World Health Organization

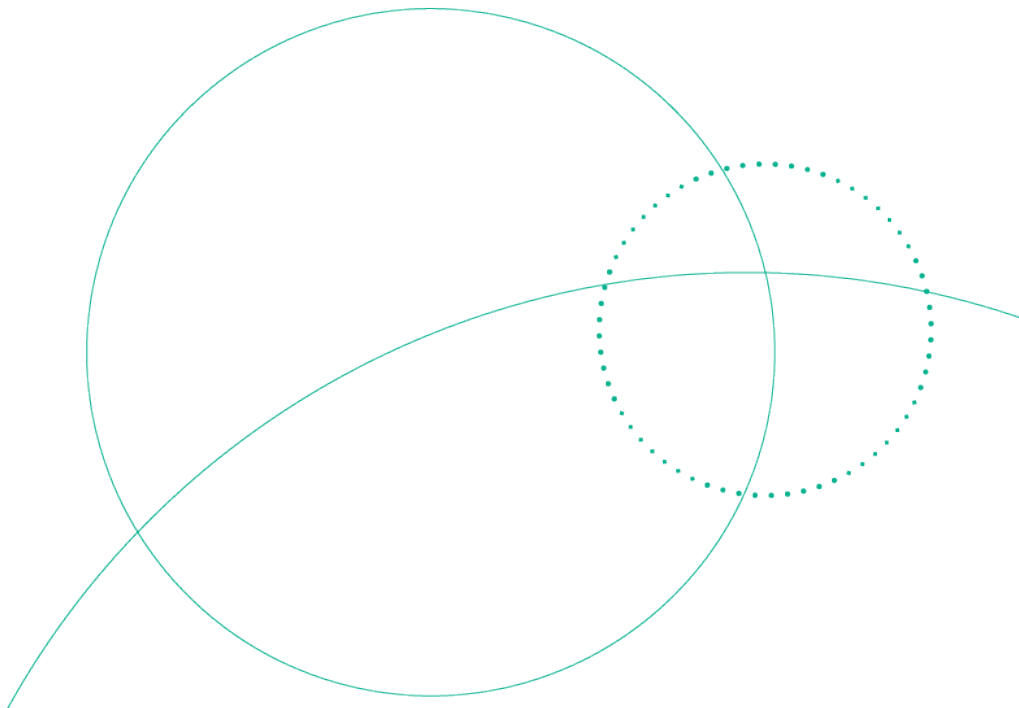
WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: Change assessment

Olyset Plus
(Sumitomo Chemical Co., Ltd) 001-005

Long-term community studies assessment

The information presented in this WHOPAR is based on the submission of WHOPES Phase III studies in 2020 following the conversion process implemented in 2018 resulting in the inclusion of the product on the list of prequalified VCPs on the 29th January 2018.



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1. Introduction

The primary purpose for the use of a pesticide is the control of a pest, including disease transmitting vectors. Vector control tools, including formulated pesticides, which provide effective management or control of vectors, may be used as part of a resistance management programme. Vector control products for use in public health are a component of Integrated Vector Management (IVM), which is a programme that relies on a suite of diverse interventions and implementations of best practices to manage the vector and chemical/behavioural resistance.

Olyset Plus is an ITN incorporated with 20 g AI/kg permethrin and 10 g AI/kg of the synergist piperonyl butoxide (PBO). The product is intended to provide personal and community protection from Anopheline mosquitoes as part of malaria control programmes. The premise of the combination of the insecticide and the synergist is that the permethrin insecticidal activity provides knockdown and/or kill of mosquitoes and the PBO inhibits mixed function oxidases implicated in resistance in pyrethroid resistant *Anopheles spp*. malaria vectors.

Evidence for the efficacy of Olyset Plus was generated under the WHOPES programme, and the product was converted to a prequalified product as part of the establishment of the prequalification programme in 2018. A full prequalification efficacy assessment has not been conducted for this product.

Community studies to characterise the performance of Olyset Plus under operational conditions using bioassays to characterise the availability of active ingredients (AI) and the insecticidal effect of the fabric of the ITN on Anopheline mosquitoes at selected durations of operational use were conducted under the WHOPES programme and submitted for incorporation in the available knowledge base of the product to WHO as a post-prequalification change application (PPQC2020-024).

2. Long-term community studies

Studies conducted in community settings include the investigation of endpoints other than mortality, knockdown and blood-feeding inhibition, for example the community acceptance, fabric integrity and attrition rate of the ITN under investigation. Based on the existing requirements and established decision framework, mosquito knockdown and mortality are considered the primary endpoints for assessment. Therefore, results for these are included within the summaries of these studies. Calculations of blood-feeding inhibition were also included for further entomological characterization of the product.

2.1 Operational studies and supplementary bioassays

Data on the operational performance of Olyset Plus in long-term community studies were provided. These data were obtained from studies conducted according to established standards. These summary results are based on ITNs drawn from batch P2903BAS.

Two long-term community studies were presented to evaluate the operational performance of Olyset Plus, in India and Kenya, conducted in 2014-2017. Both studies were conducted as prospective, household-randomised trials. The endpoints used to evaluate bioavailability were 60-minute post-exposure knockdown and 24-hour mortality in cone tests and 24-hour mortality and blood-feeding inhibition in tunnel tests, and in bioassays Olyset Plus was considered to meet the WHO requirements for community studies if, after three years, at least

80% of sampled ITNs met the criteria of >95% KD or 80% mortality in cone tests and/or >80% mortality or >90% blood-feeding inhibition in tunnel tests.

The negative control for bioassays was untreated net. In the household-randomised trials, the positive control was a prequalified product treated with 2% w/w permethrin, hereafter referred to as PC1.

One thousand, three hundred and fifty-five Olyset Plus ITNs were distributed in the study in India to 460 households and 1,562 Olyset Plus ITNs were distributed in the study in Kenya. A randomised sampled of thirty ITNs were sampled per study arm at the baseline of each study, and at pre-determined time points of 6, 12, 18, 24 and 30 months. At the conclusion of the study (36 months), fifty ITNs were sampled from each study arm. Sampled ITNs were subject to destructive sampling and the sampled fabric pieces were used in bioassays to determine the bioavailability of the treatments on the fabric and analysed for chemical content using the high-performance liquid chromatography (HPLC) method referenced in the product specifications. WHO cone tests and tunnel tests were the experimental methods used in bioavailability experiments.

In bioassays, the product was tested against pyrethroid susceptible colonised mosquitoes of: *An. culicifacies* in India and *An. gambiae* s.s. Kisumu strain in Kenya. The insecticide resistance status of the vector population in the study sites in India was characterised yearly using F1 mosquitoes; this population demonstrated between 63% and 92% mortality following exposure to the diagnostic dose of permethrin.

The results from bioavailability experiments are presented in Table 1, presented as the proportion of sampled ITNs at each time point that met the current WHO criteria for bioassays. In the study in India, greater than 80% of Olyset Plus ITNs sampled from the community study sites after three years of routine household usage conditions met the applicable WHO bioassay criteria for determining the bioavailability of ITN treatments, when tested against pyrethroid susceptible mosquito strains. In the study in Kenya, 42% of Olyset Plus ITNs sampled from the community study sites after three years of routine household usage conditions met the applicable WHO bioassay criteria for determining the bioavailability of ITN treatments, when tested against pyrethroid susceptible mosquito strains.

2.1.1 Chemical characterization

Data on the permethrin and piperonyl butoxide content of sampled ITNs in long-term community studies conducted in Kenya and India were provided. The data were collected at the following timepoints: baseline, 12-, 24- and 36- months post-net distribution.

A summary of the chemical characterization data is presented in Table 2. The chemical analysis of permethrin content in PC1 and Olyset Plus at the baseline were within the manufacturer's specifications for all study sites. The mean PBO content in Olyset Plus at the baseline was also within manufacturer's specifications for all study sites.

Table 1. Proportion of sampled ITNs in long-term community studies conducted in India and Kenya that met the applicable WHO criteria for demonstration of bioavailability in laboratory bioassays (>95% KD or 80% mortality in cone tests and/or >80% mortality or >90% blood-feeding inhibition in tunnel tests).

Product	Number of sampled ITNs and the proportion passing bioavailability criteria	Study timepoint						
		Baseline	6	12	18	24	30	36
India (*An. culicifacies*)								
Olyset Plus	Sampled ITNs	30	30	30	30	30	30	50
	Proportion passed (%)	100	100	100	100	96.7	100	100
PC1	Sampled ITNs	30	30	30	30	30	30	50
	Proportion passed (%)	100	100	100	100	83.3	100	100
Kenya (*An. gambiae* s.s. Kisumu strain)								
Olyset Plus	Sampled ITNs	30	30	29	29	30	31	50
	Proportion passed (%)	100	96.7	93.3	86.7	76.7	70	42
PC1	Sampled ITNs	30	30	30	30	30	29	50
	Proportion passed (%)	100	93.3	83.3	73.3	66.7	63.3	36

Table 2. AI content of sampled ITNs in long-term community studies conducted in Kenya and India.

Net and fabric type	AI content	Study timepoint			
		Baseline	12	24	36
Kenya					
Olyset Plus	**Number of net samples**	30	30	30	49
	Mean Permethrin content (g/kg)	18.40	11.70	11.10	8.80
	RSD (%)	2.20			
	95% CI	(18.3-18.6)	(10.6-12.7)	(10.2-12.0)	(7.9-9.7)
	Permethrin content lost (%)	-	37.00	40.00	52.00
	Mean PBO content (g/kg)	8.98	3.01	1.70	1.16
	RSD (%)				
	95% CI	(8.86-9.10)	(2.30-3.80)	(1.20-2.20)	(0.8-1.5)
	PBO content lost (%)	-	84.00	91.00	94.00
PC1	**Number of net samples**	30	30	30	50
	Mean Permethrin content (g/kg)	19.60	16.50	15.90	14.80
	RSD (%)	1.20			
	95% CI	(19.5-19.7)	(16.0-17.0)	(15.1-16.7)	(13.9-15.7)
	Permethrin content lost (%)	-	11.00	14.00	20.00
India					
Olyset Plus	**Number of net samples**	30	30	30	50
	Mean Permethrin content (g/kg)	19.00	14.14	12.30	10.50
	RSD (%)	1.90	12.10	24.00	29.00
	95% CI	0.14	0.64	1.10	0.90
	Permethrin content lost (%)				
	Mean PBO content (g/kg)	10.11	3.88	2.26	1.00
	RSD (%)	2.20	44.80	95.00	135.00
	95% CI	0.08	0.65	0.84	0.50
	PBO content lost (%)				
PC1	**Number of net samples**	30	30	30	50
	Mean Permethrin content (g/kg)	19.86	17.12	16.50	14.40
	RSD (%)	1.40	6.60	11.20	19.00
	95% CI	0.10	0.42	0.70	0.80
	Permethrin content lost (%)				

* Between net variation, expressed as the relative standard deviation (RSD)

2.2 Operational studies and chemical characterisation conclusions

The submitted long-term community studies demonstrate that the bioavailability of sampled Olyset Plus ITNs after three years of routine household use was sustained against pyrethroid susceptible *Anopheles spp.* using the cone and tunnel tests in the study in India. The permethrin and PBO content of the distributed ITNs were within the manufacturer's specifications at baseline in Kenya and India. In Kenya, at 12 months post-distribution, the permethrin content of sampled nets was between 63.6% of the baseline content; at 24 months and 36 months post-distribution the content was 60.3% and 47.8% of the baseline content, respectively. The PBO content of sampled ITNs was 33.5% of the baseline content at 12 months, 18.9% at 24 months and 12.9% at 36 months. In India, at 12 months post-distribution, the permethrin content of sampled nets was 74.4% of the baseline content; at 24 months and 36 months post-distribution the content was 64.7% and 55.3% of the baseline content, respectively. The PBO content of sampled ITNs was 38.4% of the baseline content at 12 months, 22.4% at 24 months and 9.9% at 36 months.

3. Long-term community studies conclusions

The data assessed were generated in accordance with the WHOPES programme and oversight. The studies were conducted in accordance with the WHOPES requirements at the time of initiation of the study. The conclusion of the studies and submission of reports cut across the transition from the WHOPES programme to the PQ programme, resulting in the need for PQ to integrate the results from these studies into the knowledge base for the product. The results presented in this document are a summary of the available information on the performance of the product in operational settings.