World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

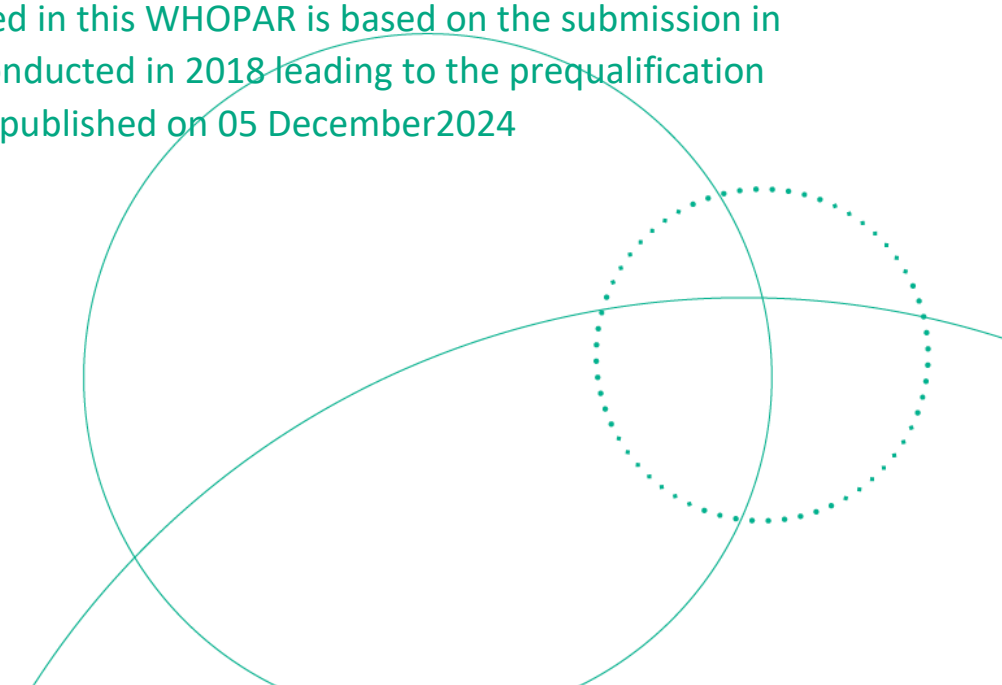
WHO Public Assessment Report: WHOPAR Part 3

Sylando 240 SC
(BASF Agro B.V. Arnhem (NL) Freienbach Branch)

P-00136

Quality Assessment

The information presented in this WHOPAR is based on the submission in 2018 and assessment conducted in 2018 leading to the prequalification decision published on 05 December2024



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1 Chemical and physical data

1.1 Chemical and physical properties

Sylando 240SC is a suspension concentrate containing 240 g/L chlorfenapyr (21.45%) as the active ingredient.

Data on the chemical and physical properties of the active ingredient and the product Sylando 240 SC were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP) and are considered complete. Product specific properties are summarized in Table 1. These summary results are based on the analysis of batches 0134S03CD, R1454-171 and AC 8053-139.

Table 1. Chemical and physical properties for Sylando 240 SC

Data requirement	Study number	Test method ID	Results
Chlorfenapyr content (Batch R1454-171)	91005/A	Chlorfenapyr HPLC method CIPAC Handbook O p 22, 2017	Chlorfenapyr content: 245.2 g/L
pH (Batch 0134S03CD)	2012/7004530 BAS 306 02 I: Determination of Physical Properties	CIPAC MT 75.3, CIPAC Handbook J, p. 131, 2000	Measured: pH neat: 6.98 pH 1% water solution: 6.19
Pourability (Batch 0134S03CD)	2012/7004530 BAS 306 02 I: Determination of Physical Properties.	CIPAC MT 148.1, CIPAC Handbook J, p.133, 2000	Result: 1.64%
Wet sieve test (Batch 0134S03CD)	2012/7004530 BAS 306 02 I: Determination of Physical Properties.	CIPAC MT 185, CIPAC Handbook K, p.149, 2003	Residue: 0.00%
Suspensibility (Batch 0134S03CD)	2012/7004530 BAS 306 02 I: Determination of Physical Properties.	MT 184, CIPAC Handbook K, p.142, 2003	Result: 93.2%
Persistent foam (Batch 0134S03CD)	2012/7004530 BAS 306 02 I: Determination of Physical Properties.	CIPAC MT 47.3, CIPAC Handbook O, p.177, 2017	Persistent foam: 8 ml
Spontaneity of dispersion (Batch 0134S03CD)	2012/7004530 BAS 306 02 I: Determination of Physical Properties.	CIPAC MT 160, CIPAC Handbook F, p.391, 1995	Result: 94.25%
Stability at elevated temperature (12 weeks at 37 °C)	91005/A	CIPAC MT 46.3, CIPAC Handbook J, p.128, 2000	All results were in accordance with WHO/FAO specifications. The tested product was AC303,630 240 g/L SC

Table 1. Chemical and physical properties for Sylando 240 SC			
Data requirement	**Study number**	**Test method ID**	**Results**
product: AC 303,630 240 g/L SC (Batch R1454-171)			A single batch was tested R1454-171.
Stability at 0°C for 3 months product: AC 303630 2 SC (Lot AC 8053-139)	F-1448	CIPAC MT 39.3, CIPAC Handbook J, p.126, 2000	No study was attached, just a copy of the summaries. According to the summaries all results were in accordance with WHO/FAO specifications

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 Sylando 240 SC 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 Sylando 240 SC	
Description of starting material	Chlorfenapyr technical, declared minimum content 940 g/kg Inert ingredients
Declaration of product formulation	Included in the confidential business information.
Production / formulation process	Chlorfenapyr technical active ingredient is mixed with the other formulation components. The mixture is milled to the desired particle size followed by viscosity adjustment. 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	Chlorfenapyr: 240 g/L, acceptable limits 225.6 g/L to 254.4 g/L

1.3 Enforcement analytical method

Table 3. Details of the analytical method used to determine chlorfenapyr in Sylando 240 SC	
Quantification of Chlorfenapyr	570/SC/M/3, CIPAC Handbook O, p.26, 2017

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 Sylando 240 SC on Anopheline mosquito species were submitted to WHO as part of the prequalification dossier.

2.1 Laboratory Studies

Data on characterization of the active ingredient in Sylando 240 SC 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 Sylando 240 SC AI

One study was presented to characterize the properties of the active ingredient and determine the LC_{50} and LC_{99}, using technical grade chlorfenapyr. This study was conducted by WHOPES under the WHOPES programme and the raw data for the study were not available for assessment by PQT/VCP.

Three *An. gambiae* test systems were used in the study: *An. gambiae* Kisumu, a colonised strain that is susceptible to insecticides; *An. gambiae* VK-Per, which is homozygous for *kdr* mutation through selection pressure with permethrin, and *An. gambiae* Acer-Kis, which is a Kisumu strain that has been introgressed with *Ace1R* allele through backcrossing.

The concentrations of chlorfenapyr used in the laboratory study to determine the intrinsic insecticidal activity of the active ingredient were determined from previous preliminary experiments and were not presented in the study report. The LD_{50} and LD_{99} results as determined using three *Anopheles gambiae* test systems and topical applications of technical grade chlorfenapyr are presented in Table 4. A significant reduction in the LD_{50} and LD_{90} was observed in the two resistant strains between 24- and 72-hours post-exposure, suggesting that the chlorfenapyr was more toxic after 72 hours to these strains.

Evaluations of the diagnostic concentration of chlorfenapyr using the *An. gambiae* Kisumu test system were conducted using a tentative concentration of 5% (2.5% also tested) with a two-hour exposure and 48 hour holding time, which had been previously established by WHO. These results are presented in Table 5. A significant increase in mortality was recorded between 24 and 48 hours at both doses (2.5%: Chi2 = 35.6, P<0.0001; 5%: Chi2 =20.7, P<0.0001).

Irritant and/or excito-repellent properties were investigated using the *An. gambiae* Kisumu test system and the tentative diagnostic concentration of 5%. The results are presented in Table 6. No irritant effect was observed.

Table 4. LD_{50} and LD_{95} concentrations of chlorfenapyr as determined using topical applications of technical grade insecticide against three *Anopheles gambiae* complex test systems (mean of three replicates)

Mosquito Strain	Timepoint	LD_{50} ng/mg (95% CI)	LD_{95} ng/mg (95% CI)
An. gambiae (Kisumu)	24h	2.19 (1.93, 2.43)	6.11 (5.17, 7.81)
An. gambiae (Kisumu)	48h	1.68 (1.41, 1.91)	4.68 (3.94, 6.02)
An. gambiae (Kisumu)	72h	1.66 (1.33, 1.98)	7.00 (5.50, 10.10)
An. gambiae (VK-Per)	24h	2.33 (2.08, 2.60)	7.35 (5.97, 9.98)
An. gambiae (VK-Per)	48h	2.02 (1.83, 2.20)	4.67 (4.07, 5.65)
An. gambiae (VK-Per)	72h	1.72 (1.47, 2.00)	4.53 (3.72, 5.85)
An. gambiae (Acer-Kis)	24h	3.10 (2.72, 3.47)	8.18 (6.73, 11.00)
An. gambiae (Acer-Kis)	48h	2.18 (1.88, 2.46)	4.91 (4.14, 6.34)
An. gambiae (Acer-Kis)	72h	1.66 (1.43, 1.86)	4.19 (3.57, 5.36)

Table 5. Twenty-four and 48-hour mortality of *An. gambiae* Kisumu strain tested in WHO cylinder tests using 2.5% and 5% chlorfenapyr.

Chlorfenapyr concentration	n	Mortality	
		M24 (%, 95% CI)	M48 (%, 95% CI)
2.5%	297	62.5 (50.9, 74.1)	84.3 (75.8, 84.9)
5%	303	71.3 (63.0, 79.6)	86.7 (79.8, 93.6)

Table 6. Time to first take off 50 (FT_{50}) and 90 (FT_{90}) of *An. gambiae* Kisumu strain tested using filter papers treated with 5% chlorfenapyr and 0.75% permethrin.

Insecticide	n	Time to first take off	
		FT_{50} (seconds, 95% CI)	FT_{90} (seconds, 95% CI)
Untreated paper	52	15.35 (11.50, 20.59)	590.5 (318.75, 1,381.27)
Chlorfenapyr 5%	51	15.33 (11.83, 19.79)	309.29 (186.88, 621.14)
Permethrin 0.75%	50	4.07 (3.38, 4.84)	18.38 (13.97, 27.11)

2.2 Entomological characterisation conclusions

The submitted laboratory studies characterize the intrinsic insecticidal properties of the AI, and present evaluations of the diagnostic concentration and irritant properties of the AI. Significantly higher mortality was observed at 72-hours post-exposure in pyrethroid resistant test systems. No irritant effects of the AI were observed.

Studies to evaluate the potential for cross-resistance between pyrethroid insecticides and to characterise the residual efficacy on various substrates were not presented.

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/entomological 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 7. 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**
2012/7004530	BAS 306 02 I: Determination of Physical Properties.
91005/A	Generation of Physical/Chemical Stability Data on AC 303,240 240g/l SC Packed in HDPE
F-1448	AC 303630 2SC: Cold temperature Stability (non GLP report)
DOC/LIN/IRD/07/11	Intrinsic toxicity and irritant properties of chlorfenapyr against *Anopheles gambiae* according to WHOPES Phase I protocols
Studies that were not used to inform decision making	
Study number	**Study title**
Manuscript	Chlorfenapyr: a new insecticide with novel mode of action can control pyrethroid resistant malaria vectors
Manuscript	Evaluation of the pyrrole insecticide chlorfenapyr for the control of *Culex quinquefasciatus* Say
Manuscript	Chlorfenapyr: A pyrrole insecticide for the control of pyrethroid or DDT resistant *Anopheles gambiae* (Diptera: Culicidae) mosquitoes
Manuscript	Evaluation of the pyrrole insecticide chlorfenapyr against pyrethroid resistant and susceptible *Anopheles funestus* (Diptera: Culicidae)

4 Manufacturing release specifications

4.1 Summary of manufacturing release specifications

Table 8. Summary of manufacturing release specifications			
Description: The material shall consist of a suspension of fine particles of technical chlorfenapyr, complying with the requirements of WHO specification 570/TC, in the form of off-white to tan, mildly sweet-smelling liquid, in an aqueous phase together with suitable formulants. After gentle agitation, the material shall be homogeneous and suitable for further dilution in water.			
ID	**Property**	**Method**	**Declared value**
1	Chlorfenapyr identity	Chlorfenapyr HPLC method CIPAC Handbook O p 22, 2017	
2	Chlorfenapyr content	Chlorfenapyr HPLC method CIPAC Handbook O p 22, 2017	240 g/L ± 6% acceptable tolerance is 225.6 to 254.4 g/L
3	Relevant impurities	Not applicable	No relevant impurities
4	pH range	CIPAC MT 75.3, CIPAC Handbook J, p.131, 2000	6.98 pH range: 6.0 to 8.0 at 1 % in CIPAC water D
5	Pourability	CIPAC MT 148, CIPAC Handbook F, p. 348	1.64% Maximum "residue": 5%
6	Spontaneity of dispersion	CIPAC MT 160, CIPAC Handbook F, p.391, 1995	94.25 % Minimum: 80% after 5 min in CIPAC Standard Water D at 30 ± 2°C.
7	Wet sieve test	CIPAC MT 185, CIPAC Handbook K, p.149, 2003	Residue: 0.00% Maximum: 2% retained on a 75 µm test sieve

8	Suspensibility	CIPAC MT 184, CIPAC Handbook K, p.142, 2003	93.2% Minimum: 70% after 30 minutes in CIPAC Standard Water D at 25 ± 5°C
9	Persistent foam	CIPAC MT 47.2 CIPAC Handbook F, p.152	8 ml Maximum: 50 ml after 1 min.

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 46.3 on Sylando 240 SC**.** Test samples were stored for 12 weeks at 35 ± 2°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	Formulation	Uses
0134S03CD	15.08.2012	BAS 306 021 SC	BAS 306 021 Determination of Physical Properties
R1454-171	24.03.1997	AC 303,630 240 g/l SC	Storage stability 12 weeks at 35 ± 2°C
AC 8053-139	19.05.2000	AC 303630 2 SC	Cold temperature stability

Appendix 2. Manufacturing release specifications: Methods and notes

Description

Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, suspension concentrates usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom. Therefore, before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example by inverting the closed container several times). Large containers must be opened and stirred adequately. After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer "cake" is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a laboratory sample taken after the recommended homogenization procedure.

Attribute 2: Chlorfenapyr content

The chlorfenapyr content shall be declared (240 g/l at 20 ± 2ºC), and when determined, the average measured content shall not differ from that declared by more than ± 6%.
Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre and in calculation of the active ingredient content (in g/l) if methods other than MT 3.3 are used. If the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

Attribute 4: pH-range

The pH value of a mixture of a sample with water or of an undiluted aqueous formulation is determined by means of a pH meter and an electrode system. The pH meter is calibrated at pH 4.00 and 7.00. Measurements made of the 1% dilution and neat sample.

Attribute 5: Pourability

The method is designed to provide information on the pourability of suspension concentrate formulations. The sample is allowed to stand for 24 hours. Then after standard pouring, the amount of residue is determined gravimetrically. The 500 ml cylinder is then rinsed and the residue determined.

Attribute 6: Spontaneity of dispersion

Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method may be used on a routine basis provided that it has been shown to give results equal to those of chemical assay. In case of dispute, chemical assay shall be the referee method.

Attribute 7: Wet sieve test

This test detects coarse particles (e.g. caused by crystal growth) or agglomerates (crust formation) or extraneous materials, which could cause blockage of spray nozzles or filters in the spray tank.
Determination of oversize particles on a 75 µm sieve in a 10 g sample under running water.
An aqueous dispersion of the test sample is prepared, poured through a 75 µm sieve, and rinsed using a low volume of water from a re-circulation reservoir. The residue remaining on the sieve is quantified.

Attribute 8: Suspensibility

Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method may be used on a routine basis provided that it has been shown to give results equal to those of chemical assay. In case of dispute, chemical assay shall be the referee method.
The formulation was tested at 1.5% and 2.14% concentration in CIPAC water D.
The mass in the sediment at the bottom 25 ml of 250 ml cylinder was determined gravimetrically.
A suspension of known concentration in CIPAC Standard Water D was prepared, placed in a prescribed measuring cylinder at a constant temperature, and allowed to remain undisturbed for a specified time. The top 9/10ths are drawn off and the remaining 1/10th is then assayed either chemically, gravimetrically, or bysolvent extraction, and the suspensibility calculated.

Attribute 9: Persistent foam

The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D at 25 ± 5°.
The formulation was tested at 0.4% concentration in CIPAC water D.
The specified amount of test substance was added to the standard water in 100 mL graduated cylinder, inverted 30 times. Volume of foam was noted after 10 sec, 1 min, 3 min, and 12 min.