World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 3

SOVRENTA 15WP

(Syngenta Crop Protection AG)

P-11568

Quality Assessment

Contents

1 Chemical and physical data

1.1 Chemical and physical properties

SOVRENTA 15WP is a wettable powder (WP) packaged in 200 g water-soluble bags for use as an indoor residual spray.
Data on the chemical and physical properties of the active ingredient and the product SOVRENTA 15WP were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP) and are considered complete. Three batches were tested in accordance with WHO requirements for testing physical/chemical properties. The results are presented in Table 1. These summary results are based on the analysis of batches: 1222763, 1257375, 1257373.

Table 1. Chemical and physical properties for SOVRENTA 15WP.

Data requirement	Study number	Test method ID	Results
Isocycloseram content (initial, test item stored at room temperature)	USGR210339 USGR220275 USGR220274 (GLP studies)	SF-1165/1 Isocycloseram HPLC method fully validated identical with CIPAC/5349	Three batches and five samples/batch were tested: Mean value Batch No.1222763: 15.1 % w/w Mean value Batch No.1257375: 14.7 % w/w Mean value Batch No.1257373: 14.8 % w/w Mean value of three batches: 14.9 % w/w
Isocycloseram content (after accelerated storage stability, 2 weeks at 54 °C)	USGR220365 USGR220400 USGR220384 (GLP studies)	SF-1165/1 Isocycloseram HPLC method fully validated identical with CIPAC/5349	Measured values: Three batches and five samples/batch were tested: Mean value Batch No.1222763: 15.0 % w/w Mean value Batch No.1257375: 15.0 % w/w Mean value Batch No.1257373: 15.0 % w/w Mean value of three batches: 15.0 % w/w No significant differences between isocycloseram concentration values before and after storage stability test.
Physical state	300226235 300225950 300225931 (GLP studies)	visual inspection	Solid (three batches were tested) Same physical state before and after accelerated storage stability test.
Colour	300226235 300225950 300225931 (GLP studies)	visual inspection	Off white (three batches were tested) Same colour before and after accelerated storage stability test.
Odour	USGR220366 USGR220401 USGR220385 (GLP studies)	physical examination	Faint sweetish odour (three batches were tested) Same odour before and after accelerated storage stability test.
Water Content (optional)	USGR220362 USGR220398 USGR220382 (GLP studies)	CIPAC MT 30.6 CIPAC Handbook P, p. 222, 2021	Three batches were tested: Batch No.1222763: 3.3 % w/w Batch No.1257375: 3.6 % w/w Batch No.1257373: 3.7 % w/w Mean value of three batches: 3.5 % w/w

Table 1. Chemical and physical properties for SOVRENTA 15WP.

Data requirement	Study number	Test method ID	Results
Acidity / alkalinity	USGR220362 USGR220398 USGR220382 (GLP studies)	CIPAC MT 191 CIPAC Handbook L, p. 143, 2006	Three batches have been tested (no replicates) Batch No.1222763: pH = 7.00* Batch No.1257375: alkalinity (calculated as NaOH) 0.007% w/w Batch No.1257373: pH = 7.00* Mean value of three batches: < 0.007% w/w *Since pH of diluted sample is neutral, determination of acidity/alkalinity not necessary
pH (1% w/v aqueous dilution, initial, test item stored at room temperature)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 75.3, CIPAC Handbook J, p. 131, 2000	Measured values: Three batches were tested: Mean value Batch No.1222763: 7.4 Mean value Batch No.1257375: 7.6 Mean value Batch No.1257373: 7.6 Mean value of three batches: 7.5
pH (1% w/v aqueous dilution, after accelerated storage stability test)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 75.3, CIPAC Handbook J, p. 131, 2000	Measured values: Three batches were tested: Mean value Batch No.1222763: 7.6 Mean value Batch No.1257375: 7.7 Mean value Batch No.1257373: 7.8 Mean value of three batches: 7.7 No significant differences between pH values before and after storage stability test.
Wet sieve test (initial, test item stored at room temperature) 75 µm sieve, with watersoluble bag material	300225931 (GLP Study)	CIPAC MT 185, CIPACHandbook K, p. 149, 2003	Measured values: One batch was tested: Batch No.1222763: residue 75 µm: 0.44 %
Wet sieve test (initial, test item stored at room temperature) 75 µm sieve	300225931 300225950 300226235 (GLP studies)	CIPAC MT 185, CIPAC Handbook K, p. 149, 2003	Measured values: Three batches and five replicates/batch were tested: Mean value Batch No.1222763: residue 75 µm: 0.50 % Mean value Batch No.1257375: residue 75 µm: 0.73 % Mean value Batch No.1257373: residue 75 µm: 0.82 %
Wet sieve test (after accelerated storage stability test) 75 µm sieve, with water soluble bag material	USGR220366 (GLP Study)	CIPAC MT 185, CIPAC Handbook K, p. 149, 2003	Measured values: One batch was tested: Batch No.1222763: residue 75 µm: 0.32 %
Wet sieve test (after accelerated storage stability test) 75 µm sieve	USGR220366 USGR220401 USGR220385 (GLP Study)	CIPAC MT 185, CIPAC Handbook K, p. 149, 2003	Measured values: Three batches and five replicates/batch were tested: Mean value Batch No.1222763: residue 75 µm: 0.40 % Mean value Batch No.1257375: residue 75 µm: 0.40 % Mean value Batch No.1257373: residue 75 µm: 0.22 % Mean value of three batches: residue 75 µm: 0.34 %

Table 1. Chemical and physical properties for SOVRENTA 15WP.

Data requirement	Study number	Test method ID	Results
			No significant differences between wet sieve test values before and after storage stability test.
Wettability (initial, test item stored at room temperature) without water soluble bag material	300226235 300225950 300225931 (GLP studies)	CIPAC MT 53.3 CIPAC Handbook F, p. 164, 1995	Measured values: Three batches and three replicates/batch were tested: Mean value Batch No.1222763: 15 s Mean value Batch No.1257375: 15 s Mean value Batch No.1257373: 14 s Mean value of three batches: 15 s
Wettability (after accelerated storage stability test) without water soluble bag material	300226235 300225950 300225931 (GLP studies)	CIPAC MT 53.3 CIPAC Handbook F, p. 164, 1995	Measured values: Three batches and three replicates/batch were tested: Mean value Batch No.1222763: 14 s Mean value Batch No.1257375: 12 s Mean value Batch No.1257373: 12 s Mean value of three batches: 13 s No significant differences between wettability values before and after storage stability test.
Wettability (after accelerated storage stability test) with water soluble bag material	USGR220366	CIPAC MT 53.3 CIPAC Handbook F, p. 164, 1995	Measured values: Only Batch No.1222763 was tested (no replicates): Value in the presence of 1.6% water soluble bag material: 13 s
Dissolution rate of water soluble bags (CIPAC water D, initial, test item stored at room temperature)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 176, CIPAC Handbook F, p. 440, 1995	Measured values: Three batches were tested: Mean value Batch No.1222763: 13 s Mean value Batch No.1257375: 14 s Mean value Batch No.1257373: 20 s Mean value of three batches: 16 s
Dissolution rate of water soluble bags (CIPAC water D, after accelerated storage stability test)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 176, CIPAC Handbook F, p. 440, 1995	Measured values: Three batches were tested: Mean value Batch No.1222763: 10 s Mean value Batch No.1257375: 10 s Mean value Batch No.1257373: 10 s Mean value of three batches: 10 s No significant differences between dissolution rates before and after storage stability test.
Persistent foam 2.0 %w/v CIPAC water D (initial, test item stored at room temperature)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 47.3, CIPAC Handbook O, p. 177, 2017	Measured values: Three batches and three replicates/batch were tested: Mean value Batch No.1222763: 2 ml Mean value Batch No.1257375: 0 ml Mean value Batch No.1257373: 2 ml Mean value of three batches: 1 ml
Persistent foam 2.0 %w/v CIPAC water D	300226235 300225950 300225931 (GLP studies)	CIPAC MT 47.3, CIPAC Handbook O, p. 177, 2017	Measured values: Three batches and three replicates/batch were tested: Mean value Batch No.1222763: 2 ml Mean value Batch No.1257375: 0 ml

Table 1. Chemical and physical properties for SOVRENTA 15WP.

Data requirement	Study number	Test method ID	Results
(after accelerated storage stability test)			Mean value Batch No.1257373: 4 ml Mean value of three batches: 2 ml No significant differences between persistent foam values before and after storage stability test at 2.0 % w/v concentration.
Persistent foam 3.3 %w/v CIPAC water D (initial, test item stored at room temperature)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 47.3, CIPAC Handbook O, p. 177, 2017	Measured values: Three batches and three replicates/batch were tested: Mean value Batch No.1222763: 1 ml Mean value Batch No.1257375: 0 ml Mean value Batch No.1257373: 0 ml Mean value of three batches: 0 ml
Persistent foam 3.3 %w/v CIPAC water D (after accelerated storage stability test)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 47.3, CIPAC Handbook O, p. 177, 2017	Measured values: Three batches and three replicates/batch were tested: Mean value Batch No.1222763: 0 ml Mean value Batch No.1257375: 0 ml Mean value Batch No.1257373: 0 ml Mean value of three batches: 0 ml No significant differences between persistent foam values before and after storage stability test at 3.3 % w/v concentration.
Suspensibility (chemical assay, initial,test item stored at room temperature)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 184.1, CIPAC Handbook P, p. 245, 2021	Measured values: Three batches and three replicates/batch were tested at two use rates: **Lowest use rate (2.0 % w/v):** Initial measurement: Mean value Batch No.1222763: 44 % Mean value Batch No.1257375: 52 % Mean value Batch No.1257373: 44 % Mean value of three batches: 47 % Re-suspensibility – Measured values: Mean value Batch No.1222763: 98 % Mean value Batch No.1257375: 98 % Mean value Batch No.1257373: 97 % Mean value of three batches: 98 % **Highest use rate (3.3 % w/v):** Initial measurement: Mean value Batch No.1222763: 58 % Mean value Batch No.1257375: 56 % Mean value Batch No.1257373: 58 % Mean value of three batches: 57 % Re-suspensibility – Measured values: Mean value Batch No.1222763: 98 % Mean value Batch No.1257375: 98 % Mean value Batch No.1257373: 97 % Mean value of three batches: 98 %

Table 1. Chemical and physical properties for SOVRENTA 15WP.

Data requirement	Study number	Test method ID	Results
Suspensibility (chemical assay, after accelerated storage stability test)	300226235 300225950 300225931 (GLP studies)	CIPAC MT 184.1, CIPAC Handbook P, p. 245, 2021	Measured values: Three batches and three replicates/batch were tested at two use rates: **Lowest use rate (2.0 % w/v):** Initial measurement: Mean value Batch No.1222763: 59 % Mean value Batch No.1257375: 60 % Mean value Batch No.1257373: 57 % Mean value of three batches: 59 % Re-suspensibility – Measured values: Mean value Batch No.1222763: 99 % Mean value Batch No.1257375: 99 % Mean value Batch No.1257373: 99 % Mean value of three batches: 99 % **Highest use rate (3.3 % w/v):** Initial measurement: Mean value Batch No.1222763: 63 % Mean value Batch No.1257375: 67 % Mean value Batch No.1257373: 66 % Mean value of three batches: 65 % Re-suspensibility – Measured values: Mean value Batch No.1222763: 99 % Mean value Batch No.1257375: 99 % Mean value Batch No.1257373: 98 % Mean value of three batches: 99 % No significant differences between the suspensibility and re-suspensibility values before and after storage stability test.
Suspensibility (Gravimetric assay) 2.0 % w/v; CIPAC water D 30°C with water soluble bag material	300226235 300225950 300225931 (GLP studies)	CIPAC MT 184.1 CIPAC Handbook P, p. 245, 2021	Initial measurement: Three samples/batch were tested: Initial/after accelerated storage Mean value Batch No.1222763: 86 % / 88 % Mean value Batch No.1257375: 85 % / 87 % Mean value Batch No.1257373 84 % / 89 % Mean value of three batches: 85 % / 88 % Re-suspensibility - Measured values: Three samples/batch were tested: Initial/after accelerated storage Mean value Batch No.1222763: 103 % / 104 % Mean value Batch No.1257375: 102 % / 104 % Mean value Batch No.1257373: 103 % / 104 % Mean value of three batches: 103 % / 104 %

Table 1. Chemical and physical properties for SOVRENTA 15WP.

Data requirement	Study number	Test method ID	Results
Suspensibility (Gravimetric assay) 3.3 % w/v; CIPAC water D 30°C With water soluble bag material	300226235 300225950 300225931 (GLP studies)	CIPAC MT 184.1 CIPAC Handbook P, p. 245, 2021	Initial measurement: Three samples/batch were tested: Initial/after accelerated storage Mean value Batch No.1222763: 88 % / 88 % Mean value Batch No.1257375: 88 % / 89 % Mean value Batch No.1257373 90 % / 90 % Mean value of three batches: 89 % / 89 % Re-suspensibility -Measured values: Three samples/batch were tested: Initial/after accelerated storage Mean value Batch No.1222763: 103 % / 103 % Mean value Batch No.1257375: 102 % / 103% Mean value Batch No.1257373:103 % / 104 % Mean value of three batches: 103 % / 103 %
Surface Tension	USGR220362	EEC A5	One batch has been tested (no replicates) Measured values: value Batch No.1222763: 0.1%, in distilled water, 20°C 42.4 N/m 2.0%, in distilled water, 20°C 32.4 mN/m 3.3%, in distilled water, 20°C 32.2 mN/m
Density (pour and tap)	USGR220362	CIPAC MT 186	One batch has been tested (no replicates) Measured values: value Batch No.1222763: pour density 0.350 g/mL tap density 0.370 g/mL
Resistance of the packaging material to its contents	300226235 300225950 300225931	Packaging Evaluation Technical Monograph 17	The packaging was shown to be resistant to its contents
Flammability	HT22/514*	UN method N.1.	The test substance propagates combustion by burning with a flame. The minimum burning time over 100 mm was 100 seconds and the test substance extinguished on reaching the wetted zone, therefore the test item is not classified as a flammable solid.
Explosivity	HT22/514*	ASTM E537 (DSC)	Differential scanning calorimetry (DSC) measurements reported show the total heat of decomposition to be 185 J/g. As this figure is well below the 500 J/g threshold, no further testing is necessary. The test substance is not classified as an explosive substance.
Self-heating properties	HT22/514*	UN Test N.4	In accordance with the criteria of UN Test N.4, the test substance is exempt from classification as a self-heating substance if packaged in sizes of not more than 3 cubic meters

Table 1. Chemical and physical properties for SOVRENTA 15WP.			
Data requirement	**Study number**	**Test method ID**	**Results**
Oxidizing Properties	HT22/514*	UN Test O.1	In accordance with the criteria of UN Test O.1, the test substance is not classified as an oxidizing solid.
Heat of decomposition	HT22/514*	ASTM E537 (DSC)	The total normalized energy output from the exothermic peaks, i.e. the heat of decomposition, is 185 J/g.

* Results from study HT22/514 are presented for completeness; however, this study was not relied upon for decision making as the properties are not requirements for prequalification of wettable powder products.

No significant differences were recorded among the properties of the product kept at ambient temperature and after accelerated storage stability test conditions.

1.2 Manufacturing, composition and formulant information

Data on the manufacturing process and product composition for SOVRENTA 15WP have been provided and are adequate. A summary is presented in Table 2. Detailed information on the manufacturing process and product formulation is considered Confidential Business Information (CBI).

Table 2. Manufacturing process and product composition data submitted for SOVRENTA 15WP.	
Description of starting material	Isocycloseram technical, isocycloseram content ≥96 % w/w.
Declaration of product formulation	Included in the confidential business information.
Production / formulation process	Isocycloseram technical active substance is mixed with the other formulation components such as solvents, dispersing agents, wetting agents, antifoaming agents and carriers. The mixture is milled to the desired particle size. After this step the obtained material is packed into containers with approved labels. The packed products are organized and arranged for delivery.
Discussion of impurities	No relevant impurities are present in the product.
Certification of limits	Isocycloseram: 15 % w/w, acceptable limits 14.1 to 15.9 % w/w

1.3 Enforcement analytical method

Table 3. Details of the analytical method used to determine isocycloseram in SOVRENTA 15WP.	
Quantification of isocycloseram	Isocycloseram CIPAC/5349

The method is appropriate for the determination of the active ingredient content of the product.

2 Entomological characterisation

Laboratory studies to characterize the effect of the active ingredient in SOVRENTA 15WP on Anopheline mosquito species were submitted to WHO as part of the prequalification dossier.

2.1 Laboratory Studies

Primary and supplementary evidence on the characterization of the active ingredient in SOVRENTA 15WP and the residual efficacy under laboratory conditions were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP).

2.1.1 Characterisation of the SOVRENTA 15WP AI

One supplemental study was presented to characterize the properties of the active ingredient and determine the LD_{50}, LD_{90}, and LD_{95}, using technical grade isocycloseram.

One *Anopheles stephensi* test system was used in the study: *An. stephensi* DUB S strain, a colonised insecticide susceptible strain originating from Dubai.

Experiments were conducted to determine the range of isocycloseram concentrations that caused between 0% and 100% mortality in the selected test system. The results from the experiments were used to select the range of concentrations of isocycloseram that were tested in the laboratory study to determine the intrinsic insecticidal activity of the active ingredient. The LD_{50}, LD_{90} and LD_{95} results as determined using one *An. stephensi* test system and topical applications of technical grade isocycloseram are presented in Tables 4 - 7.

Table 4. Isocycloseram concentrations tested in mortality range finding experiments

Concentration (PPM)	Control	Dose A	Dose B	Dose C	Dose D	Dose E
Isocycloseram	0	0.05	0.2	0.5	1	5

Table 5. Twenty-four and 72-hour mortality of *An. stephensi* DUB S strain tested using topical applications of isocycloseram technical material in mortality range finding experiments.

Isocycloseram concentration (PPM)	n	Mortality	
		M24 (%)	M72 (%)
0	50	4	4
0.05	50	8	12
0.2	50	4	16
0.5	50	50	94
1	50	52	96
5	50	92	100

Table 6. Intrinsic insecticidal activity of isocycloseram against *An. stephensi* DUB S strain tested using topical applications of isocycloseram technical material.

Isocycloseram concentration (PPM)	n	Mortality	
		M24 (%, 95% CI)	M72 (%, 95% CI)
0	150	3 (0 - 7.6)	6 (1.5 - 9.2)
0.1	150	8 (1.9 - 14.1)	15 (3.0 - 27.7)
0.2	150	19 (11.6 - 27)	51 (28.6 - 72.7
0.5	150	25 (11.8 - 37.5)	71 (47.8 - 94.9)
1	150	45 (28.2 - 61.2)	85 (71.7 - 97.7)
5	150	93 (87.2 - 98.2)	99 (98.0 - 100)

Table 7. LD_{50}, LD_{90}, and LD_{95} concentrations of isocycloseram as determined using topical applications against *Anopheles stephensi*.

Mosquito Strain	Sample size (n)	Timepoint	LD_{50}* (95% CI)	LD_{90}* (95% CI)	LD_{95}* (95% CI)
Anopheles stephensi	150	24	1.98 (1.54 - 2.53)	4.41 (3.56 - 4.96)	5 (4.91 - 5.98)
		48	0.55 (0.09 - 1.09)	1.58 (0.75 - 2.54)	1.88 (0.98 - 2.88)
		72	0.46 (0.01 - 0.94)	1.39 (0.55 - 2.34)	1.68 (0.77 - 2.67)

* ng/mg per mosquito.

2.1.2 Characterisation of residual efficacy

Four studies (two primary evidence, two supplementary evidence) were presented to characterize the residual efficacy of the product on test surfaces under laboratory conditions. The primary evidence studies were conducted in Tanzania (Study 1) and Benin (Study 2); the supplementary evidence studies were conducted in South Africa (Study 3) and Ghana (Study 4). In all studies, prepared substrate blocks were treated with 120 mg AI/m^2 of SOVRENTA 15WP. In Studies 1, 2, and 4, concrete (cement), mud and wood substrates were used; in Study 3, cement, mud, painted cement and tin substrates were used. Residual efficacy was tested using WHO cone tests and two (Studies 1, 2 and 4) and one (Study 3) mosquito test systems, respectively. The endpoint used to assess mosquito mortality in the residual efficacy studies was 168-hour mortality, with the exception of the supplemental Study 4, in which 72-hour mortality was used.

In Study 1, the mosquito test systems were insecticide susceptible *An. gambiae* s.s. Ifakara strain and pyrethroid resistant *An. arabiensis* Kingani strain. Each test system was characterised for insecticide resistance using WHO cylinder tests; insecticide susceptibility was confirmed in the insecticide susceptible test system and the insecticide resistant test system showed <30% mortality to the diagnostic doses of permethrin, deltamethrin, lambda-cyhalothrin and alpha-cypermethrin, and full susceptibility to bendiocarb and pirimiphos methyl. In Study 2, the mosquito test systems were insecticide susceptible *An. gambiae* Kisumu strain and pyrethroid resistant *An. gambiae* Covè strain. The pyrethroid resistance in the Covè strain is mediated by >90% L1014 *kdr* frequency and over-expression of CYP6P3 metabolic enzymes. Each test system was characterised for insecticide resistance using WHO cylinder tests; insecticide susceptibility was confirmed in the insecticide susceptible test system and the insecticide resistant test system showed <50% mortality to the diagnostic doses of permethrin, deltamethrin, lambda-cyhalothrin and alpha-cypermethrin.

In the supplemental evidence studies, Study 3 was conducted using insecticide susceptible *An. arabiensis* KGB strain and Study 4 was conducted using insecticide susceptible *An. gambiae* Kisumu strain and *An. gambiae* s.l. mosquitoes reared from larvae collected in natural breeding sites. The *An. gambiae* s.l. mosquitoes were characterised for insecticide resistance using CDC bottle bioassays and showed susceptibility to 4µg AI/bottle of clothianidin and resistance to 20 µg AI/bottle of permethrin.

The results for the residual efficacy studies are presented in Tables 8 (Studies 1 - 3) and 9 (Study 4). In Study 1, mortality above 80% was observed on all substrates to 12 months post-treatment using the insecticide susceptible test system. For the pyrethroid resistant test system, mortality greater than 80% was observed to nine, 10- and 11-months post-treatment for mud, concrete and wood substrates, respectively. In Study 2, mortality greater than 80% was observed on all substrates to 12 months post-treatment using the insecticide susceptible test system. For the pyrethroid resistant test system, mortality greater than 80% was observed on all substrates to 11 months (12 months for cement). In Study 3, mortality greater than 80% was observed on all substrates to 12 months post-treatment using the insecticide susceptible test system. In Study 4, combined mortality of greater than 80% was observed on all substrates for up to 12 months for the insecticide susceptible test system and for up to 11 months for the pyrethroid resistant test system.

Table 8. One hundred and sixty-eight-hour mortality (%) for WHO cone tests conducted on prepared substrate blocks treated with 120 mg AI/m² of SOVRENTA 15WP and tested against insecticide susceptible and pyrethroid resistant strains of the *An. gambiae* complex.

Substrate	Month												
	0.25	1	2	3	4	5	6	7	8	9	10	11	12
An. gambiae* (Ifakara)													
Concrete	-	100	100	99.3 (97.8 – 100)	100	100	100	100	97.7 (94.0 – 100)	98.6 (96.6 – 100)	95.4 (91.3 – 99.5)	92.9 (84.0 – 100)	94.6 (90.3 – 98.7)
Mud	-	100	100	98.5 (96.4 – 100)	100	98.8 (96.1 – 100)	97.7 (95.2 – 100)	94.3 (88.6 – 100)	80.7 (71.1 – 90.4)	86.9 (79.5 – 94.3)	78.6 (64.7 – 92.6)	93.0 (86.5 – 99.4)	92.5 (87.0 – 98.0)
Wood	-	100	99.3 (97.8 – 100)	97.9 (94.7 – 100)	100	95.8 (90.6 – 100)	97.7 (94.0 – 100)	89.8 (81.3 – 98.3)	84.8 (76.6 – 93.0)	96.4 (92.2 – 100)	89.1 (79.7 – 98.4)	99.3 (97.8 – 100)	96.2 (93.1 – 99.3)
An. arabiensis* (Kingani)													
Concrete	-	100	99.4 (98.0 – 100)	97.0 (94.2 – 99.9)	99.3 (97.8 – 100)	98.0 (95.7 – 100)	97.2 (94.6 – 99.9)	98.4 (95.1 – 100)	96.4 (91.6 – 100)	92.7 (85.6 – 99.8)	93.8 (88.9 – 98.6)	79.8 (68.4 – 91.1)	69.4 (58.5 – 80.2)
Mud	-	99.4 (98.0 – 100)	99.3 (97.8 – 100)	84.7 (85.8 – 93.6)	95.8 (92.9 – 98.8)	94.8 (91.9 – 97.7)	92.4 (87.1 – 97.8)	100	88.0 (80.5 – 95.5)	85.2 (76.4 – 94.1)	79.0 (67.3 – 90.8)	72.7 (61.7 – 83.6)	64.9 (52.7 – 77.2)
Wood	-	99.4 (98.0 – 100)	98.8 (95.9 – 100)	68.8 (60.0 – 77.5)	93.1 (87.4 – 98.7)	91.8 (85.9 – 97.7)	93.8 (89.4 – 98.1)	98.4 (95.1 – 100)	88.9 (83.6 – 94.2)	89.9 (81.4 – 98.4)	85.1 (78.1 – 92.0)	92.2 (86.1 – 98.2)	75.1 (65.7 – 84.5)
***An. gambiae* (Kisumu)**													
Cement	100	100	100	100	100	100	100	100	100	100	100	100	93.1 (87.8 - 98.4)
Mud	100	100	100	100	100	100	100	100	100	98.8 (96.6 – 100)	100	100	96.7 (93.1 - 100)
Wood	100	100	100	100	100	100	100	100	98.6 (96- 100)	92.7 (87.1 - 98.3)	100	100	100
***An. gambiae* (Covè)**													
Cement	100	100	100	100	100	100	100	97.6	97.6	83.3	83.7	98.7	90.6

Table 8. One hundred and sixty-eight-hour mortality (%) for WHO cone tests conducted on prepared substrate blocks treated with 120 mg AI/m^2 of SOVRENTA 15WP and tested against insecticide susceptible and pyrethroid resistant strains of the *An. gambiae* complex.

								(94.4 - 100)	(94.4 - 100)	(74.7 - 91.9)	(71.9 - 95.5)	(96.3 - 100)	(84.4 - 96.8)
Mud	100	100	100	100	100	100	100	97.4 (93.9 - 100)	92.2 (86.3 - 98.1)	82.8 (74.4 - 91.2)	94.4 (87 - 100)	98.6 (96.1 - 100)	74 (64.3 - 83.7)
Wood	100	100	100	100	100	98.7 (96.3 - 100)	92.4 (87.1 - 97.7)	82.9 (74.5 - 91.3)	76.7 (67.0 - 86.4)	81.6 (72.9 - 90.3)	85.8 (74.3 - 97.1)	98.7 (96.3 - 100)	78.7 (69.8 - 87.6)
***An. arabiensis* (KGB)**													
Concrete		100	100	100	100	100	100	100	100	100	100	100	100
Mud		100	100	100	100	100	100	100	100	100	100	100	100
Painted cement		100	100	100	100	100	100	100	100	100	100	100	100
Tin		100	100	100	100	100	100	100	100	100	100	100	100

* Corrected mortality.

Table 9. Combined 72-hour mortality (%) results for WHO cone tests conducted on prepared substrate blocks treated with 120 mg AI/m² of SOVRENTA 15WP and tested against insecticide susceptible and pyrethroid resistant strains of the *An. gambiae* complex for up to 11 (*An. gambiae* s.l.) and 12 (*An. gambiae* Kisumu) months of testing.

Substrate	Month	
	11	12
***An. gambiae* (Kisumu)**		
Cement	-	100
Northern mud	-	100
Southern mud	-	100
Wood	-	99.4 (99.3 - 99.5)
***An. gambiae* s.l.**		
Cement	97.7 (97.6 - 97.7)	-
Northern mud	96.9 (96.8 - 97)	-
Southern mud	93.8 (93.7 - 93.9)	-
Wood	95.0 (94.9 - 95.03)	-

2.2 Entomological characterisation conclusions

The submitted laboratory studies characterize the properties of the active ingredient and determine the LD_{50}, LD_{90}, and LD_{95} using technical grade isocycloseram. Studies were presented to characterise the residual efficacy under laboratory conditions on cement (painted and bare), mud, tin and wood substrates, against insecticide susceptible and pyrethroid resistant test systems, using 168-hour mortality as the endpoint. Overall, the product maintained residual efficacy for up to 11 months under laboratory conditions when tested against pyrethroid resistant test systems and for up to 12 months when tested against insecticide susceptible test systems.

3 Overall quality conclusions

Based on the studies and information provided, all data requirements for the prequalification assessment of product quality have been satisfied. These data have been relied upon to assess the formulation, manufacturing process, and physical/chemical characteristics of the proposed product for the purpose of establishing the identity of the product and assuring that the product can be produced consistently.

The methods for assessing the physical/chemical properties of the product were CIPAC methods and/or validated methods.

The quality component of the dossier is considered complete, and the assessment of the submitted information on quality supports prequalification of the product.

Table 9. List of studies related to quality submitted to WHO as part of the prequalification dossier.

Studies that were relied upon for decision making	
Study number	**Study title**
USGR210339	A23752B - Chemical Characterization of Batch ID 1222763, Syngenta Crop Protection, LLC, Syngenta File No. VV-937370
USGR220275	A23752B - Chemical Characterization of Batch ID 1257375, Syngenta Crop Protection, LLC, Syngenta File No. VV-966493
USGR220274	A23752B - Chemical Characterization of Batch ID 1257373, Syngenta Crop Protection, LLC, Syngenta File No. VV-966271
USGR220365	A23752B - Content of Active Ingredient after Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-980193
USGR220400	A23752B - Content of Active Ingredient after Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-980887
USGR220384	A23752B - Content of Active Ingredient after Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-980200
USGR220362	A23752B - Physico-chemical characteristics of Batch 1222763 Syngenta Crop Protection, LLC, Syngenta File No. VV-982239
USGR220398	A23752B - Physico-chemical characteristics of Batch 1257375 Syngenta Crop Protection, LLC, Syngenta File No. VV-980420
USGR220382	A23752B - Physico-chemical characteristics of Batch 1257373 Syngenta Crop Protection, LLC, Syngenta File No. VV-980418
USGR220366	A23752B - Physical and Technical Properties of Batch 1222763 After Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-983504
USGR220401	A23752B - Physical and Technical Properties of Batch 1257375 After Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-983673
USGR220385	A23752B - Physical and Technical Properties of Batch 1257373 After Storage in Water Soluble Bag in PE/PET Packaging for 2 Weeks at 54°C, Syngenta Crop Protection, LLC, Syngenta File No. VV-983524

Table 9. List of studies related to quality submitted to WHO as part of the prequalification dossier.	
300225950	A23752B - Storage Stability and Shelf Life Statement for Batch 1257373 (2 Weeks 54°C) in Water Soluble Bags in PE/PET packaging according to CIPAC MT 46.4, Syngenta Crop Protection, LLC, Syngenta File No. VV-985789
300225931	23752B - Storage Stability and Shelf Life Statement for Batch 1222763 (2 Weeks 54°C) in Water Soluble Bags in PE/PET packaging according to CIPAC MT 46.4, Syngenta Crop Protection, LLC, Syngenta File No. VV-985791
300226235	A23752B - Storage Stability and Shelf Life Statement for Batch 1257375 (2 Weeks 54°C) in Water Soluble Bags in PE/PET packaging according to CIPAC MT 46.4, Syngenta Crop Protection, LLC, Syngenta File No. VV-986934
SYN1786	Intrinsic toxicity testing of one compound (Plinazolin AI tech) against three mosquito species
BIT 094 P1 PPMG22100	Laboratory residual efficacy study of SYN547407 (120 mg ai/m^2 and 150 mg ai/m^2)
22-03-A/GLP	Phase I laboratory evaluation of SYN547407 WP (A23752B) (by Syngenta Crop Protection AG), a new insecticide for indoor residual spraying against susceptible and pyrethroid-resistant strains of *Anopheles gambiae sensu lato*
PPMG22106	Efficacy of new IRS insecticide: SYN54707 WP
PPME22852	Evaluation of the efficacy of SYN547407 15WP (A23752B) an isocycloseram formulation for IRS against wild populations of *Anopheles gambiae* in Ghana
Studies that were not used to inform decision making	
Study number	**Study title**
HT22/514	Isocycloseram - A23752B - Safety Study, Syngenta Crop Protection, LLC, Syngenta File No. VV-951659

4 Manufacturing release specifications

4.1 Summary of manufacturing release specifications

Table 10. Summary of manufacturing release specifications.

Description: The material shall consist of a homogeneous mixture of isocycloseram active ingredient, together with filler(s) and any other necessary formulants. It shall be in the form of a fine powder, free from visible extraneous matter and hard lumps, contained in a water-soluble bag.

ID	Property	Method	Declared value
1*	Sub-sampling	See Appendix	
2	Isocycloseram identity	CIPAC/5349	
3	Isocycloseram content	CIPAC/5349	15 % w/w (± 6% of the declared content)
4	pH range	CIPAC MT 75.3, CIPAC Handbook J, p.131, 2000	6 to 9 (1% deionized water)
5	Wet sieve test	CIPAC MT 185.1, Handbook K, p. 149, 2003	Maximum: 2% retained on a 75 µm test sieve
6*	Suspensibility	CIPAC MT 184.1, CIPAC Handbook P, p. 245, 2021	The suspensibility (chemical assay) should be minimum 35% in CIPAC Standard water D, after 30 min. If the suspensibility is determined to be below 60 %, the re-suspensibility (chemical assay) should be minimum 95% in CIPAC Standard water D, after 30 min.
7*	Persistent foam	CIPAC MT 47.3, CIPAC Handbook O, p. 177, 2017	Maximum: 40 ml after 1 min in CIPAC Standard water D
8	Wettability	CIPAC MT 53.3, CIPAC Handbook F, p.164, 1995	The formulation shall be completely wetted in 60 seconds without swirling in CIPAC Standard water D
9*	Dissolution of the bag	CIPAC MT 176, CIPAC Handbook F, p.440, 1995	Flow time of the suspension: maximum 30 sec. in CIPAC Standard water D

*Indicates that additional information is available in Appendix 2.

Manufacturers are expected to rely on the information above as part of a QC management plan and for validation of product quality when released. To the extent required, Certificates of Analysis to support the release of products should present results for the attributes identified in the above table.

4.2 Storage

Accelerated storage stability data were generated as per CIPAC MT 46.4 on SOVRENTA 15WP. Test samples were stored for 2 weeks at 54 °C. No significant differences were observed and recorded among the properties of the product after accelerated storage stability test conditions.

Products should be stored and transported in accordance with the conditions recommended by the manufacturer.

Where products that have been subjected to prolonged storage, adverse conditions, or in opened/damaged packaging/containers, product testing is recommended to assess its suitability for use.

Appendix 1. Summary of available data considered in Module 3

Batches used to generate the physical/chemical data

Batch number	Date of production	Description
1222763	October 2021	Off white solid
1257375	July 2022	Off white solid
1257373	July 2022	Off white solid

Appendix 2. Manufacturing release specifications: Methods and notes

Sub-sampling

Lay the bag on a bench and carefully open one side of the bag with a cutter, taking care not to damage the seals. Transfer the contents of the bag into a suitable flask. This material shall be used to carry out the tests for:

- active ingredient identity
- active ingredient content
- pH range
- wettability
- wet sieve test
- suspensibility
- persistent foam
- dissolution of the bag

The bag is then opened on three sides, completely cleaned from adhering powder by brushing or suction and weighed to the nearest 0.01 g. Aliquots of an aqueous solution of the bag material shall be used in the suspensibility and persistent foam tests.
In the case of delay with the above tests, the bag shall be stored in a watertight container (glass bottle or equivalent) to avoid any change in its properties.

Attribute 6: Suspensibility

The mass of sample to be used in the test should be specified at the highest rate recommended for SOVRENTA 15WP (3.3% or 3.3 g test item in 100 ml). The test is to be conducted in CIPAC Standard water D.

1.6 % water-soluble bag material (relative to the amount of formulation) must be dissolved in the water prior to performing this test.

A minimum of 35 % of the isocycloseram content shall be in suspension after 30 min in CIPAC Standard water D at 30 ± 2 °C (chemical assay).

If the suspensibility is determined to be below 60 %, then the re-suspensibility (chemical assay) should be determined. A minimum of 95 % of the isocycloseram content found in the wettable powder shall be in suspension after 30 min in CIPAC Standard water D at 30 ± 2 °C.

Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric and solvent extraction determination may be used on a routine basis provided that these methods have been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the "referee method".

Attributes 6 and 7: Suspensibility and Persistent foam

The procedure for adding the bag material to the solution for the suspensibility and persistent foam tests should be as follows:
Prepare a stock solution of the bag material (1 mg/ml) by weighing a sample (1 g) of the bag (excluding sealed parts) to the nearest mg. Dissolve this sample by stirring in the standard water used for the tests to give a final volume of 1 L (the stock solution can be prepared differently if desired, as long as the stock solution has a prepared concentration of 1 mg/ml). Store the stock solution in a stoppered bottle before use.
Calculate the volume (V ml) of the stock solution of the bag to be added to the test suspension of the wettable powder according to the following equation:
$V(ml) = X \times 1000B/W$
Where: B (g) = weight of the emptied and cleaned bag
W (g) = nominal weight of the WP contained in the bag
X (g) = weight of the WP sample used in the test

Attribute 7: Persistent foam

The mass of sample to be used in the test should be specified at the highest rate recommended for SOVRENTA 15WP (3.3% or 3.3 g test item in 100 ml). The test is to be conducted in CIPAC Standard water D.

1.6 % water-soluble bag material (relative to the amount of formulation) must be dissolved in the CIPAC Standard water D prior to performing this test.

Attribute 9: Dissolution of the bag

The sampling of the bag for the dissolution test should be as follows:
Lay the empty cleaned bag in its original configuration (double layer). Delineate and then cut up a test sample including part of the upper seal (5 cm) and symmetrically including the vertical seal (10 cm). If the size of the bag is less than this dimension, use the whole bag.
Carry out the dissolution test immediately to avoid any modification of the sample.