluation of the below sunscreen active ingredient which you might need to consider during your safety evaluation. These issues are as follows:

1. The SCCS has noted that, the solubility of methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate in PEG 300 was not provided. This is considered critical as PEG 300 was the solvent used for toxicological tests.
2. The 1H-NMR results provided indicated a mixture of geometrical isomers (i.e. a mixture of E- and Z-isomers). Although the substance is synthesised as the Z-isomer, the results obtained from different NMR experiments revealed a time dependent isomerisation of the test item (Z-isomer) to the corresponding E-isomer upon dissolution. The time-dependent investigation yielded equilibrium after ca. 5 hours of the isomeric mixture with a ratio of 1.98 : 1.00 for Z-isomer to E-isomer (i.e. approximately 60% Z-isomer and 40% E-isomer). The E- and Z-isomers are two different compounds and safety profiles for individual components should be considered.
3. According to the SCCS final opinion, Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate is a secondary amine, and thus it is prone to nitrosation and formation of nitrosamines.

Please let me know if you require any further information.

Thanks and regards,

s22

s22

s22

[redacted]

From: Complementary Medicines
To: s47G
Bcc: s22
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]
Date: Friday, 15 September 2023 12:19:21 PM

Dear s47G

s47G

[redacted]

s47G

[redacted]

s47G

s47G [redacted]

Please do not hesitate to contact us if you have any further questions.

Kind regards,

s22 [redacted]

Complementary Medicines
Complementary and OTC Medicines Branch
Phone: s22 [redacted]
Email: complementary.medicines@health.gov.au
Therapeutic Goods Administration
Department of Health and Aged care
PO Box 100
Woden ACT 2606
www.tga.gov.au

This information is given to you without prejudice and is not binding on the TGA. It is the responsibility of the sponsor to ensure that all of the legislative requirements are met.

---

[1] https://www.ncbi.nlm.nih.gov/books/NBK424638/

[2] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out_199.pdf

[3] EU. Prohibited Substances: Annex II, Regulation 1223/2009/EC on Cosmetic Products, as amended by Regulation (EU) 2021/1902, OJ L 387 of 3 November 2021

[4] Registration dossier of European Chemicals Agency; 3-methoxypropylamine (Registration Dossier - ECHA (europa.eu))

From: Complementary Medicines
To: s22 ; CMES
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]
Date: Monday, 12 February 2024 1:39:22 PM
Attachments: Answer to TGA AUS MCE 2024 QM Fin_2.docx
Batch analysis 22S01838 March 2022.pdf
Batch analysis 22S01965 march 2022.pdf
GCFID.pdf
HPLC.pdf

Hi CMES,

For your review please

Thank you, s22

From: s47G
Sent: Monday, February 12, 2024 10:28 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Part 1

Dear Officer

Please find attached the response to the question below. Since the file sizes are large the information will be sent over several emails. The attachments are imbedded in the main documents (Answer to TGA AUS MCE 2024 QM Fin_2). But I have also attached them separately.

Please let me know if any further information is required.

Regards

s47

---

s47G

s47G [redacted]

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Friday, September 15, 2023 12:19 PM
To: s47G [redacted] >
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Dear s47G [redacted]

s47G [redacted]

s47G

[redacted]

s47G

[redacted]

s47G

Document 6

[redacted]

Please do not hesitate to contact us if you have any further questions.

Kind regards,

s22

Complementary Medicines
Complementary and OTC Medicines Branch
Phone: s22
Email: complementary.medicines@health.gov.au
Therapeutic Goods Administration
Department of Health and Aged care
PO Box 100
Woden ACT 2606
www.tga.gov.au

This information is given to you without prejudice and is not binding on the TGA. It is the responsibility of the sponsor to ensure that all of the legislative requirements are met.

---

[1] https://www.ncbi.nlm.nih.gov/books/NBK424638/

[2] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out_199.pdf

[3] EU. Prohibited Substances: Annex II, Regulation 1223/2009/EC on Cosmetic Products, as amended by Regulation (EU) 2021/1902, OJ L 387 of 3 November 2021

[4] Registration dossier of European Chemicals Agency; 3-methoxypropylamine (Registration Dossier - ECHA (europa.eu))

BASF
We create chemistry

s47G [redacted]

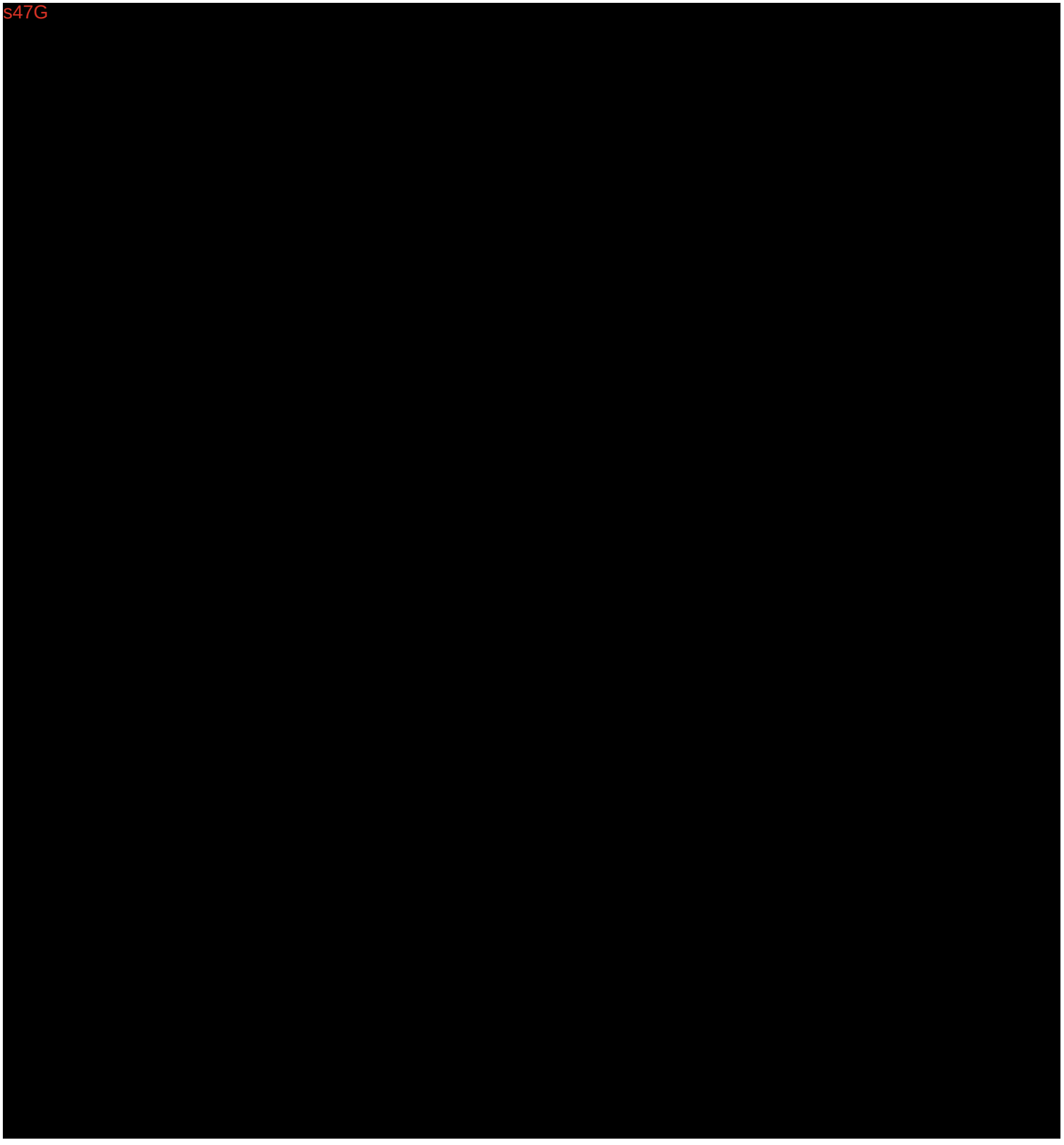
CONFIDENTIAL INFORMATION

s47G [redacted]

We create chemistry

January 24, 2024

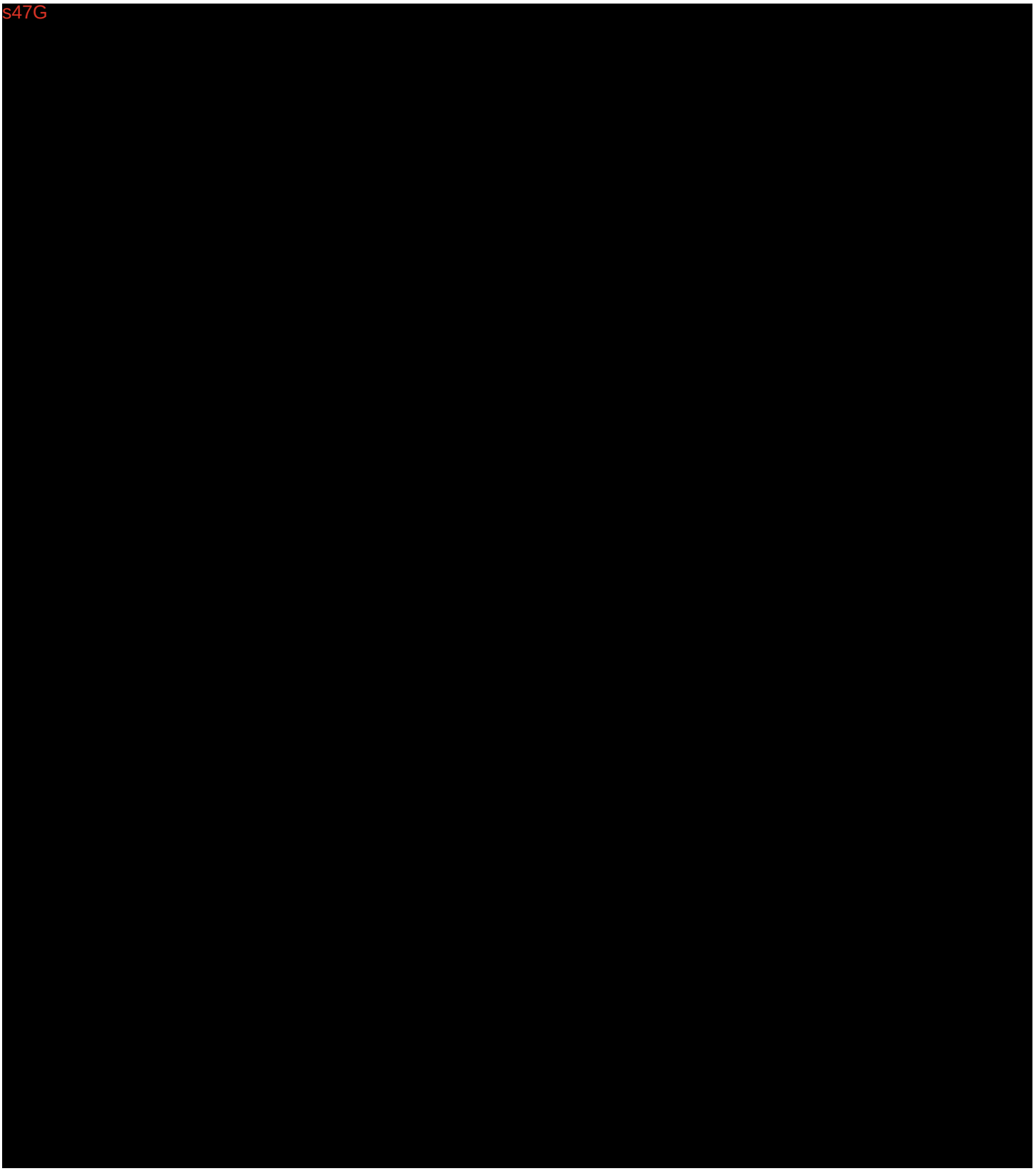
s47G



BASF
We create chemistry

January 24, 2024

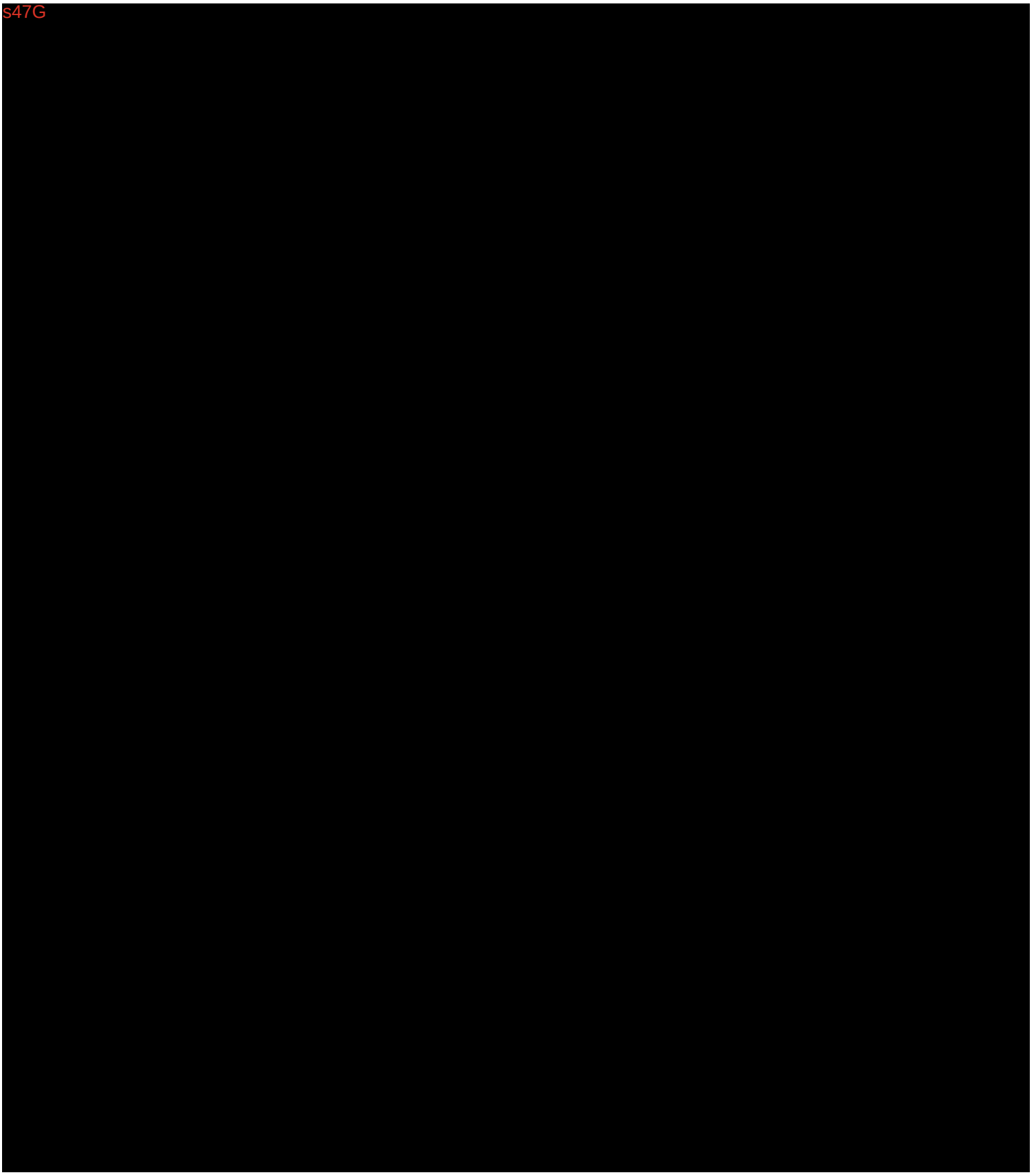
s47G



We create chemistry

January 24, 2024

s47G



We create chemistry

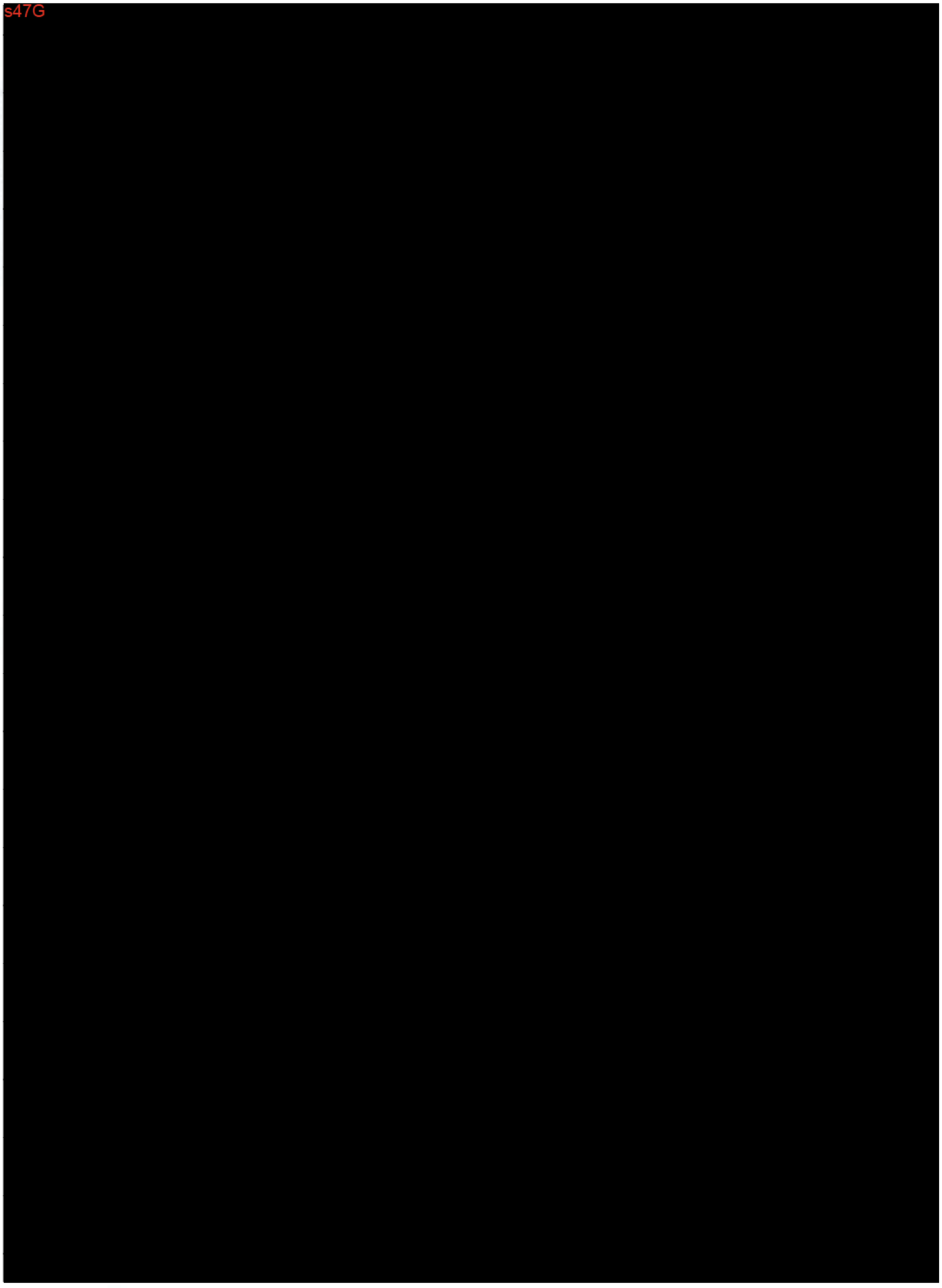
January 24, 2024

s47G

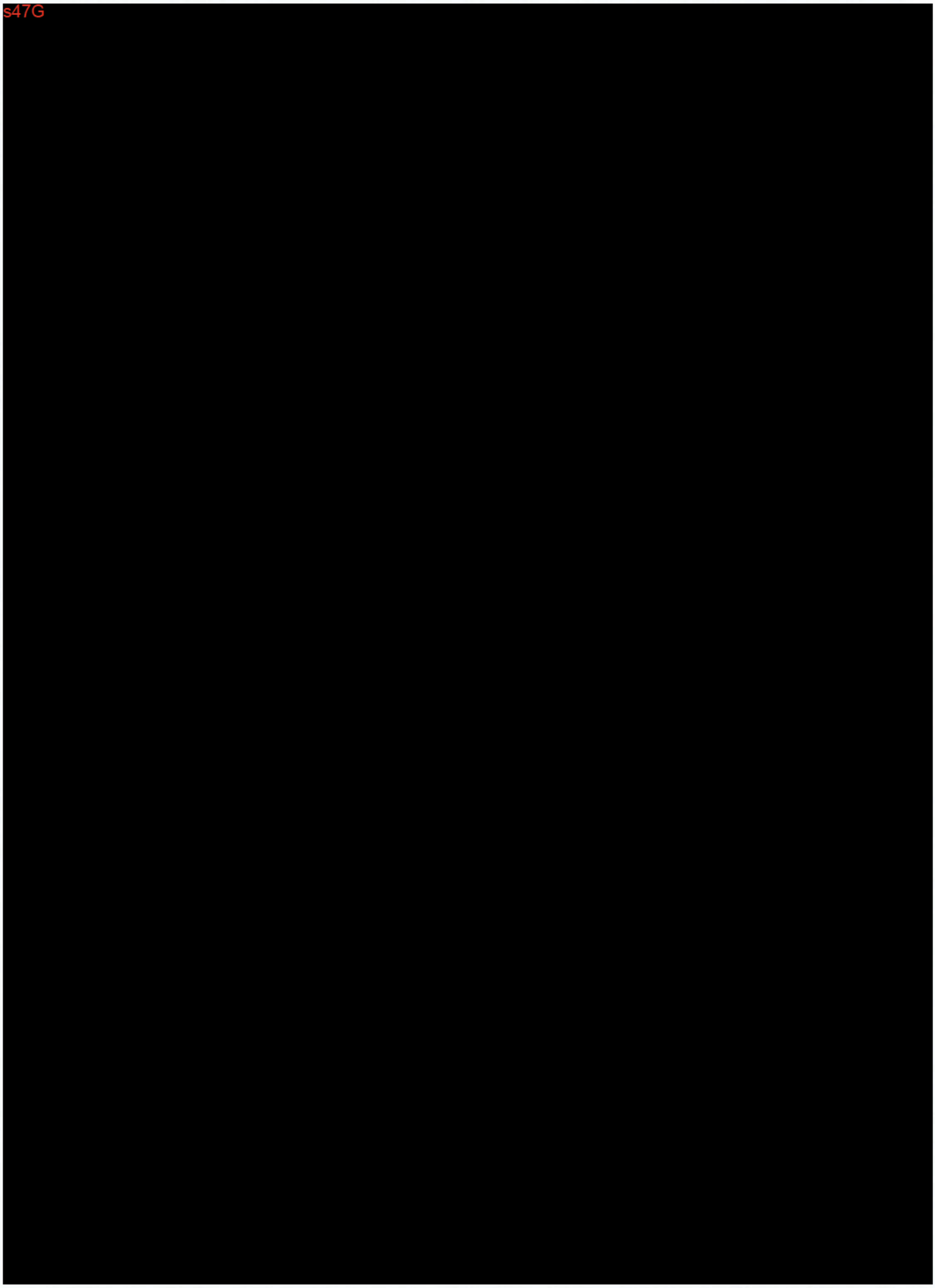
s47G

[redacted]

s47G

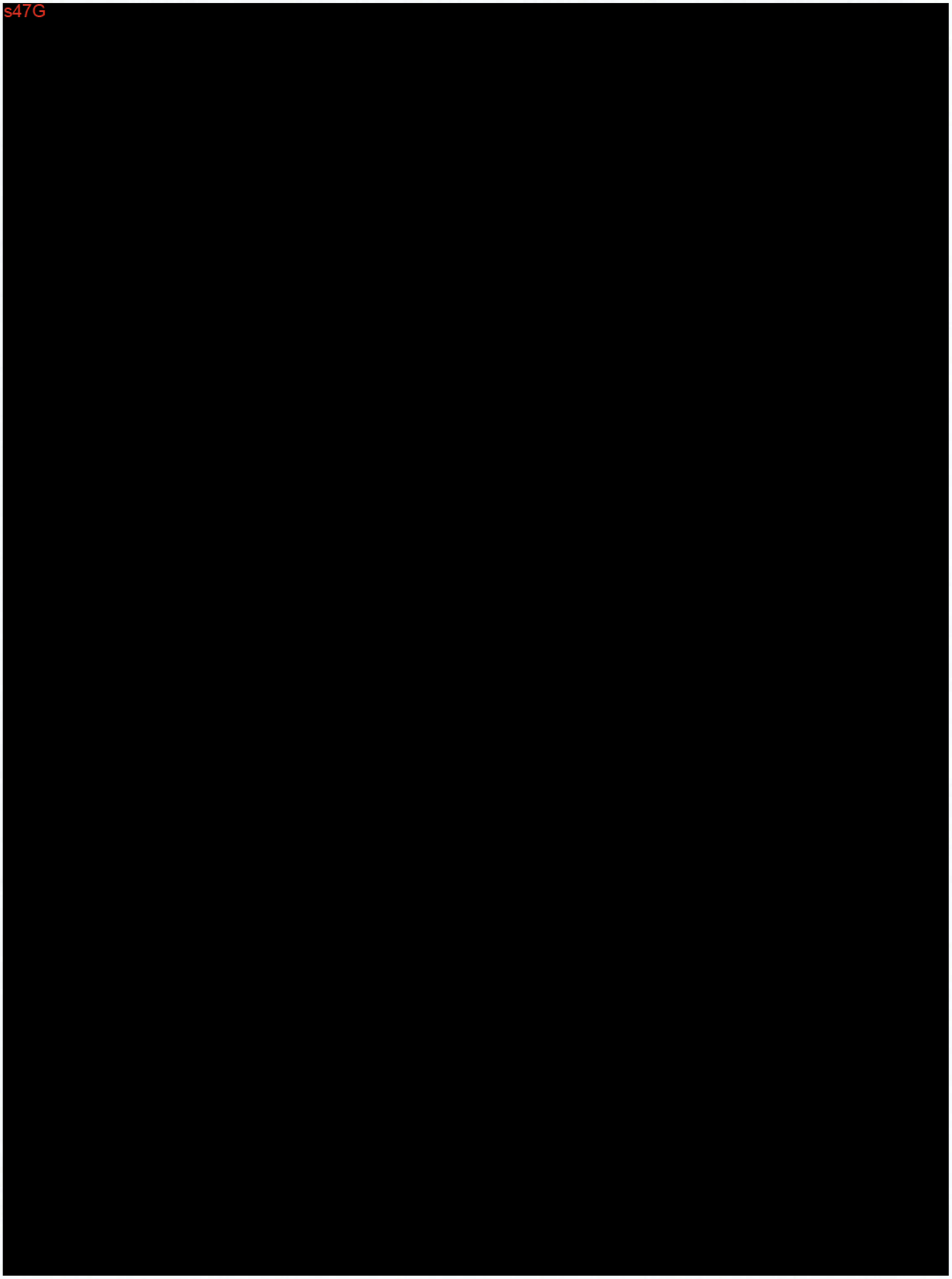


s47G

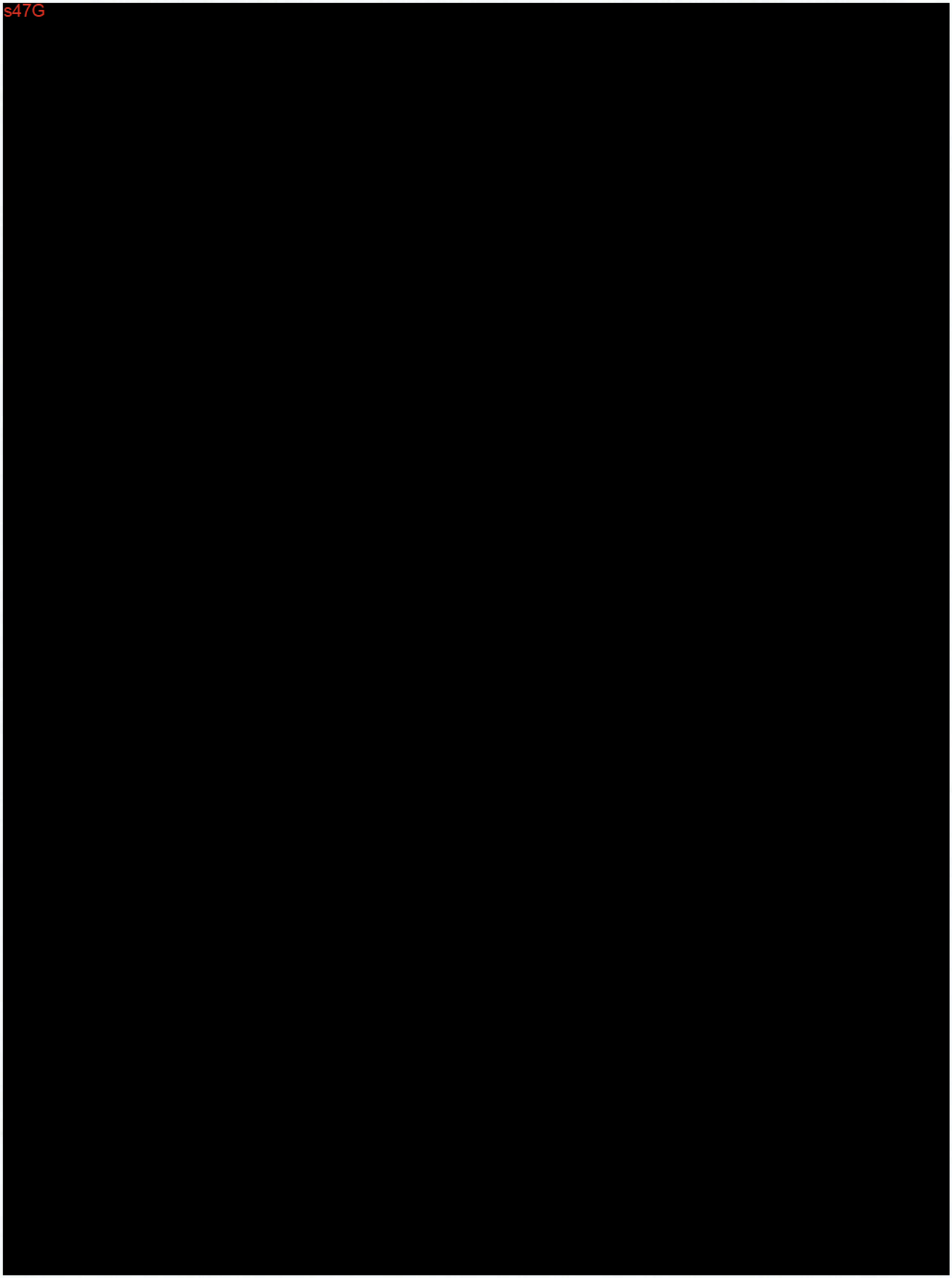


s47G

[redacted]


s47G

s47G



s47G

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Document 6

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Document 6

From: Complementary Medicines
To: s22 ; CMES
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]
Date: Monday, 12 February 2024 1:41:10 PM
Attachments: Determination of 2-ethoxyethanol.pdf
Diethyl sulpahte content.pdf
Ethoxy ethanol contect.pdf
Photostability of C1701.pdf
Residual solvents.pdf
Worksheet in E Stability.xlsx

Hi CMES,

For your review please

Thank you, s22

From: s47G
Sent: Monday, February 12, 2024 10:29 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Part 2

---

s47G

message.
You are not permitted to copy, disclose or use the content in any way. Thank you.

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Friday, September 15, 2023 12:19 PM
To: s 4
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Dear s47G

s47G

s47G

[redacted]

s47G

[redacted]

s47G [redacted]

Please do not hesitate to contact us if you have any further questions.

Kind regards,

s22 [redacted]

Complementary Medicines
Complementary and OTC Medicines Branch
Phone: s22 [redacted]
Email: complementary.medicines@health.gov.au
Therapeutic Goods Administration
Department of Health and Aged care
PO Box 100
Woden ACT 2606
www.tga.gov.au

This information is given to you without prejudice and is not binding on the TGA. It is the responsibility of the sponsor to ensure that all of the legislative requirements are met.

[1] https://www.ncbi.nlm.nih.gov/books/NBK424638/

[2] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out_199.pdf

[3] EU. Prohibited Substances: Annex II, Regulation 1223/2009/EC on Cosmetic Products, as amended by Regulation (EU) 2021/1902, OJ L 387 of 3 November 2021

[4] Registration dossier of European Chemicals Agency; 3-methoxypropylamine (Registration Dossier - ECHA (europa.eu))

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Document 7

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From:	Complementary Medicines
To:	s22 ; CMES
Subject:	FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]
Date:	Monday, 12 February 2024 1:42:31 PM
Attachments:	BASF answer AUS Safety MCE 2024 fin.docx

Hi CMES,

For your review please

Thank you, s22

From: s47G
Sent: Monday, February 12, 2024 10:29 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Part 3 Toxicology

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s47G

From: Complementary Medicines <complementary.medicines@health.gov.au>

Sent: Friday, September 15, 2023 12:19 PM
To: s47G
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Dear s47G

s47G

s47G

[redacted]

s47G

[redacted]

s47G

Document 8

Please do not hesitate to contact us if you have any further questions.

Kind regards,

s22

Complementary Medicines
Complementary and OTC Medicines Branch
Phone: s22
Email: complementary.medicines@health.gov.au
Therapeutic Goods Administration
Department of Health and Aged care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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"Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."

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[1] https://www.ncbi.nlm.nih.gov/books/NBK424638/

[2] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out_199.pdf

[3] EU. Prohibited Substances: Annex II, Regulation 1223/2009/EC on Cosmetic Products, as amended by

Regulation (EU) 2021/1902, OJ L 387 of 3 November 2021

[4] Registration dossier of European Chemicals Agency; 3-methoxypropylamine (Registration Dossier - ECHA (europa.eu))

s47G

Document 8

s47G

Document 8

s47G

Document 8

From: s47G
To: Complementary Medicines
Cc: s22
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]
Date: Monday, 15 April 2024 10:11:37 AM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png

Dear Officer

I am seeking an update on the TGA review for this substance.

We need to know urgently if there any gaps in the information and data provided so far which still remain - Please advise.

Also can you please provide an estimate of when this could be completed.

Regards

s47G

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s47G

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Thursday, February 29, 2024 3:22 PM
To: s47G
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Dear s47G

I can confirm that we have received all three emails along with the associated attachments.

TGA is currently reviewing the information provided and we endeavour to get back to you in the near future. Unfortunately I'm unable to provide an expected completion date at this stage.

Regards,

s22

Complementary Medicines
Complementary and OTC Medicines Branch
Phone: s22
Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

For information regarding compliance activities for listed medicines, please subscribe to the TGA Newsletters at https://www.tga.gov.au/subscribe-updates

Stay in touch by following us on

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From: s47G
Sent: Thursday, February 29, 2024 10:58 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Dear Officer

The response to TGA questions was sent on 12 February over 3 emails.

Could you please confirm if all three emails were received. What is the expected timeline for completion of the review?

Regards

s47G

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s47G

From: s 4
Sent: Monday, February 12, 2024 10:28 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Part 1

Dear Officer

Please find attached the response to the question below. Since the file sizes are large the information will be sent over several emails. The attachments are imbedded in the main documents (Answer to TGA AUS MCE 2024 QM Fin_2). But I have also attached them separately.

Please let me know if any further information is required.

Regards

s47

s47G [redacted]

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Friday, September 15, 2023 12:19 PM
To: s47G [redacted]
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE [SEC=OFFICIAL]

Dear s47G [redacted]

s47G [redacted]

s47G

[redacted]

s47G

[redacted]

s47G

[redacted]

Please do not hesitate to contact us if you have any further questions.

Kind regards,

s22 [redacted]

Complementary Medicines
Complementary and OTC Medicines Branch
Phone: s22 [redacted]
Email: complementary.medicines@health.gov.au
Therapeutic Goods Administration
Department of Health and Aged care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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[1] https://www.ncbi.nlm.nih.gov/books/NBK424638/

[2] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out_199.pdf

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[4] Registration dossier of European Chemicals Agency; 3-methoxypropylamine (Registration Dossier - ECHA (europa.eu))

From: Complementary Medicines
To: s47G
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Tuesday, 23 April 2024 1:22:52 PM
Attachments: image002.jpg

Dear s47G

I refer to your application (OM-2022-00102-1) under regulation 16GA of the *Therapeutic Goods Regulations 1990* to evaluate the suitability of the ingredient *methoxypropylaminocyclohexenylidene ethoxyethylcyanoacetate* (MCE) for use as an active ingredient in listed sunscreens (i.e. for topical use). The TGA is still evaluating the new information provided by you on 12 February 2024. To assist the TGA to progress with this evaluation, please provide the following information:

1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.

2. In your response dated 12 February 2024, you provided the following information in a language wither than English:
    a. analytical method used for analysing Diethyl sulfate (Labormethode LM/05554/01);
    b. analytical method used for analysing Ethoxyethanol (Labormethode LM/05097/02);
    c. analytical method used for analysing Residual solvents (Labormethode LM/05555/01); and
    d. batch analysis reports for Batches 22S01965 and 22S01838 (Analysenbericht 22S01965 and 22S01838).

    As per the requirements for all dossiers, all information provided should be in English and readable. Hence, **please provide** English translation of the above-mentioned information or **provide** English versions of these documents. Please note that, it is the applicant's responsibility to ensure the accuracy of any provided translations.

3. As the proposed substance is not subject to a default standard, a compositional guideline (CG) that summarise descriptions, tests and acceptance criteria that define the characteristics and specify the composition of the proposed substance is required. As such, **please provide** a CG using the appropriate CG template according to the substance type. You may wish to refer to recently published CG for Theanine as an example. Please note that, if the proposed substance is recommended for inclusion in the Permissible (Ingredients) Determination, the proposed CG will be published on the TGA website.

4. In the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for 2-ethoxyethanol was reported to be *'<=50ppm'* and the testing results were reported to be *'< 20ppm'*. Based on '*[t]he detection limit for 2-ethoxyethanol is 20 ppm*', as reported in your response, the following specification is recommended for 2-ethoxyethanol:
    a. Not detectable (limit of detection: 20 ppm).

    Please confirm if you accept the above specification.

5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).

6. In your response, BASF requested 'more guidance on the *in silico* tools'. Please find the TGA's comment on *in silico* analyses below:

a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

It should be noted that supply of additional information does not imply finalisation of the evaluation phase. All additional data will be reviewed and may generate further questions. Should you wish to provide more information to address the deficiencies, additional fees may be required depending on page count of all the information associated with the application.

Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care

PO Box 100

Woden ACT 2606

www.tga.gov.au

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From: s47G
To: Complementary Medicines
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Wednesday, 28 August 2024 8:59:28 AM
Attachments: image001.jpg
Analytical report 22S01838(en) (1).pdf
Analytical report batch 22S01965(en).pdf
composition-MCE-AUS.pdf
ICH M7 Report Nexus Impurity A_LCMS 8,7.pdf
ICH M7 Report Nexus Impurity B_LCMS 21,8.pdf
ICH M7 Report Nexus Impurity C_LCMS 22,6.pdf
ICH M7 Report Nexus Impurity D_LCMS 26,1.pdf
ICH M7 Report Nexus Impurity E_LCMS 27,5.pdf
Information received by Julie on 28th August.docx
LM0509702(en) (1).pdf
LM0555401(en).pdf
LM0555501(en).pdf
Uvinul_LR_LM_05555_06_en fin.pdf

Dear Officer

In response to the question below. Please find attached the requested information.

Regards

s47

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Tuesday, 23 April 2024 1:23 PM
To: s47G
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G

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1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.
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    b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

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Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch
Phone: s22 [redacted]
Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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From: s22
To: TGA Toxicology
Cc: s22
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Thursday, 26 September 2024 2:00:51 PM

Hi s22

How are you?

We have received a response from the sponsor in regard to MCE. Please see the full response at D24-3722957.

I wonder if you can reconsider the safety data provided and advise if they address the outstanding safety related matters.

Thank you and regards,

s22

From: s22
Sent: Monday, September 2, 2024 7:45 AM
To: s22 @Health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Thanks, s22 appreciated.

Regards,

s22

From: s22 @Health.gov.au>
Sent: Friday, August 30, 2024 10:37 AM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Good morning s22

We received response back from the applicant for MCE. Thanks.

Regards,
s22

From: s47G
Sent: Wednesday, August 28, 2024 8:56 AM

To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer
In response to the question below. Please find attached the requested information.
Regards
s47

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Tuesday, 23 April 2024 1:23 PM
To: s47G
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Dear s47G

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1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.
2. In your response dated 12 February 2024, you provided the following information in a language wither than English:
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    b. analytical method used for analysing Ethoxyethanol (Labormethode LM/05097/02);
    c. analytical method used for analysing Residual solvents (Labormethode LM/05555/01); and
    d. batch analysis reports for Batches 22S01965 and 22S01838 (Analysenbericht 22S01965 and 22S01838).

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4. In the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for 2-ethoxyethanol was reported to be *'<=50ppm'* and the testing results were reported to be *'< 20ppm'*. Based on '*[t]he detection limit for 2-ethoxyethanol is 20 ppm*', as reported in your response, the following specification is recommended for 2-ethoxyethanol:

    a. Not detectable (limit of detection: 20 ppm).

    Please confirm if you accept the above specification.

5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).

6. In your response, BASF requested 'more guidance on the *in silico* tools'. Please find the TGA's comment on *in silico* analyses below:

    a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

    b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

It should be noted that supply of additional information does not imply finalisation of the evaluation phase. All additional data will be reviewed and may generate further questions. Should you wish to provide more information to address the deficiencies, additional fees may be required depending on page count of all the information associated with the application.

Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care

PO Box 100

Woden ACT 2606

www.tga.gov.au

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From: s22
To: s47G Complementary Medicines
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Monday, 30 September 2024 2:47:20 PM
Attachments: image002.png

Dear s47G

Thank you for providing additional information in support of your application.

Can you please also confirm that the content of each of the impurities for which in silico analysis was performed (page 10 of the SCCS OPINION ON Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)) will not be more than 0.15% (qualification threshold).

Thank you again and regards,

s22
Senior Regulatory Scientist - Quality | Complementary Medicines Evaluation Section
Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 | E: complementary.medicines@health.gov.au
PO Box 100, Woden ACT 2606, Australia
www.tga.gov.au

From: s47G
Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer
In response to the question below. Please find attached the requested information.
Regards
s47

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Tuesday, 23 April 2024 1:23 PM
To: s47G
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Dear John,

I refer to your application (OM-2022-00102-1) under regulation 16GA of the *Therapeutic Goods Regulations 1990* to evaluate the suitability of the ingredient *methoxypropylaminocyclohexenylidene ethoxyethylcyanoacetate* (MCE) for use as an active

ingredient in listed sunscreens (i.e. for topical use). The TGA is still evaluating the new information provided by you on 12 February 2024. To assist the TGA to progress with this evaluation, please provide the following information:

1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.
2. In your response dated 12 February 2024, you provided the following information in a language wither than English:
    a. analytical method used for analysing Diethyl sulfate (Labormethode LM/05554/01);
    b. analytical method used for analysing Ethoxyethanol (Labormethode LM/05097/02);
    c. analytical method used for analysing Residual solvents (Labormethode LM/05555/01); and
    d. batch analysis reports for Batches 22S01965 and 22S01838 (Analysenbericht 22S01965 and 22S01838).

    As per the requirements for all dossiers, all information provided should be in English and readable. Hence, **please provide** English translation of the above-mentioned information or **provide** English versions of these documents. Please note that, it is the applicant's responsibility to ensure the accuracy of any provided translations.
3. As the proposed substance is not subject to a default standard, a compositional guideline (CG) that summarise descriptions, tests and acceptance criteria that define the characteristics and specify the composition of the proposed substance is required. As such, **please provide** a CG using the appropriate CG template according to the substance type. You may wish to refer to recently published CG for Theanine as an example. Please note that, if the proposed substance is recommended for inclusion in the Permissible (Ingredients) Determination, the proposed CG will be published on the TGA website.
4. In the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for 2-ethoxyethanol was reported to be *'<=50ppm'* and the testing results were reported to be *'< 20ppm'*. Based on '*[t]he detection limit for 2-ethoxyethanol is 20 ppm*', as reported in your response, the following specification is recommended for 2-ethoxyethanol:
    a. Not detectable (limit of detection: 20 ppm).

    Please confirm if you accept the above specification.
5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).
6. In your response, BASF requested 'more guidance on the *in silico* tools'. Please find the TGA's comment on *in silico* analyses below:
    a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either

spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

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Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

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Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care

PO Box 100

Woden ACT 2606

www.tga.gov.au

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From: s22
To: s22
Cc: TGA Toxicology; s22
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Wednesday, 9 October 2024 9:58:51 AM
Attachments: image001.png
image002.jpg

Hi s22
I'm well, thanks. Hope you're well too.
I have updated the report with the Sponsor's response.
There are no further questions for the Sponsor and there are no objections to the substance's registration from a nonclinical perspective.
Kind regards
s22

From: s22 @health.gov.au>
Sent: Wednesday, October 9, 2024 9:13 AM
To: s22 @health.gov.au>
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Morning s22

How are you?

Please see BASF response as below

Thanks and regards,

s22

From: s47G
Sent: Wednesday, October 9, 2024 9:09 AM
To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have stated:

"*We can confirm, that each of these side compounds will remain below 0.15 % in the product.*"

Regards

s47

---

s47G

From: s22 @health.gov.au>
Sent: Monday, 30 September 2024 2:47 PM
To: s47G Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G

Thank you for providing additional information in support of your application.

Can you please also confirm that the content of each of the impurities for which in silico analysis was performed (page 10 of the SCCS OPINION ON Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)) will not be more than 0.15% (qualification threshold).

Thank you again and regards,

s22
Senior Regulatory Scientist - Quality | Complementary Medicines Evaluation Section
Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 | E: complementary.medicines@health.gov.au
PO Box 100, Woden ACT 2606, Australia
www.tga.gov.au

From: s47G

Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer
In response to the question below. Please find attached the requested information.
Regards
s47

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Tuesday, 23 April 2024 1:23 PM
To: s47
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Dear John,

I refer to your application (OM-2022-00102-1) under regulation 16GA of the *Therapeutic Goods Regulations 1990* to evaluate the suitability of the ingredient *methoxypropylaminocyclohexenylidene ethoxyethylcyanoacetate* (MCE) for use as an active ingredient in listed sunscreens (i.e. for topical use). The TGA is still evaluating the new information provided by you on 12 February 2024. To assist the TGA to progress with this evaluation, please provide the following information:

1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.
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    b. analytical method used for analysing Ethoxyethanol (Labormethode LM/05097/02);
    c. analytical method used for analysing Residual solvents (Labormethode LM/05555/01); and
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(Ingredients) Determination, the proposed CG will be published on the TGA website.

4. In the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for 2-ethoxyethanol was reported to be *'<=50ppm'* and the testing results were reported to be *'< 20ppm'*. Based on '*[t]he detection limit for 2-ethoxyethanol is 20 ppm*', as reported in your response, the following specification is recommended for 2-ethoxyethanol:

    a. Not detectable (limit of detection: 20 ppm).

    Please confirm if you accept the above specification.

5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).

6. In your response, BASF requested 'more guidance on the *in silico* tools'. Please find the TGA's comment on *in silico* analyses below:

    a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

    b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

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Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care

PO Box 100

Woden ACT 2606

www.tga.gov.au

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From: s22
To: s47G Complementary Medicines
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Monday, 14 October 2024 10:43:27 AM
Attachments: image001.png

Dear s47G

Thank you for your response below.

We also note that you provided a compositional guideline (CG) for the substance in the response dated 28/04/2024. However, the provided CG is not in the TGA's CG template for chemical entities.

As such, **please provide** the CG for the substance in the TGA template.

Thank you again and regards,

s22
Senior Regulatory Scientist - Quality | Complementary Medicines Evaluation Section
Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
PO Box 100, Canberra ACT 2601, Australia

From: s47G
Sent: Wednesday, October 9, 2024 9:09 AM
To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have stated:

"*We can confirm, that each of these side compounds will remain below 0.15 % in the product.*"

Regards

s47
s47G

s47G [redacted]

From: s22 [redacted] @health.gov.au>
Sent: Monday, 30 September 2024 2:47 PM
To: s47G [redacted] Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G [redacted]

Thank you for providing additional information in support of your application.

Can you please also confirm that the content of each of the impurities for which in silico analysis was performed (page 10 of the SCCS OPINION ON Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)) will not be more than 0.15% (qualification threshold).

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Senior Regulatory Scientist - Quality | Complementary Medicines Evaluation Section
Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 [redacted] | E: complementary.medicines@health.gov.au
PO Box 100, Woden ACT 2606, Australia
www.tga.gov.au

From: s47G [redacted]
Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer

In response to the question below. Please find attached the requested information.

Regards

s47

From: Complementary Medicines <complementary.medicines@health.gov.au>

Sent: Tuesday, 23 April 2024 1:23 PM

To: s47G [redacted]

Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear John,

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    a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

    b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

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s22

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Complementary and OTC Medicines Branch

Phone: s22

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delete all copies of this transmission.

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From: s47G
To: s22 ; Complementary Medicines
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Tuesday, 12 November 2024 11:24:24 AM
Attachments: image001.png
image002.jpg
compositional-guideline-Methoxypropylamino Cyclohexenylidene.DOCX

Dear Complementary Medicines

Please find attached the compositional guideline using the template.

Regards

s47

s47G

From: s 4
Sent: Wednesday, 9 October 2024 9:09 AM
To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have stated:

"*We can confirm, that each of these side compounds will remain below 0.15 % in the product.*"

Regards

s47

s47G

From: s22 @health.gov.au>
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To: s47G Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

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Medicines Regulation Division | Health Products Regulation Group
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From: s47G [redacted]
Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer
In response to the question below. Please find attached the requested information.
Regards
s47 [redacted]

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Tuesday, 23 April 2024 1:23 PM
To: s47G [redacted]
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Dear John,

I refer to your application (OM-2022-00102-1) under regulation 16GA of the *Therapeutic Goods Regulations 1990* to evaluate the suitability of the ingredient *methoxypropylaminocyclohexenylidene ethoxyethylcyanoacetate* (MCE) for use as an active ingredient in listed sunscreens (i.e. for topical use). The TGA is still evaluating the new information provided by you on 12 February 2024. To assist the TGA to progress with this evaluation, please provide the following information:

1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.
2. In your response dated 12 February 2024, you provided the following information in a language wither than English:
    a. analytical method used for analysing Diethyl sulfate (Labormethode LM/05554/01);
    b. analytical method used for analysing Ethoxyethanol (Labormethode LM/05097/02);
    c. analytical method used for analysing Residual solvents (Labormethode LM/05555/01); and
    d. batch analysis reports for Batches 22S01965 and 22S01838 (Analysenbericht 22S01965 and 22S01838).

    As per the requirements for all dossiers, all information provided should be in English and readable. Hence, **please provide** English translation of the above-mentioned information or **provide** English versions of these documents. Please note that, it is the applicant's responsibility to ensure the accuracy of any provided translations.
3. As the proposed substance is not subject to a default standard, a compositional guideline (CG) that summarise descriptions, tests and acceptance criteria that define the characteristics and specify the composition of the proposed substance is required. As such, **please provide** a CG using the appropriate CG template according to the substance type. You may wish to refer to recently published CG for Theanine as an example. Please

note that, if the proposed substance is recommended for inclusion in the Permissible (Ingredients) Determination, the proposed CG will be published on the TGA website.

4. In the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for 2-ethoxyethanol was reported to be *'<=50ppm'* and the testing results were reported to be *'< 20ppm'*. Based on '*[t]he detection limit for 2-ethoxyethanol is 20 ppm*', as reported in your response, the following specification is recommended for 2-ethoxyethanol:

    a. Not detectable (limit of detection: 20 ppm).

    Please confirm if you accept the above specification.

5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).

6. In your response, BASF requested 'more guidance on the *in silico* tools'. Please find the TGA's comment on *in silico* analyses below:

    a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

    b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

It should be noted that supply of additional information does not imply finalisation of the evaluation phase. All additional data will be reviewed and may generate further questions. Should you wish to provide more information to address the deficiencies, additional fees may be required depending on page count of all the information associated with the application.

Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care

PO Box 100

Woden ACT 2606
www.tga.gov.au

This information is given to you without prejudice and is not binding on the TGA. It is the responsibility of the sponsor to ensure that all of the legislative requirements are met.

s47G

Document 16

s47G

Document 16

Version	Description of change (for official use only)	Effective date

From: s47G
To: s22 ; Complementary Medicines
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Tuesday, 12 November 2024 11:24:24 AM
Attachments: image001.png
image002.jpg
compositional-guideline-Methoxypropylamino Cyclohexenylidene.DOCX

Dear Complementary Medicines

Please find attached the compositional guideline using the template.

Regards

s47

s47G

From: s47G
Sent: Wednesday, 9 October 2024 9:09 AM
To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have stated:

"*We can confirm, that each of these side compounds will remain below 0.15 % in the product.*"

Regards

s47

s47G

From: s22 @health.gov.au>
Sent: Monday, 30 September 2024 2:47 PM
To: s47G Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G

Thank you for providing additional information in support of your application.

Can you please also confirm that the content of each of the impurities for which in silico analysis was performed (page 10 of the SCCS OPINION ON Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)) will not be more than 0.15% (qualification threshold).

Thank you again and regards,

s22
Senior Regulatory Scientist - Quality | Complementary Medicines Evaluation Section
Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 | E: complementary.medicines@health.gov.au
PO Box 100, Woden ACT 2606, Australia
www.tga.gov.au

From: s47G [redacted]
Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

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Kind regards,

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Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care

PO Box 100

Woden ACT 2606
www.tga.gov.au

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s47G

Document 17

s47G

Document 17

Version	Description of change (for official use only)	Effective date

From: s47G
To: s22
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Thursday, 28 November 2024 9:51:20 AM
Attachments: image003.png
image004.png
image005.png
image006.png
image007.png
image008.png
image009.jpg
image001.png
Draft - Compositional-guideline-Methoxypropylamino Cyclohexenylidene - Draft (MPT).docx

---

Dear s22

BASF have made some amendments (see attached). BASF regard certain information as confidential business information and do not want it to appear in the CG. Also, some of the measurements are not considered to be batch related such as particle size is not determined for each batch and is also not a quality information. As well as water solubility is also not a batch related information.

Regards

s47

s47G

From: s22 @health.gov.au>
Sent: Wednesday, 20 November 2024 12:14 PM

To: s47G [redacted]
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G [redacted]

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I am attaching a suggested CG for the proposed substance that is in line with the information that was submitted and evaluated by the TGA.

Please carefully review the suggested CG attached and address the comments included. Also, please let us know if you have any comments/suggestions.

Thank you again and regards,

s22 [redacted]
Senior Scientist - Quality | Complementary Medicines Evaluation Section

Complementary and OTC Medicines Branch
Australian Government, Department of Health and Aged Care
Therapeutic Goods Administration

Phone: s22 [redacted]
Email: s22 [redacted] @health.gov.au

PO Box 100, Woden ACT 2606
www.tga.gov.au

From: s47G [redacted]
Sent: Tuesday, 12 November 2024 11:22 AM
To: s22 [redacted] @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

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s47G

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BASF have stated:

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Sent: Monday, 30 September 2024 2:47 PM
To: s47G [redacted] >; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

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Senior Regulatory Scientist - Quality | Complementary Medicines Evaluation Section

Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 [redacted] | E: complementary.medicines@health.gov.au
PO Box 100, Woden ACT 2606, Australia
www.tga.gov.au

From: s47G [redacted]
Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
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Complementary and OTC Medicines Branch

Phone: s22

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Therapeutic Goods Administration

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s47G

Document 18

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From: s47G
To: Complementary Medicines
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Friday, 20 December 2024 2:35:12 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
image007.png

From: s47G
Sent: Friday, 20 December 2024 2:34 PM
To: s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

Could you please advise on the status of this application? Are you waiting on any further information or action from our side? Is there an expected completion date?

Regards

s47G

s47G

From: s47G
Sent: Thursday, 28 November 2024 9:49 AM
To: s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

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From: s22 @health.gov.au>
Sent: Wednesday, 20 November 2024 12:14 PM
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Australian Government, Department of Health and Aged Care
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Phone: s22
Email: s22 @health.gov.au

PO Box 100, Woden ACT 2606
www.tga.gov.au

From: s4
Sent: Tuesday, 12 November 2024 11:22 AM
To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
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s47G

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Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 [redacted] | E: complementary.medicines@health.gov.au
PO Box 100, Woden ACT 2606, Australia
www.tga.gov.au

From: s4 [redacted]
Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer
In response to the question below. Please find attached the requested information.
Regards
s47 [redacted]

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Tuesday, 23 April 2024 1:23 PM
To: s47G [redacted]
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear John,

I refer to your application (OM-2022-00102-1) under regulation 16GA of the *Therapeutic Goods Regulations 1990* to evaluate the suitability of the ingredient *methoxypropylaminocyclohexenylidene ethoxyethylcyanoacetate* (MCE) for use as an active ingredient in listed sunscreens (i.e. for topical use). The TGA is still evaluating the new information provided by you on 12 February 2024. To assist the TGA to progress with this evaluation, please provide the following information:

1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.
2. In your response dated 12 February 2024, you provided the following information in a language wither than English:
    a. analytical method used for analysing Diethyl sulfate (Labormethode LM/05554/01);
    b. analytical method used for analysing Ethoxyethanol (Labormethode LM/05097/02);
    c. analytical method used for analysing Residual solvents (Labormethode LM/05555/01); and
    d. batch analysis reports for Batches 22S01965 and 22S01838 (Analysenbericht 22S01965 and 22S01838).

    As per the requirements for all dossiers, all information provided should be in English and readable. Hence, **please provide** English translation of the above-mentioned information or **provide** English versions of these documents. Please note that, it is the applicant's responsibility to ensure the accuracy of any provided translations.
3. As the proposed substance is not subject to a default standard, a compositional guideline (CG) that summarise descriptions, tests and acceptance criteria that define the characteristics and specify the composition of the proposed substance is required. As such, **please provide** a CG using the appropriate CG template according to the substance type. You may wish to refer to recently published CG for Theanine as an example. Please note that, if the proposed substance is recommended for inclusion in the Permissible (Ingredients) Determination, the proposed CG will be published on the TGA website.
4. In the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for 2-ethoxyethanol was reported to be *'<=50ppm'* and the testing results were reported to be *'< 20ppm'*. Based on '*[t]he detection limit for 2-ethoxyethanol is 20 ppm*', as reported in your response, the following specification is recommended for 2-ethoxyethanol:
    a. Not detectable (limit of detection: 20 ppm).

    Please confirm if you accept the above specification.
5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).
6. In your response, BASF requested 'more guidance on the *in silico* tools'. Please find the TGA's comment on *in silico* analyses below:

a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

It should be noted that supply of additional information does not imply finalisation of the evaluation phase. All additional data will be reviewed and may generate further questions. Should you wish to provide more information to address the deficiencies, additional fees may be required depending on page count of all the information associated with the application.

Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care

PO Box 100

Woden ACT 2606

www.tga.gov.au

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From: s22
To: s47G
Cc: CMES
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Tuesday, 14 January 2025 9:54:44 AM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
image007.png
image009.png
Compositional-guideline-Methoxypropylamino Cyclohexenylidene - Draft.DOCX

Dear s47G

Happy new year and thank you for sending the sponsor's comments on the suggested CG. Please find attached a revised copy of the suggested CG after addressing the sponsor's suggestions.

We would like to emphasise that the CG is not a legal requirement, but exists to assist sponsors in determining if an ingredient that is being considered for use in a listed medicine is one that has been evaluated by the TGA and found to be of appropriate quality and safety. It is expected that there will be improvements in testing methods as equipment and technology advances. Sponsors may choose to impose tighter limits, include additional tests, or use different validated analytical methods where there is a sound scientific justification that the ingredient is the same as what has been approved for use in listed medicines.

s47G

Please carefully review the suggested CG attached and address the comments included.

Please let us know if you have any questions.

Thanks and regards,

s22
Senior Scientist - Quality | Complementary Medicines Evaluation Section

Complementary and OTC Medicines Branch

Australian Government, Department of Health and Aged Care
Therapeutic Goods Administration

Phone: s22
Email: s22 @health.gov.au

PO Box 100, Woden ACT 2606
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-

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From: s47G
Sent: Thursday, 28 November 2024 9:49 AM
To: s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have made some amendments (see attached). BASF regard certain information as confidential business information and do not want it to appear in the CG. Also, some of the measurements are not considered to be batch related such as particle size is not determined for each batch and is also not a quality information. As well as water solubility is also not a batch related information.

Regards

s47

s47G

s47G [redacted]

From: s22 [redacted]@health.gov.au>
Sent: Wednesday, 20 November 2024 12:14 PM
To: s47G [redacted]
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G [redacted]

Thank you for sending the draft CG.

I am attaching a suggested CG for the proposed substance that is in line with the information that was submitted and evaluated by the TGA.

Please carefully review the suggested CG attached and address the comments included. Also, please let us know if you have any comments/suggestions.

Thank you again and regards,

s22 [redacted]
Senior Scientist - Quality | Complementary Medicines Evaluation Section

Complementary and OTC Medicines Branch
Australian Government, Department of Health and Aged Care
Therapeutic Goods Administration

Phone: s22 [redacted]
Email: s22 [redacted]@health.gov.au

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-

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From: s47G [redacted]
Sent: Tuesday, 12 November 2024 11:22 AM
To: s22 [redacted]@health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Complementary Medicines

Please find attached the compositional guideline using the template.

Regards

s47 [redacted]

s47G [redacted]

From: s [redacted]4
Sent: Wednesday, 9 October 2024 9:09 AM
To: s22 [redacted]@health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22 [redacted]

BASF have stated:

"*We can confirm, that each of these side compounds will remain below 0.15 % in the product.*"

Regards

s47

s47G

From: s22 @health.gov.au>
Sent: Monday, 30 September 2024 2:47 PM
To: s47G ; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G

Thank you for providing additional information in support of your application.

Can you please also confirm that the content of each of the impurities for which in silico analysis was performed (page 10 of the SCCS OPINION ON Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)) will not be more than 0.15% (qualification threshold).

Thank you again and regards,

s22
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Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 | E: complementary.medicines@health.gov.au

PO Box 100, Woden ACT 2606, Australia
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To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer
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Regards
s47 [redacted]

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Sent: Tuesday, 23 April 2024 1:23 PM
To: s47G [redacted]
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5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).

6. In your response, BASF requested 'more guidance on the *in silico* tools'. Please find the TGA's comment on *in silico* analyses below:

    a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

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Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch

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Email: complementary.medicines@health.gov.au

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s47G

s47G

s47G

s47G

From: s22
To: s22
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Tuesday, 14 January 2025 9:27:15 AM
Attachments: image001.png

Thanks Guys,

s22 - I was wondering if there is no issue from a safety point of view of having the limit represented as <500 ppm. Maybe worth presenting it as that since batches can differ greatly depending on the manufacturing processes.

Considering this is the only aspect of the CG that will need to be resolved for a outcome, I think the risk associated is very low. Besides anything <500 ppm is still true and compliant so I don't have a n issue with keeping it at that.

We may also propose a Market Exclusivity approach with the applicant/sponsor if they are still not comfortable with the CG details.

s22 – Thanks s22 yes let's get in touch with Tox and let them know that this application has been ongoing since 2022 (please confirm the date before talking to tox). So we really need it finalised ASAP. It is also already been through the Tox approval, we just need the additional MoS calc added. If it will help we can add it to their report and get them to do a quick review?

In the meantime, can we send the CG back with <500 ppm and get it through please?

Regards
s22

From: s22 @health.gov.au>
Sent: Tuesday, 14 January 2025 8:37 AM
To: s22 @Health.gov.au>; s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Morning s22 and s22

For 3-methoxypropylamine, the sponsor proposed a <500 ppm limit for 3-methoxypropylamine. However, the submitted batch data for batches 22S01838 and 22S01965 are showing results of 53 ppm and 48 ppm, respectively. As such, a suggested revised limit was proposed to the sponsor to align with the submitted batch data.

Happy to discuss further if required.

Regards,

s22

From: s22 @Health.gov.au>
Sent: Monday, 13 January 2025 6:33 PM
To: s22 @health.gov.au>; s22
s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Hi both,

As per current safety report, wrt 3-methoxypropylamine:

- '***The Sponsor should declare limits for 3-methoxypropylamine (update 10/04/2024: Sponsor's declared limits are <500 ppm; issue resolved).***

I think as long as the limits for 3-methoxypropylamine being declared, there will not be any further safety issue on this impurity.

The report has not been updated since my last convo with the Tox. Will check with them again this week. We might need to take the delegate overview approach we discussed briefly last week.

Regards,
s22

From: s22 @health.gov.au>
Sent: Monday, 13 January 2025 4:43 PM
To: s22 @health.gov.au>; s22 @Health.gov.au>
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Hi Both

Can we discuss this CG something this week?

s47G

I note that the SCCS report gives a <500 ppm limit based on the Tox batches tested. Is it an issue from safety perspective to have it mentioned at s47G instead of ≤500 ppm ?

s22 – Has tox progressed on the Safety report?

Have we discussed the prospect of Market Exclusivity with the applicant?

Regards
s22

From: s22 @health.gov.au>
Sent: Friday, 20 December 2024 2:52 PM
To: s22 @health.gov.au>

Cc: s22 @health.gov.au>
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Hi s22

As discussed, this was sitting with me for a while. See draft response by s22 and also comment for the CG attached.

Over to you as delegate.

Thanks,
s22

From: s22 @Health.gov.au>
Sent: Friday, 29 November 2024 3:23 PM
To: s22 @health.gov.au>; s22 <s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Hi s22

As discussed, I added the facts that the sponsor has already agreed limits for 2-Ethoxyethanol and 3-methoxypropylamine. This will make our argument on this point stronger. Cheers.

Regards,
s22

From: s22 @health.gov.au>
Sent: Friday, 29 November 2024 3:01 PM
To: s22 @health.gov.au>
Cc: s22 @Health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Hi Again s22

I have spoken with s22 and we have agreed that Methanesulfonic Acid, Ethyl propionate, 2-Ethoxyethyl cyanoacetate, and Propionic acid can be omitted from the substance CG. Revised suggested CG is at D24-5045278.

Amended draft is as below.

Thanks and regards,

s22

s47G

Document 21

From: s22

Sent: Friday, 29 November 2024 12:24 PM

To: s22 @health.gov.au>

Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Hi s22

I have drafted the below response to s47G if you would like to clear it before I send it away.

The revised suggested CG is at D24-5045278.

Thanks and regards,

s22

---

s47G

From: s47G
Sent: Tuesday, 12 November 2024 11:22 AM
To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>

Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Complementary Medicines

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s47G

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BASF have stated:

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s47

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s47G

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Dear Officer

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s47

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Sent: Tuesday, 23 April 2024 1:23 PM

To: s4

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a. Not detectable (limit of detection: 20 ppm).

Please confirm if you accept the above specification.

5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).

6. In your response, BASF requested 'more guidance on the *in silico* tools'. Please find the TGA's comment on *in silico* analyses below:

   a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

   b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

It should be noted that supply of additional information does not imply finalisation of the evaluation phase. All additional data will be reviewed and may generate further questions. Should you wish to provide more information to address the deficiencies, additional fees may be required depending on page count of all the information associated with the application.

Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care

PO Box 100

Woden ACT 2606

www.tga.gov.au

responsibility of the sponsor to ensure that all of the legislative requirements are met.

"Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."

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From: s47G
To: s22
Cc: CMES
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Friday, 31 January 2025 11:38:08 AM
Attachments: image011.png
image012.png
image013.png
image014.png
image015.png
image016.png
image017.png
image018.jpg
image002.png
Compositional-guideline-Methoxypropylamino Cyclohexenylidene - Draft (003).docx

---

Dear s22

Please see attached suggested amendments to CG. BASF have replied:

s47G

Regards

s47G

s47G

From: s22 @health.gov.au>
Sent: Tuesday, 14 January 2025 9:55 AM
To: s47G
Cc: CMES <CMES@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G

Happy new year and thank you for sending the sponsor's comments on the suggested CG. Please find attached a revised copy of the suggested CG after addressing the sponsor's suggestions.

We would like to emphasise that the CG is not a legal requirement, but exists to assist sponsors in determining if an ingredient that is being considered for use in a listed medicine is one that has been evaluated by the TGA and found to be of appropriate quality and safety. It is expected that there will be improvements in testing methods as equipment and technology advances. Sponsors may choose to impose tighter limits, include additional tests, or use different validated analytical methods where there is a sound scientific justification that the ingredient is the same as what has been approved for use in listed medicines.

Please carefully review the suggested CG attached and address the comments included.

Please let us know if you have any questions.

Thanks and regards,

s22
Senior Scientist - Quality | Complementary Medicines Evaluation Section

Complementary and OTC Medicines Branch
Australian Government, Department of Health and Aged Care

Therapeutic Goods Administration

Phone: s22
Email: s22 @health.gov.au

PO Box 100, Woden ACT 2606
www.tga.gov.au

-

This information is given to you without prejudice and is not binding on the TGA. It is the responsibility of the sponsor to ensure that all of the legislative requirements are met.

From: s47G
Sent: Thursday, 28 November 2024 9:49 AM
To: s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have made some amendments (see attached). BASF regard certain information as confidential business information and do not want it to appear in the CG. Also, some of the measurements are not considered to be batch related such as particle size is not determined for each batch and is also not a quality information. As well as water solubility is also not a batch related information.

Regards

s47

---

s47G

s47G [redacted]

From: s22 [redacted] @health.gov.au>
Sent: Wednesday, 20 November 2024 12:14 PM
To: s47G [redacted]
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G [redacted]

Thank you for sending the draft CG.

I am attaching a suggested CG for the proposed substance that is in line with the information that was submitted and evaluated by the TGA.

Please carefully review the suggested CG attached and address the comments included. Also, please let us know if you have any comments/suggestions.

Thank you again and regards,

s22 [redacted]
Senior Scientist - Quality | Complementary Medicines Evaluation Section

Complementary and OTC Medicines Branch
Australian Government, Department of Health and Aged Care
Therapeutic Goods Administration

Phone: s22 [redacted]
Email: s22 [redacted] @health.gov.au

PO Box 100, Woden ACT 2606
www.tga.gov.au

From: s47G

Sent: Tuesday, 12 November 2024 11:22 AM

To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>

Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Complementary Medicines

Please find attached the compositional guideline using the template.

Regards

s47

s47G

From: s47G

Sent: Wednesday, 9 October 2024 9:09 AM

To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>

Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have stated:

"*We can confirm, that each of these side compounds will remain below 0.15 % in the product.*"

Regards

s47

s47G

From: s22 @health.gov.au>
Sent: Monday, 30 September 2024 2:47 PM
To: s47G Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G

Thank you for providing additional information in support of your application.

Can you please also confirm that the content of each of the impurities for which in silico analysis was performed (page 10 of the SCCS OPINION ON Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87)) will not be more than 0.15% (qualification threshold).

Thank you again and regards,

s22
Senior Regulatory Scientist - Quality | Complementary Medicines Evaluation Section
Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 | E: complementary.medicines@health.gov.au
PO Box 100, Woden ACT 2606, Australia

www.tga.gov.au

From: s47G [redacted]
Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer
In response to the question below. Please find attached the requested information.
Regards
s47 [redacted]

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Tuesday, 23 April 2024 1:23 PM
To: s47G [redacted]
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Dear John,

I refer to your application (OM-2022-00102-1) under regulation 16GA of the *Therapeutic Goods Regulations 1990* to evaluate the suitability of the ingredient *methoxypropylaminocyclohexenylidene ethoxyethylcyanoacetate* (MCE) for use as an active ingredient in listed sunscreens (i.e. for topical use). The TGA is still evaluating the new information provided by you on 12 February 2024. To assist the TGA to progress with this evaluation, please provide the following information:

1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.
2. In your response dated 12 February 2024, you provided the following information in a language wither than English:
    a. analytical method used for analysing Diethyl sulfate (Labormethode LM/05554/01);
    b. analytical method used for analysing Ethoxyethanol (Labormethode LM/05097/02);
    c. analytical method used for analysing Residual solvents (Labormethode LM/05555/01); and
    d. batch analysis reports for Batches 22S01965 and 22S01838 (Analysenbericht 22S01965 and 22S01838).

    As per the requirements for all dossiers, all information provided should be in English and readable. Hence, **please provide** English translation of the above-mentioned information or **provide** English versions of these documents. Please note that, it is the applicant's responsibility to ensure the accuracy of any provided translations.
3. As the proposed substance is not subject to a default standard, a compositional guideline (CG) that summarise descriptions, tests and acceptance criteria that define the characteristics and specify the composition of the proposed substance is required. As

such, **please provide** a CG using the appropriate CG template according to the substance type. You may wish to refer to recently published CG for Theanine as an example. Please note that, if the proposed substance is recommended for inclusion in the Permissible (Ingredients) Determination, the proposed CG will be published on the TGA website.

4. In the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for 2-ethoxyethanol was reported to be *'<=50ppm'* and the testing results were reported to be *'< 20ppm'*. Based on '*[t]he detection limit for 2-ethoxyethanol is 20 ppm*', as reported in your response, the following specification is recommended for 2-ethoxyethanol:

    a. Not detectable (limit of detection: 20 ppm).

    Please confirm if you accept the above specification.

5. In your response, you stated '*[t]he detection limit of diethyl sulfate is 200 ppm*.' However, in the batch analysis reports for Batches 22S01965 and 22S01838, it appears that the specification for diethyl sulfate was reported to be *'<=200ppb'* and the testing results were reported to be *'< 200ppb'*. **Please clarify** the discrepancies of the units (ppm/ppb).

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    a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

    b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

It should be noted that supply of additional information does not imply finalisation of the evaluation phase. All additional data will be reviewed and may generate further questions. Should you wish to provide more information to address the deficiencies, additional fees may be required depending on page count of all the information associated with the application.

Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

s22

Complementary Medicines

Complementary and OTC Medicines Branch

Phone: s22

Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration

Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

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s47G

Document 22

s47G

Document 22

s47G

Document 22

s47G

Document 22

From: s22
To: s47G
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Date: Wednesday, 12 February 2025 1:30:48 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
image007.png
image008.png

Dear s47G

Thank you for confirming the below.

Here is the link to the 'Notification of an authorisation to use a protected ingredient' form: https://www.tga.gov.au/sites/default/files/notification-of-an-authorisation-to-use-a-protected-ingredient.pdf

We will send you the updated CG and the proposed recommendation for review in the next couple of weeks.

Regards
s22

From: s47G
Sent: Monday, 10 February 2025 4:09 PM
To: s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

Could you please send a copy of the Market Exclusivity application form. I could not locate it on the TGA website.

BASF have agreed to your proposals as follows:

s47G

s47G

Please let us know if the above are acceptable and if BASF wishes to opt in for Market exclusivity. We will send you the updated CG and the proposed recommendation for review once confirmed" s47G

Regards

s47G

s47G

From: s22 [redacted] @health.gov.au>
Sent: Friday, 7 February 2025 2:14 PM
To: s47G [redacted]
Subject: FW: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G [redacted]

Thank you for forwarding the response from BASF and for your time over the phone this afternoon.

Based on the response we are proposing the following updates, as discussed over the phone:

s47G [redacted]

Please let us know if the above are acceptable and if BASF wishes to opt in for Market exclusivity. We will send you the updated CG and the proposed recommendation for review once confirmed.

Kind Regards

s22

s22
Senior Evaluator – Complementary Medicines Evaluation Section
Complementary and OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 | E s22 @health.gov.au
Location: Level 1, 27 Scherger Drive, Fairbairn ACT
PO Box 100, Woden ACT 2606, Australia

From: s47G
Sent: Friday, 31 January 2025 11:36 AM
To: s22 @health.gov.au>
Cc: CMES <CMES@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

Please see attached suggested amendments to CG. BASF have replied:

s47G

Regards

s47G

---

s47G

s47G [redacted]

From: s22 [redacted] @health.gov.au>
Sent: Tuesday, 14 January 2025 9:55 AM
To: s47G [redacted]
Cc: CMES <CMES@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G [redacted]

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s47G [redacted]

Please carefully review the suggested CG attached and address the comments included.

Please let us know if you have any questions.

Thanks and regards,

s22
Senior Scientist - Quality | Complementary Medicines Evaluation Section

Complementary and OTC Medicines Branch
Australian Government, Department of Health and Aged Care
Therapeutic Goods Administration

Phone: s22
Email: s22 @health.gov.au

PO Box 100, Woden ACT 2606
www.tga.gov.au

From: s47G
Sent: Thursday, 28 November 2024 9:49 AM
To: s22 @health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have made some amendments (see attached). BASF regard certain information as confidential business information and do not want it to appear in the CG. Also, some of the measurements are not considered to be batch related such as particle size is not determined for each batch and is also not a quality information. As well as water solubility is also not a batch related information.

Regards

s47

s47G [redacted]

From: s22 [redacted] @health.gov.au>
Sent: Wednesday, 20 November 2024 12:14 PM
To: s47G [redacted]
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G [redacted]

Thank you for sending the draft CG.

I am attaching a suggested CG for the proposed substance that is in line with the information that was submitted and evaluated by the TGA.

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Thank you again and regards,

s22 [redacted]
Senior Scientist - Quality | Complementary Medicines Evaluation Section

Complementary and OTC Medicines Branch
Australian Government, Department of Health and Aged Care
Therapeutic Goods Administration

Phone: s22 [redacted]
Email: s22 [redacted] @health.gov.au

PO Box 100, Woden ACT 2606

www.tga.gov.au

From: s47G [redacted]
Sent: Tuesday, 12 November 2024 11:22 AM
To: s22 [redacted] @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Complementary Medicines

Please find attached the compositional guideline using the template.

Regards

s47 [redacted]

s47G [redacted]

From: s47G [redacted]

Sent: Wednesday, 9 October 2024 9:09 AM
To: s22 @health.gov.au>; Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s22

BASF have stated:

"*We can confirm, that each of these side compounds will remain below 0.15 % in the product.*"

Regards

s47

s47G

From: s22 @health.gov.au>
Sent: Monday, 30 September 2024 2:47 PM
To: s47G Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear s47G

Thank you for providing additional information in support of your application.

Can you please also confirm that the content of each of the impurities for which in silico analysis was performed (page 10 of the SCCS OPINION ON Methoxypropylamino Cyclohexenylidene

Ethoxyethylcyanoacetate (S87)) will not be more than 0.15% (qualification threshold).

Thank you again and regards,

s22
Senior Regulatory Scientist - Quality | Complementary Medicines Evaluation Section
Medicines Regulation Division | Health Products Regulation Group
Complementary & Over the Counter Medicines Branch
Therapeutic Goods Administration
Department of Health and Aged Care
T: s22 | E: complementary.medicines@health.gov.au
PO Box 100, Woden ACT 2606, Australia
www.tga.gov.au

From: s47G
Sent: Wednesday, August 28, 2024 8:56 AM
To: Complementary Medicines <complementary.medicines@health.gov.au>
Subject: RE: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]

Dear Officer
In response to the question below. Please find attached the requested information.
Regards
s47

From: Complementary Medicines <complementary.medicines@health.gov.au>
Sent: Tuesday, 23 April 2024 1:23 PM
To: s47G
Subject: Outcome of evaluation of new Substance application OM-2022-GL-01043-1 - METHOXYPROPYLAMINO CYCLOHEXENY [SEC=OFFICIAL]
Dear John,

I refer to your application (OM-2022-00102-1) under regulation 16GA of the *Therapeutic Goods Regulations 1990* to evaluate the suitability of the ingredient *methoxypropylaminocyclohexenylidene ethoxyethylcyanoacetate* (MCE) for use as an active ingredient in listed sunscreens (i.e. for topical use). The TGA is still evaluating the new information provided by you on 12 February 2024. To assist the TGA to progress with this evaluation, please provide the following information:

1. In your response dated 12 February 2024, you have provided validation data for the in-house HPLC method used for assay, however no validation data was provided for the in-house analytical methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents. As such, **please provide** full validation data for the in-house methods used for analysing 3-Methoxypropylamine, Diethyl sulfate, Ethoxyethanol, and Residual solvents.
2. In your response dated 12 February 2024, you provided the following information in a language wither than English:
    a. analytical method used for analysing Diethyl sulfate (Labormethode LM/05554/01);

b. analytical method used for analysing Ethoxyethanol (Labormethode LM/05097/02);

c. analytical method used for analysing Residual solvents (Labormethode LM/05555/01); and

d. batch analysis reports for Batches 22S01965 and 22S01838 (Analysenbericht 22S01965 and 22S01838).

As per the requirements for all dossiers, all information provided should be in English and readable. Hence, **please provide** English translation of the above-mentioned information or **provide** English versions of these documents. Please note that, it is the applicant's responsibility to ensure the accuracy of any provided translations.

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   a. Not detectable (limit of detection: 20 ppm).

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   a. A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. It is up to the Sponsor to decide which prediction methodologies to use, but the (Q)SAR models should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) would be sufficient to conclude that the impurity is of no mutagenic concern, and no further testing would be required. If there was an identified structural alert, a bacterial reverse mutation assay (Ames) should be conducted, including either spiking with the impurity (minimum quantity of 250 µg of the impurity per plate) or testing of the neat impurity (at a concentration of at least 250 ug/plate)**. A negative Ames result would generally outweigh a (Q)SAR alert. If an alerting feature is identified but is shared by the API, the impurity may be qualified by negative genotoxicity data with the API. (**Kenyon MO et al. Regul Toxicol Pharmacol 48: 75-86, 2007.)

   b. **Alternatively**, if very low levels of these five impurities are being detected in currently manufactured batches, such as that the level of each individual impurity is below the identification/qualification thresholds as per ICH Q3A (R2)(0.05%), in which case, the *in silico* analysis would not be required.

It should be noted that supply of additional information does not imply finalisation of the evaluation phase. All additional data will be reviewed and may generate further questions.

Should you wish to provide more information to address the deficiencies, additional fees may be required depending on page count of all the information associated with the application.

Please do not hesitate to contact us if you need any further assistance or clarification.

Kind regards,

[redacted]
Complementary Medicines
Complementary and OTC Medicines Branch
Phone: [redacted]
Email: complementary.medicines@health.gov.au

Therapeutic Goods Administration
Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

This information is given to you without prejudice and is not binding on the TGA. It is the responsibility of the sponsor to ensure that all of the legislative requirements are met.

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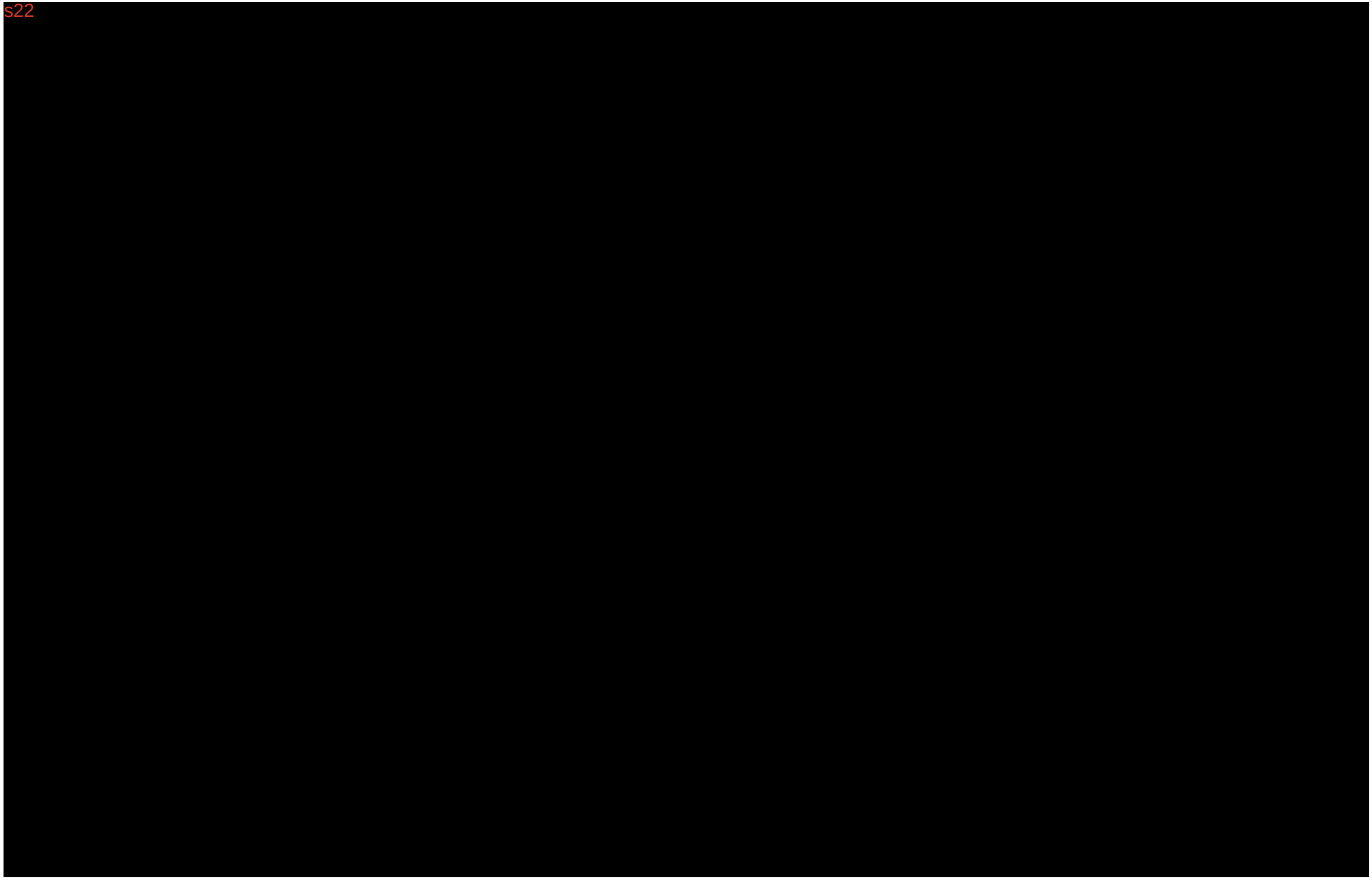
	Ingredient name	Variation Reason	Final Purpose	Final Specific Requirements	Prior Purpose	Prior Specific Requirements
1	s22					
2	METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYET	Addition	A	Until 20 June 2027, Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate must only be used in a medicine where:	-	-

	HYLCYANO ACETATE			(a) BASF Australia Ltd (Client ID 13479) is the sponsor of the medicine (the ***primary sponsor***); or (b) another person is the sponsor of the medicine (the ***secondary sponsor***) and the TGA has been notified that the secondary sponsor has been authorised by the primary sponsor to use the ingredient in the medicine. Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate must: (a) only be used as an active ingredient in sunscreens in topical medicines for dermal application; and (b) not be included in medicines that are intended for use on: (i) the eye; or (ii) broken skin. The total concentration of methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate the medicine must not be more than 3%. Methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate must not be used in combination with nitrosating substances. The concentration of nitrosamine in the medicine must be less than 0.000005% or 50 ppb. When used in primary sunscreen products, the following warning statements (or words to the same effect) must be included on the medicine label:		

				- (AVOID) ' Avoid prolonged exposure in the sun.'; - (SUNPRO) ' Wear protective clothing - hats and eyewear when exposed to the sun.'.		

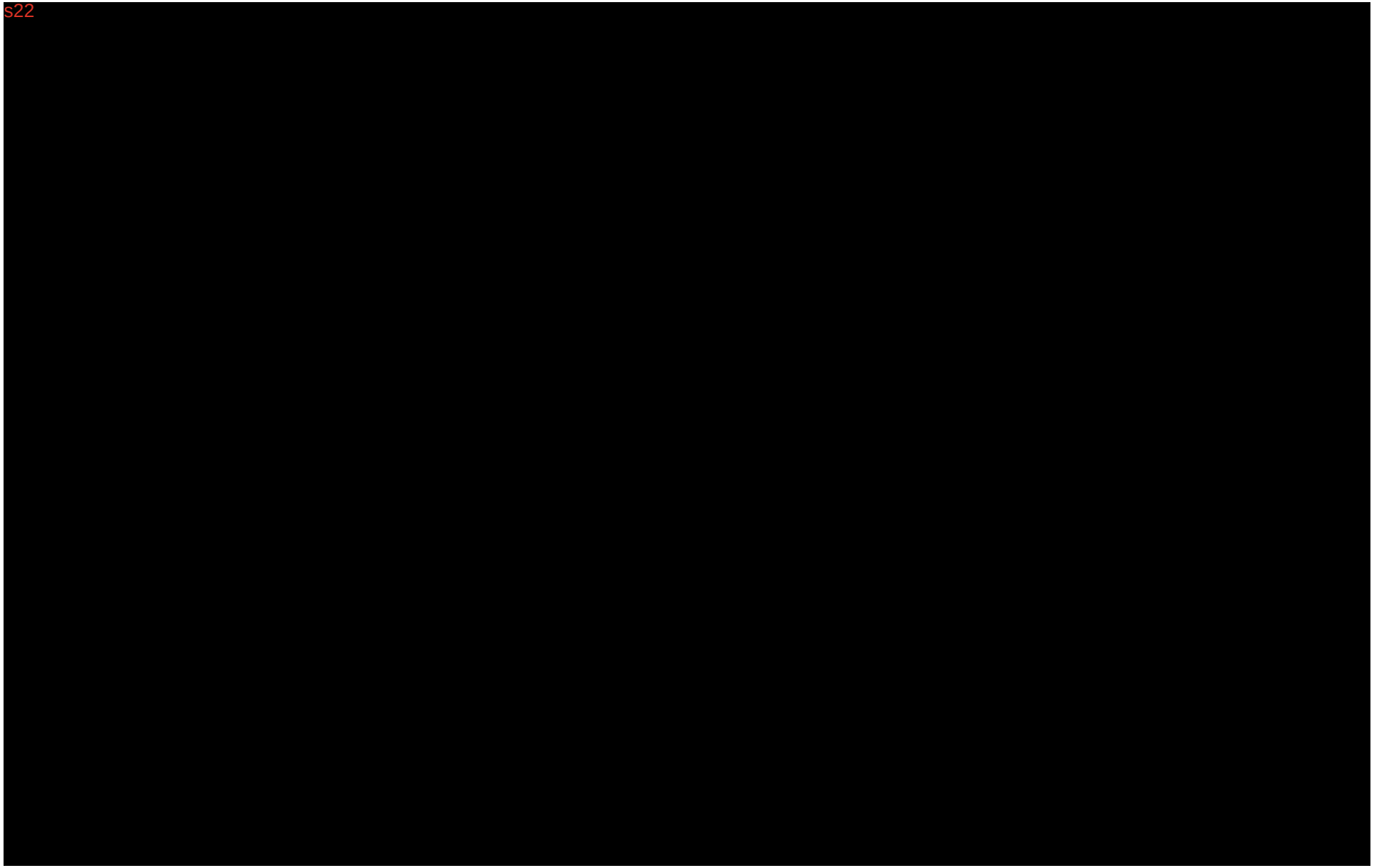
s22

[redacted]


s22

s22

[redacted]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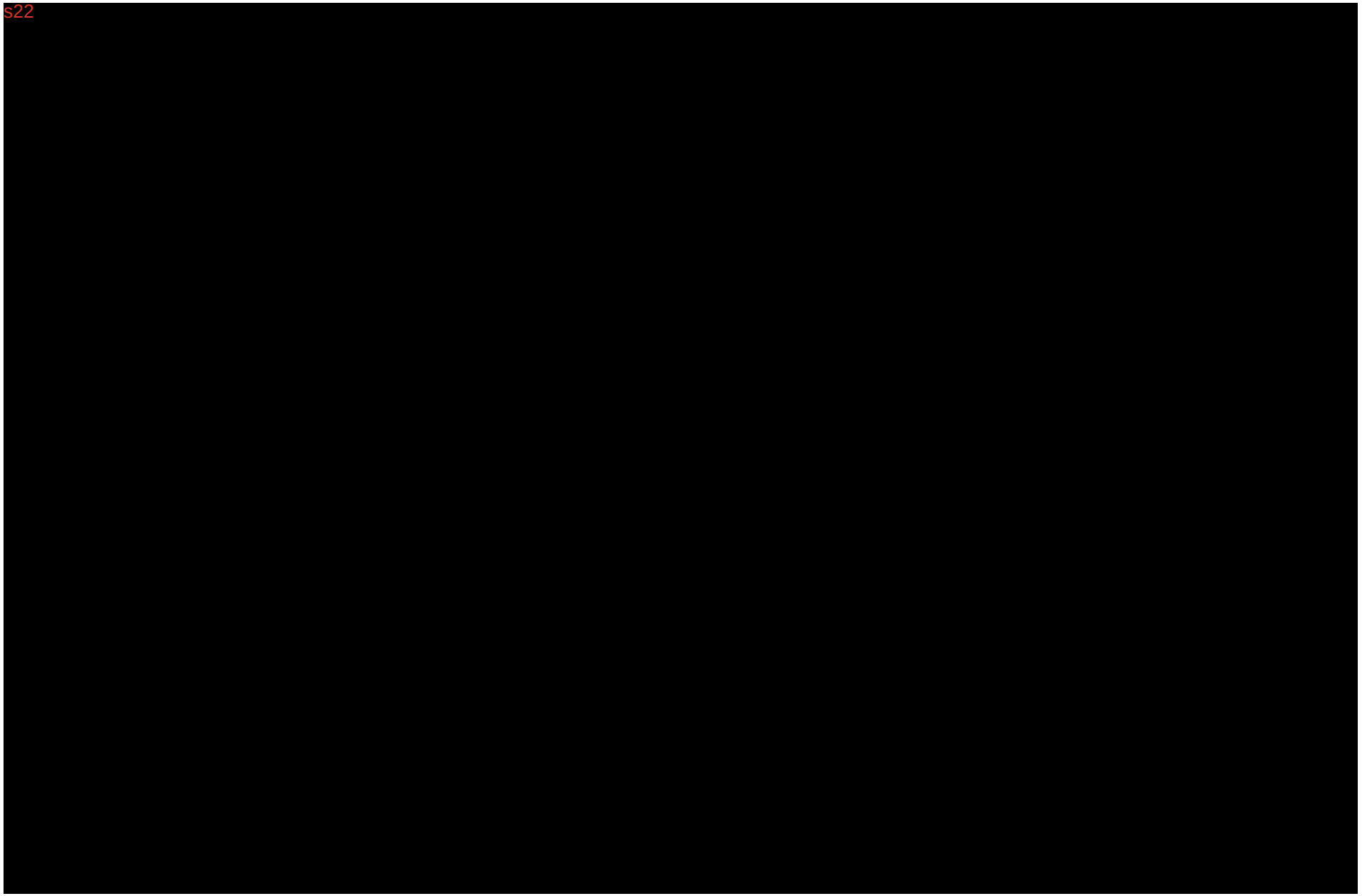
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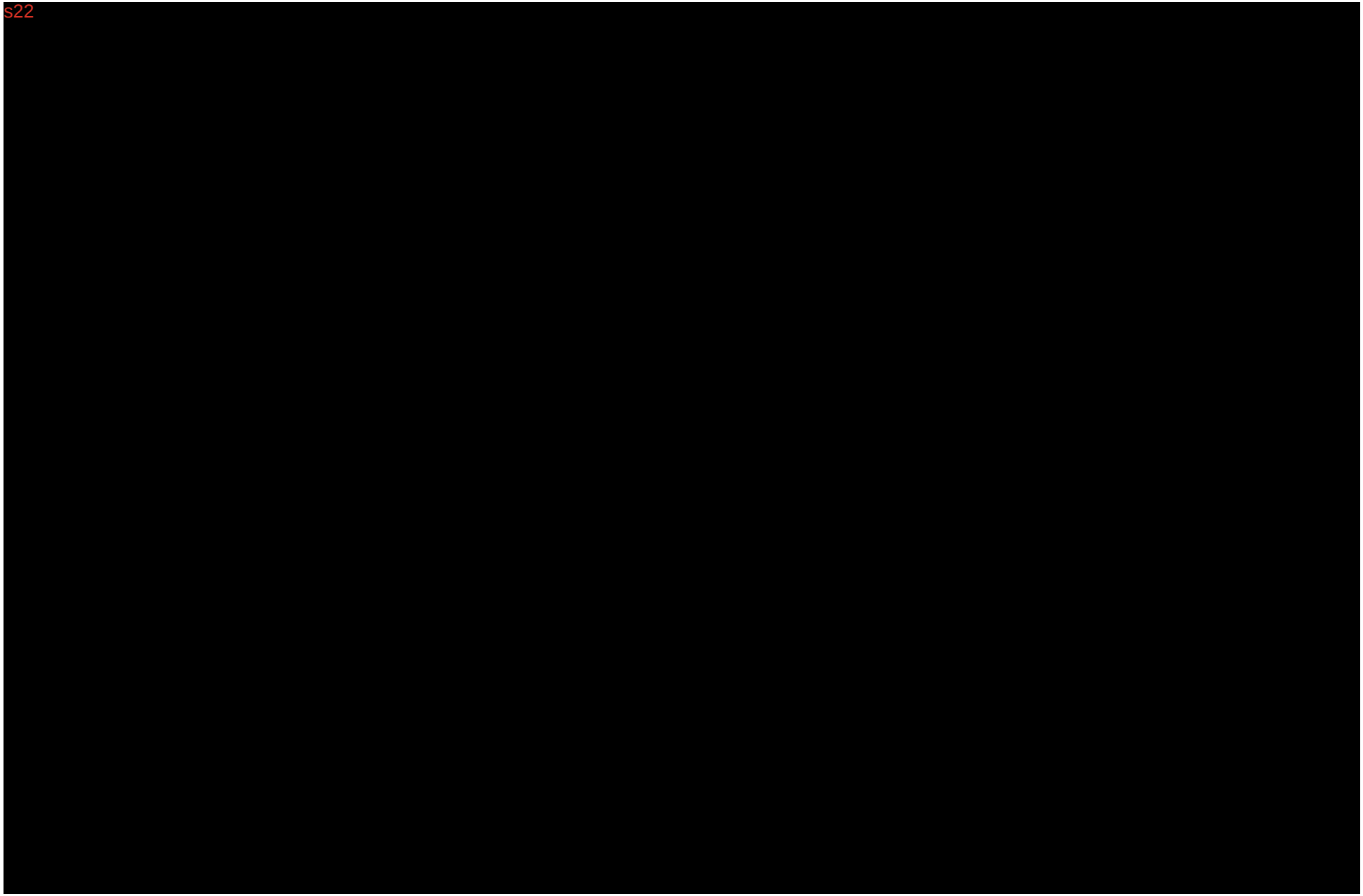
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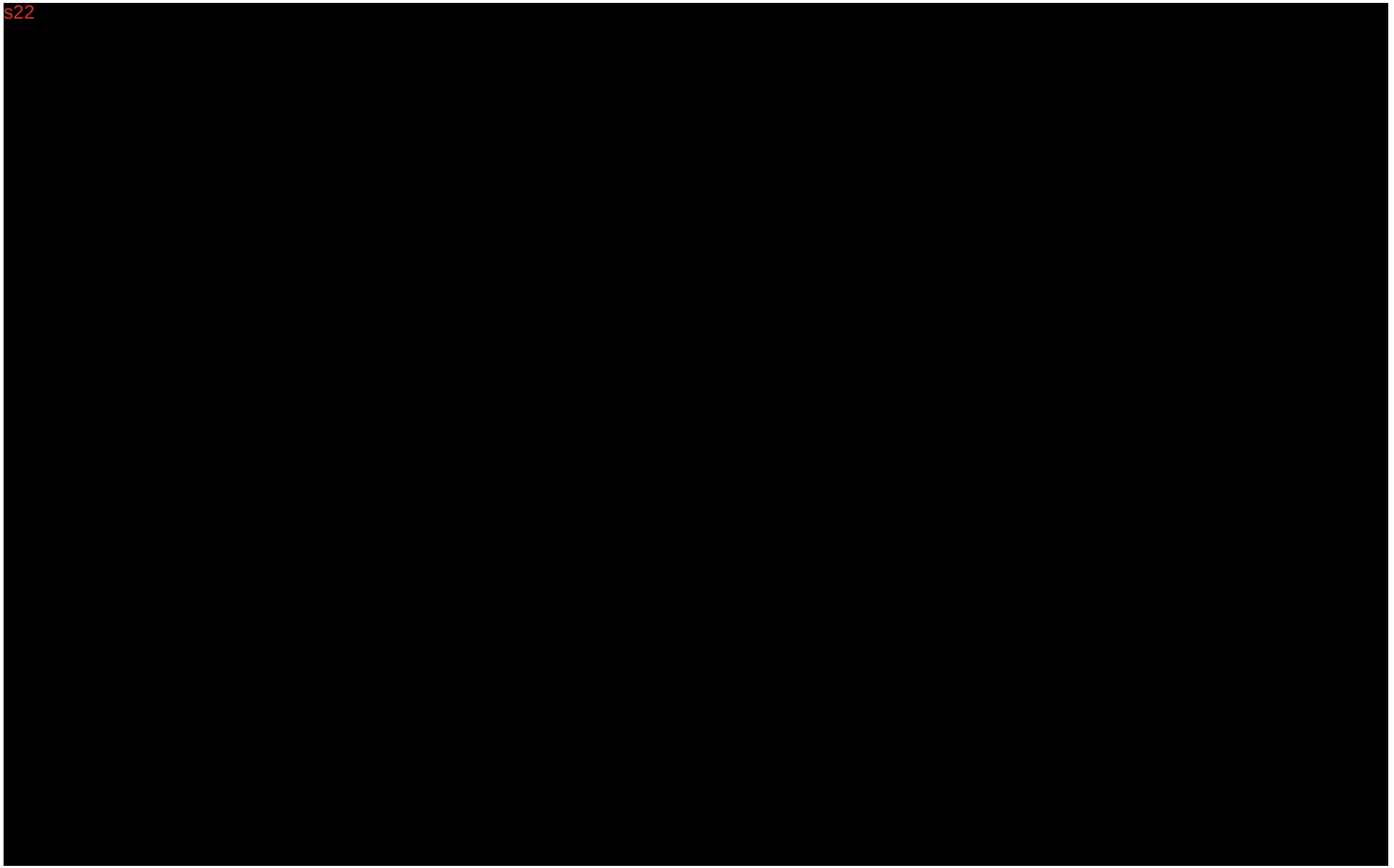
s22


s22

Web updates: Permissible Ingredients Determination (No. 2) 2025

Contents

Changes to Existing Pages

1. https://www.tga.gov.au/products/medicines/non-prescription-medicines/listed-medicines/updates-listed-medicine-ingredients

- Include link/notice to new page 1 to be created below.

2. https://www.tga.gov.au/resources/legislation/therapeutic-goods-permissible-ingredients-determination

- Replace the hyperlink of 'Read the legislation' with the following:

[Hyperlink to Therapeutic Goods (Permissible Ingredients) Determination (No.2) 2025 (legislation.gov.au)]

Summary of Comments on Document 26.PDF

Page: 2

Number: 1 Author: s22 [redacted] Date: 20/06/2025 9:34:00 AM +10'00'

I noticed that this page also has a link to the determination above the search bar. This will also need to be updated to link to the current determination.

New Pages to be created

1. https://www.tga.gov.au/news/notices/update-listed-medicine-ingredients-june-2025

Update to listed medicine ingredients in June 2025

Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025

Listed medicine ingredients and requirements for their use have been updated in the Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025 [Hyperlink to Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025 (legislation.gov.au)], which commenced on 20 June 2025. This determination replaces the previous instrument, the Therapeutic Goods (Permissible Ingredients) Determination (No. 1) 2025 [Hyperlink to previous TGA update page: https://www.tga.gov.au/news/notices/update-listed-medicine-ingredients-march-2025].

This instrument is updated frequently and there may be a more recent version of the instrument. Ensure you are accessing the current version of the instrument through the Therapeutic Goods Determination[Hyperlink to TGA Determinations page: https://www.tga.gov.au/therapeutic-goods-determinations#permissible-ingredients] page.

A complete list of the 25 changed ingredients is below:

Changed ingredients

Substance name	Change
CITICOLINE	Addition
METHOXYPROPYLAMINO CYCLOHEXENYLIDENE ETHOXYETHYLCYANOACETATE	Addition
CALANUS FINMARCHICUS OIL	Change
GALACTOOLIGOSACCHARIDES	Change
ALMOND OIL	Change
BITTER ALMOND OIL	Change
ERIOBOTRYA JAPONICA	Change
PERSIC OIL	Change
PRUNUS AFRICANA	Change
PRUNUS ARMENIACA	Change
PRUNUS AVIUM	Change
PRUNUS CERASIFERA	Change
PRUNUS CERASUS	Change
PRUNUS DOMESTICA	Change
PRUNUS DULCIS	Change
PRUNUS HUMILIS	Change

Substance name	Change
PRUNUS JAPONICA	Change
PRUNUS LAUROCERASUS	Change
PRUNUS MUME	Change
PRUNUS PERSICA	Change
PRUNUS SALICINA	Change
PRUNUS SEROTINA	Change
PRUNUS SPINOSA	Change
WILD CHERRY BARK DRY	Change
WILD CHERRY BARK POWDER	Change

Email to peak industry bodies regarding June 2025 update to the Permissible Ingredients Determination under section 26BB

Send to:
CMA: Technical@cmaustralia.org.au;
Lucy.Lang@cmaustralia.org.au
Accord: Coh@accord.asn.au
s47G s47F s47G
ATGC: Rachael@regsolutions.com.au;
Talktous@qualitymatterssafetymatters.com.au

From: s22 @health.gov.au
BCC: s22 @health.gov.au; s22 @health.gov.au

Attachment: List of amendments – TRIM D25-1741318

Subject header: Update to Permissible Ingredients Determination under section 26BB – June 2025

Dear all,

I am pleased to inform you that the delegate has approved the new Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025 ('the Determination'), which will commence on 20 June 2025.

A number of changes have been made in the Determination. The changes include:

Addition of new ingredients

- the addition of the following two new ingredients for use in listed and assessed listed medicines, and specific requirements for the use of the ingredients in medicines:
  - *methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate;* and
  - *citicoline.*

Changes to existing ingredients

- amendments to the requirements for the following 21 ingredients to align with the update to the Poisons Standard (which principally revises the concentration limit of specific components of the stated ingredients), as indicated in the *Notice of final decision to amend (or not amend) the current Poisons Standard – amygdalin, hydrocyanic acid and Wild Cherry Bark, Joint ACMS ACCS #34* (www.tga.gov.au/resources/publication/scheduling-decisions-final/notice-final-decision-amend-or-not-amend-current-poisons-standard-amygdalin-hydrocyanic-acid-and-wild-cherry-bark-joint-acms-accs-34) with an implementation date of 1 June 2025, as well as minor formatting changes and correction of minor typographical errors for the purpose of improving the internal consistency of the Determination:
  - *Almond oil;*
  - *Bitter almond oil;*
  - *Eriobotrya japonica;*
  - *Persic oil;*
  - *Prunus Africana;*
  - *Prunus armeniaca*
  - *Prunus avium;*
  - *Prunus cerasifera;*
  - *Prunus cerasus;*

- *Prunus domestica;*
- *Prunus dulcis;*
- *Prunus humilis;*
- *Prunus japonica;*
- *Prunus laurocerasus;*
- *Prunus mume;*
- *Prunus persica;*
- *Prunus salicina;*
- *Prunus serotina;*
- *Prunus spinosa;*
- *Wild cherry bark dry;* and
- *Wild cherry bark powder.*

- the removal of requirements for the following two ingredients to reflect the expiry of the periods of exclusive use for the applicant, and minor formatting changes for the purpose of improving the internal consistency of the Determination:
  - *Calanus finmarchicus oil*; and
  - *Galactooligosaccharides*.

The Changes to the Permissible Ingredients Determination page on the TGA website will be updated shortly with a notice including a complete list of amendments.

If you have any concerns or would like to discuss this matter further, please do not hesitate to contact us.

Regards,

Non-PrescriptionMedicines
Complementary and OTC Medicines Branch
Phone: s22 [redacted]
Email: nonprescriptionmedicines@health.gov.au
Therapeutic Goods Administration
Department of Health, Disability and Ageing
PO Box 100
Woden ACT 2606
www.tga.gov.au

This information is given to you without prejudice and is not binding on the TGA. It is the responsibility of the sponsor to ensure that all of the legislative requirements are met.