Interceptor® G2 –
the second-generation net to control insecticide resistant mosquitoes
Introduction and background

The best method to overcome malaria is to prevent it. Bed nets as physical barriers against mosquitoes have been used for centuries even dating back to the ancient Egypt. Treatment of bed nets with insecticides by dipping them in water baths containing the insecticide has been performed since the 1980s. The application of insecticide helped to control mosquitoes in addition to providing personal protection, thus disrupting the malaria transmission. This concept was improved beginning of the 21st century by the development of long-lasting insecticide-treated nets (LNs) making them wash proof and more evenly treated. The new LNs provided longer efficacy, are easy to handle and safe to the user as no on the spot treatment and handling of chemicals is needed any more.

In comparison to other Public Health interventions for malaria prevention, such as Indoor Residual Spray (IRS), it also empowers the individual to participate personally in the protection against malaria as LNs are tangible and visible. This has made LNs a huge success in the malaria prevention as an astonishing 1.4 bn LNs have been distributed globally from 2004 to 2016.3 Thereof 1.2 bn were distributed in Sub-Saharan Africa, where still 90% of the 212 million new cases of malaria worldwide in 2015 occurred.2 It is estimated that the distribution of these LNs in Sub-Saharan Africa averted 457 million cases (uncertainty interval: 418–484 million cases)3.

The golden standard and the only insecticide class used so far to treat bed nets are pyrethroids. The pyrethroids are excellent for the use on LNs based on the following properties:

- Low toxicity to humans, safe to use
- Cheap active ingredient (a.i.) readily available
- Excellent efficacy against mosquitoes in general (neurotoxic with fast killing results; effective knock-down providing personal protection; act as a repellent)

In addition, the chemical-physical profile of pyrethroids is perfect for the application on LNs:

- Solid at room temperature
- Very low solubility in water so the active ingredient survives 20 washes
- Very low vapor pressure minimizing losses during production and use
- Easy to handle in production of LNs, coated PET as well as incorporated PE
- Standard textile production processes suitable without losing active ingredient

Innovative second-generation mosquito net Interceptor® G2

- Innovative active ingredient system containing a combination of chlorfenapyr and alpha-cypermethrin
- New mode of action provided by chlorfenapyr
- Highly effective against insecticide resistant mosquitoes
- Based on well proven BASF technology used in Interceptor® mosquito nets
- Ready and safe to use
- Long-lasting efficacy
- WHOPES interim recommendation
- PQ listed

Content

Introduction and background 3
Insecticide resistance 4
Chlorfenapyr – a new insecticide for vector control 6
Interceptor® G2 with chlorfenapyr and alpha-cypermethrin 8
Biological efficacy of Interceptor® G2 9
What is so special about chlorfenapyr? 13
Why use Interceptor® G2? 16
Technical information 17

The best method to overcome malaria is to prevent it. Bed nets as physical barriers against mosquitoes have been used for centuries even dating back to the ancient Egypt. Treatment of bed nets with insecticides by dipping them in water baths containing the insecticide has been performed since the 1980s. The application of insecticide helped to control mosquitoes in addition to providing personal protection, thus disrupting the malaria transmission. This concept was improved beginning of the 21st century by the development of long-lasting insecticide-treated nets (LNs) making them wash proof and more evenly treated. The new LNs provided longer efficacy, are easy to handle and safe to the user as no on the spot treatment and handling of chemicals is needed any more.

In comparison to other Public Health interventions for malaria prevention, such as Indoor Residual Spray (IRS), it also empowers the individual to participate personally in the protection against malaria as LNs are tangible and visible. This has made LNs a huge success in the malaria prevention as an astonishing 1.4 bn LNs have been distributed globally from 2004 to 2016.3 Thereof 1.2 bn were distributed in Sub-Saharan Africa, where still 90% of the 212 million new cases of malaria worldwide in 2015 occurred.2 It is estimated that the distribution of these LNs in Sub-Saharan Africa averted 457 million cases (uncertainty interval: 418–484 million cases)3.

The golden standard and the only insecticide class used so far to treat bed nets are pyrethroids. The pyrethroids are excellent for the use on LNs based on the following properties:

- Low toxicity to humans, safe to use
- Cheap active ingredient (a.i.) readily available
- Excellent efficacy against mosquitoes in general (neurotoxic with fast killing results; effective knock-down providing personal protection; act as a repellent)

In addition, the chemical-physical profile of pyrethroids is perfect for the application on LNs:

- Solid at room temperature
- Very low solubility in water so the active ingredient survives 20 washes
- Very low vapor pressure minimizing losses during production and use
- Easy to handle in production of LNs, coated PET as well as incorporated PE
- Standard textile production processes suitable without losing active ingredient

Innovative second-generation mosquito net Interceptor® G2

- Innovative active ingredient system containing a combination of chlorfenapyr and alpha-cypermethrin
- New mode of action provided by chlorfenapyr
- Highly effective against insecticide resistant mosquitoes
- Based on well proven BASF technology used in Interceptor® mosquito nets
- Ready and safe to use
- Long-lasting efficacy
- WHOPES interim recommendation
- PQ listed

Introduction and background
Insecticide resistance

This success story of pyrethroids on LNs is one of the reasons for the development of insecticide resistance in mosquitoes on a global level and more intensely in the main malaria region Sub-Saharan Africa (Figure 2). Of the 42 African countries deploying LNs, pyrethroid resistance was reported in 29 countries in 2010–2015. At the same time the application of other insecticide classes as organochlorines, organophosphates and carbamates in other Public Health interventions like IRS increases the danger of the development of insecticide resistance (Figure 1).

Leading experts consider this situation a threat to malaria control, especially with the limited tool box of Public Health insecticide classes available. They urgently ask for the introduction of new active ingredients with different mode of actions (MoA) – especially for LNs, where the dependence on one insecticide class is the biggest risk.

The Global Plan for Insecticide Resistance Management (GPIRM) recommends the use of insecticide mixtures as one of several strategies for successful Insecticide Resistance Management (IRM). This strategy can have a dramatic effect on populations of resistant vectors by exposing them to multiple insecticides. LN products containing a mixture of novel active ingredients could be effective in delaying the evolution of insecticide resistance.

Figure 2: Trends in pyrethroid resistance for Anopheles

Figure 1: Development and status of insecticide resistance

HARSH SELECTION: HOW INSECTICIDE RESISTANCE INCREASES IN THE MOSQUITO POPULATION

The naturally occurring genetic mutations which allow for insecticide resistance in mosquitoes are rare.

...and the resistant population grows.

When mosquitoes are exposed to insecticides in treated bed nets, sprays and other insect controls...

...the susceptible are killed but the survivors go on to reproduce, transferring the genetic changes that confer resistance to their offspring...

...so the resistant mosquitoes eventually become numerous within the population.

WITH THEIR RELATIVELY SHORT LIFE CYCLE AND HIGH RATES OF REPRODUCTION, MOSQUITOES ARE ABLE TO DEVELOP RESISTANCE RAPIDLY.

REPORTED INSECTICIDE RESISTANCE, 2010 – 2015

60 countries reported mosquito resistance to at least one insecticide used for malaria control.

88%

Total number of countries reporting: 73

50 countries reported mosquito resistance to two or more insecticides used for malaria control.

63%

Total number of countries reporting: 73

Source: WHO World Malaria Report 2016

The resistance heat map shows current incidents of resistance in countries across the world:
http://anopheles.irmapper.com/
Chlorfenapyr – a new insecticide for vector control

Chlorfenapyr, a pyrrole, was launched by BASF’s Crop Protection division in 1995. It is registered in more than 40 countries mainly for professional pest control use (e.g. US EPA approval for use in kitchens and food storage). It is listed in Group 13 in the IRAC MoA classification as uncoupler of oxidative phosphorylation via disruption of the proton gradient.

Development work at BASF showed that it can be repurposed for the use in Public Health as a contact insecticide to control mosquitoes.

Mode of action of chlorfenapyr

Unlike other adulticides in vector control chlorfenapyr is not neurotoxic. It owes its toxicity to disruption of cellular respiration and oxidative phosphorylation in the mitochondria. Owing to its unique mode of action, chlorfenapyr is active against insecticide resistant and susceptible mosquitoes. Evaluations performed on the mosquitoes Anopheles gambiae, Anopheles funestus, Anopheles arabiensis and Culex quinquefasciatus show no cross resistance of chlorfenapyr to mechanisms that confer resistance to standard neurotoxic insecticides as organochlorines, pyrethroids, organophosphates and carbamates.

The MoA of chlorfenapyr and its effect as an insecticide requires several steps to take place. The first step is the metabolism of parent chlorfenapyr to the active drug. Chlorfenapyr is a pro-insecticide that is activated by cytochrome P450 monooxygenases to its active metabolite CL 303268.

This active metabolite then acts by disrupting the production of ATP through oxidative phosphorylation in mitochondria of cells. It facilitates proton loss from the inside to the outside of the mitochondria via the inner mitochondrial membrane.

When uncoupled from a proton energy source the mitochondria are unable to generate ATP and the cells cease to function (Figure 4). Chlorfenapyr induces mortality up to 72 h post exposure in mosquitoes.

Table 1: Chemical and physical profile of chlorfenapyr and alpha-cypermethrin

<table>
<thead>
<tr>
<th></th>
<th>Chlorfenapyr</th>
<th>Alpha-Cypermethrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight [g/mol]</td>
<td>407.6</td>
<td>416.3</td>
</tr>
<tr>
<td>Physical state at RT</td>
<td>Solid, crystalline</td>
<td>Solid, crystalline</td>
</tr>
<tr>
<td>Melting point [°C]</td>
<td>100 – 101</td>
<td>81 – 84</td>
</tr>
<tr>
<td>Solubility in water @ 20°C [mg/L]</td>
<td>0.12</td>
<td>0.004 – 0.008</td>
</tr>
<tr>
<td>Vapor pressure @ 25°C [Pa]</td>
<td>5.4 x 10⁶</td>
<td>3.4 x 10⁻³</td>
</tr>
</tbody>
</table>

It’s important to note that piperonyl butoxide (PBO), a synergist used in other second-generation nets, is known to be an antagonist of chlorfenapyr. It blocks the P450 enzyme by which the chlorfenapyr is transformed to the active metabolite.

Chemical and physical profile of chlorfenapyr

The chemical profile of chlorfenapyr is very similar to the one of alpha-cypermethrin, one of the pyrethroids used on LN’s. Both active ingredients are solid at RT, similar in molecular weight and show a very low solubility in water which helps to retain the active ingredient after 20 washes. The very low vapor pressure of both molecules is suitable to minimize losses during production and use.
Interceptor® G2 with chlorfenapyr and alpha-cypermethrin

Interceptor® G2 is the second-generation LN developed by BASF with a combination of chlorfenapyr and alpha-cypermethrin to control insecticide resistant mosquitoes. Interceptor® G2 is a multifilament polyester net produced with a unique textile-finishing process developed by BASF’s textile technologists using a proprietary polymer system. It contains 200 mg/m² chlorfenapyr and 100 mg/m² alpha-cypermethrin.

Biological efficacy of Interceptor® G2

The design of the presented experimental hut trials (see table 2) is similar. One treatment arm contained an untreated net as negative control. Interceptor® G2 nets with an alpha-cypermethrin content of 200 mg/m² on PET unwashed as well as washed 20 times were included as positive controls representing the standard pyrethroid-only LN.

The purpose of keeping the design similar was to evaluate the vector control impact of Interceptor® G2 in settings in East and West Africa with different Anopheles species with varying resistance profile and strength.

Table 2: Overview on experimental hut trials

<table>
<thead>
<tr>
<th>Country</th>
<th>Location</th>
<th>Year</th>
<th>Nets tested</th>
<th>Target species</th>
<th>Status of insecticide resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin 1</td>
<td>Cové</td>
<td>2014</td>
<td>✘</td>
<td>An. gambiae</td>
<td>kdr mutation + metabolic oxidases</td>
</tr>
<tr>
<td>Benin 2</td>
<td>Cové</td>
<td>2015</td>
<td>✘</td>
<td>An. gambiae</td>
<td>kdr mutation + metabolic oxidases</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Bama/Vallée du Kou</td>
<td>2014</td>
<td>✘</td>
<td>An. gambiae</td>
<td>kdr mutation + metabolic suspected</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Moshi</td>
<td>2014</td>
<td>✘</td>
<td>An. arabiensis</td>
<td>pyrethroid-resistant</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Muheza</td>
<td>2015</td>
<td>✘</td>
<td>An. funestus</td>
<td>pyrethroid-resistant</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Muheza</td>
<td>2016</td>
<td>✘</td>
<td>An. funestus</td>
<td>pyrethroid-resistant</td>
</tr>
<tr>
<td>Ivory Coast</td>
<td>M'bé</td>
<td>2016</td>
<td>✘</td>
<td>An. gambiae</td>
<td>kdr mutation + metabolic; DDT, pyrethroid and carbamate resistance</td>
</tr>
</tbody>
</table>

On mosquito netting, chlorfenapyr is toxic to insecticide resistant and susceptible mosquitoes. It lacks the property of typical pyrethroid excito-repellency, crucial for reducing mosquito biting rates and providing personal protection to net users. In Interceptor® G2 the pyrethroid component alpha-cypermethrin provides excito-repellency and personal protection, whilst the chlorfenapyr component restores insecticidal activity against insecticide resistant mosquitoes.

As a consequence, the regeneration time for both ingredients has been found to be only 1 day. Also, the stability of the PET fiber is not influenced by the coating, while incorporating ingredients into polyethylene fibers might weaken their strength.

Interceptor® G2 is the first LN based on coated polyester (PET) with an a.i. other than a pyrethroid. So far, all newly developed nets with ingredients other than pyrethroids are using the technology of incorporating the ingredients in polyethylene fibers. The advantage of coating the a.i. onto the surface is that it is readily available avoiding time consuming migration of the ingredients to the surface, commonly known as regeneration time (see also Figure 5).

Figure 5: Scanning electron microscope images of Interceptor® G2 showing chorfenapyr and alpha-cypermethrin crystals on netting fibers.
Interceptor® G2 LN restored the capacity of long-lasting insecticidal nets to control highly resistant populations of An. gambiae s.l showing a corrected mortality of 71% when unwashed. The corrected mortality of 65% seen with the Interceptor® G2 after 20 washes showed that the formulation is wash resistant.

Figure 6: Mortality rates of An. gambiae s.l. in experimental huts with treated versus untreated net

Figure 7: Blood feeding rates of An. gambiae s.l. in experimental huts with treated versus untreated net

Figure 8: Mortality and blood feeding inhibition of pyrethroid resistant An. gambiae in experimental huts in Côte, Benin

Blood feeding of mosquitoes was 47–60% less with Interceptor® G2 LN and Interceptor® LN relative to the untreated net (Figure 7). There was no significant difference in blood feeding between Interceptor® G2 LN and Interceptor® LN over 20 washes. The alpha-cypermethrin component made an important contribution to blood feeding inhibition (9%F) and personal protection, as indicated by the similarity of response between the pyrethroid-only LN and the mixture LN.

Second experimental hut trial in Benin

A second study was conducted at the field station of Covié near Cotonou. The purpose of this study was to assess the efficacy of deploying a combination of unrelated insecticides against pyrethroid resistant populations of malaria vectors either as a combined non-pyrethroid IRS and pyrethroid LN intervention or as a mixture LN such as Interceptor® G2.

The design included only unwashed Interceptor® and Interceptor® G2 nets. Additionally, one treatment arm was sprayed with chlorfenapyr IRS in a dose rate of 250 mg/m². Another arm contained a combination of IRS with chlorfenapyr at 250 mg/m² and Interceptor® net with alpha-cypermethrin (200 mg/m²) (Figure 8).

Interceptor® G2 LN and the combined use of chlorfenapyr IRS and Interceptor® LN provided comparable levels of improved control of insecticide resistant malaria vectors. Where pyrethroid LNs are being used, the addition of chlorfenapyr IRS is a viable strategy for improving control in high insecticide resistant settings.

Experimental hut trial in Burkina Faso

Country-wide surveys in Burkina Faso have documented increasing levels of insecticide resistance in malaria vectors with a dramatic rise in the frequency of the kdr 1014F allele over the last decade, and the occurrence of the resistant Ace-1R 1196 allele in both An. coluzzii and An. gambiae. The study was conducted at the field station of Vallée du Kou in experimental huts. WHO susceptibility tests showed high resistance against pyrethroids of the field population in Vallée du Kou.

Interceptor® G2 unwashed and washed 20 times killed significantly more An. gambiae s.l. that entered the huts compared to Interceptor® and the untreated net (Figure 9). No significant difference between the unwashed and the 20 times washed Interceptor® G2 was observed, suggesting that these nets preserved their protective effect even after being washed 20 times. In addition, Interceptor® G2 unwashed resulted in blood feeding levels significantly lower than Interceptor® and the untreated net (Figure 10).

Figure 9: Mortality rates of An. gambiae s.l. in experimental huts with treated versus untreated net

Figure 10: Blood feeding rates of An. gambiae s.l. in experimental huts with treated versus untreated net

First experimental hut trial in Tanzania

The study was conducted at the field station near Moshi. An. arabiensis raised from larvae at the test site were resistant to alpha-cypermethrin in a standard WHO cylinder assay. There is no kdr or Ace1 in the population but elevated MFO & esterase activity has been reported and increased transcription of CYP4G16 is directly linked to pyrethroid resistance at the site.

Interceptor® G2 showed significantly superior performance to Interceptor® LN after 20 washes against free-flying pyrethroid-resistant malaria vectors in experimental huts (Figure 11).

First experimental hut trial in Tanzania
Second experimental hut trial in Tanzania

The study has been conducted at the field station of Zenet, Muheza, an area where pyrethroid-resistant An. gambiae s.s. and An. funestus s.s. predominate. An. gambiae s.s. in Muheza has established phenotypic and genotypic (kdr) resistance. Less is known of the genotypic status of An. funestus at the site but clear resistance has been shown to pyrethroids in the population at the time of the Muheza trial: 50% mortality at 24 h after exposure to 0.05% permethrin in a standard WHO cylinder bioassay.

Comparison of efficacy of unwashed nets against An. funestus (Figure 13), showed highly significant differences between the pyrethroid-only net Interceptor® and the mixture net Interceptor® G2. Washing of the nets 20 times led to no significant changes in mortality for both LNs.

Although the number of An. gambiae (Figure 14) collected was very low, this species showed a similar trend in mortality to that of An. funestus. The difference in mortality between unwashed Interceptor® LN and unwashed Interceptor® G2 was statistically significant even with the low numbers of mosquitoes observed in this particular trial.

WHOPES supervised Phase II trial in Tanzania

The findings from the second Interceptor® G2 trials at the Muheza site are consistent with the first results. Both demonstrated significantly higher mortality with Interceptor® G2 LN compared to Interceptor® LN over multiple washes and provided solid evidence that pyrethroid-resistant An. funestus from Muheza are much more strongly controlled by Interceptor® G2 than by the standard pyrethroid-only Interceptor® LN.

Figure 15: Mortality rates of wild An. funestus in experimental huts with treated versus untreated net

<table>
<thead>
<tr>
<th>Country</th>
<th>Mortality after 24 h</th>
<th>Untreated</th>
<th>Interceptor®</th>
<th>Interceptor® G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>24 h</td>
<td>10%</td>
<td>25%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>72 h</td>
<td>11%</td>
<td>26%</td>
<td>21%</td>
</tr>
<tr>
<td>Benin 1</td>
<td>24 h</td>
<td>3%</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Benin 2</td>
<td>72 h</td>
<td>5%</td>
<td>24%</td>
<td>17%</td>
</tr>
<tr>
<td>Moshi, Tanzania</td>
<td>24 h</td>
<td>0%</td>
<td>61%</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>72 h</td>
<td>0%</td>
<td>63%</td>
<td>45%</td>
</tr>
<tr>
<td>Muheza, Tanzania</td>
<td>24 h</td>
<td>9%</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>72 h</td>
<td>21%</td>
<td>37%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Table 3: Mortality after 24 h vs 72 h holding period in experimental hut trials

WHOPES supervised Phase II trial in Tanzania

The phase II trial was carried out at the field station of Zenet, Muheza, an area where pyrethroid-resistant An. gambiae s.s. and An. funestus s.s. predominate. An. gambiae s.s. in Muheza has established phenotypic and genotypic resistance. Less is known of the genotypic status of An. funestus at the site but clear resistance has been shown to pyrethroids in the population at the time of the Muheza trial: 50% mortality at 24 h after exposure to 0.05% permethrin in a standard WHO cylinder bioassay.

Figure 13: Mortality rates of An. funestus in experimental huts with treated versus untreated net

Figure 14: Mortality rates of An. gambiae s.s. in experimental huts with treated versus untreated net

Figure 15: Mortality rates of wild An. funestus in experimental huts with treated versus untreated net

Figure 16: Mortality rates of wild An. gambiae in experimental huts with treated versus untreated net

Comparison of efficacy of unwashed nets against An. funestus (Figure 13), showed highly significant differences between the pyrethroid-only net Interceptor® and the mixture net Interceptor® G2. Washing of the nets 20 times led to no significant changes in mortality for both LNs.

Although the number of An. gambiae (Figure 14) collected was very low, this species showed a similar trend in mortality to that of An. funestus. The difference in mortality between unwashed Interceptor® LN and unwashed Interceptor® G2 was statistically significant even with the low numbers of mosquitoes observed in this particular trial.

The study has been conducted at the field station of Zenet, Muheza, an area where pyrethroid-resistant An. gambiae s.s. and An. funestus s.s. predominate. An. gambiae s.s. in Muheza has established phenotypic and genotypic resistance. Less is known of the genotypic status of An. funestus at the site but clear resistance has been shown to pyrethroids in the population at the time of the Muheza trial: 50% mortality at 24 h after exposure to 0.05% permethrin in a standard WHO cylinder bioassay.

Comparison of efficacy of unwashed nets against An. funestus (Figure 13), showed highly significant differences between the pyrethroid-only net Interceptor® and the mixture net Interceptor® G2. Washing of the nets 20 times led to no significant changes in mortality for both LNs.

Although the number of An. gambiae (Figure 14) collected was very low, this species showed a similar trend in mortality to that of An. funestus. The difference in mortality between unwashed Interceptor® LN and unwashed Interceptor® G2 was statistically significant even with the low numbers of mosquitoes observed in this particular trial.

The findings from the second Interceptor® G2 trials at the Muheza site are consistent with the first results. Both demonstrated significantly higher mortality with Interceptor® G2 LN compared to Interceptor® LN over multiple washes and provided solid evidence that pyrethroid-resistant An. funestus from Muheza are much more strongly controlled by Interceptor® G2 than by the standard pyrethroid-only Interceptor® LN.

Figure 15: Mortality rates of wild An. funestus in experimental huts with treated versus untreated net

What is so special about chlorfenapyr?

Chlorfenapyr – a slow acting insecticide?

Unlike the pyrethroids and all other classes of insecticide currently recommended for adult mosquito control, the chlorfenapyr target site of activity is not the insect nervous system. Instead, chlorfenapyr acts, after being metabolized by P450 enzymes at the cellular level, by disrupting respiratory pathways and proton gradients through the uncoupling of oxidative phosphorylation within the mitochondria. Current WHO guidelines for identifying new insecticides and measuring toxic activity against malaria vectors are based on historic precedents established for neurotoxins, such as pyrethroids, organochlorines, carbamates, and organophosphates.

When applied to mosquito nets occupied by human volunteers in experimental hut trials, chlorfenapyr induces relatively high rates of mortality among host-seeking mosquitoes regardless of their insecticide resistance status as their metabolic state is elevated and the demand for energy is high. Yet, in some laboratory bioassays, such as the WHO cone test, chlorfenapyr appears slow acting or induces patterns or levels of mortality that are not typical of neurotoxic insecticides and are not predictive of mortality induced by chlorfenapyr-treated nets in hut trials.

These first observations in the laboratory led to generally applying a holding time of up to 72 h after exposure. Further evaluation showed that under field conditions, meaning when wild Anopheles are host-seeking during the night like for example in experimental hut trials, the mortality observed after 24 h of holding is already very high.

Table 3 lists the mortality observed after 24 h and 72 h of holding in the experimental hut trials described in earlier chapters. The finding is that Interceptor® G2 kills about 70–97% of the total mosquitoes already after 24 h, comparable to the pyrethroid-only LN Interceptor®.
Chlorfenapyr in cone bioassays

The metabolic state of the mosquitoes is crucial for the activity of chlorfenapyr. This metabolic state is influenced by the following parameters leading to higher mortality in lab bioassays:

- time of exposure
- time of holding
- temperature during exposure and holding time
- time of the test during day or night
- physiological state of the mosquito (host-seeking)

Anopheles naturally searching for a host at night are in an elevated metabolic state. Chlorfenapyr demonstrates better performance under these conditions whereas laboratory tests during the day with mosquitoes in a sedentary or non-elevated metabolic state show more varying and lower mortalities.

Figure 18A and 18B present the proportions of pyrethroid-susceptible and resistant mosquitoes that were killed 72 h after a 3-minute exposure to insecticide-treated netting in WHO cone bioassay. On testing, unwashed netting against the pyrethroid-resistant Cové strain, mortality did not exceed 12% with any of Interceptor® LN and Interceptor® G2 LN.

Comparing the laboratory bioassay results on the pyrethroid-resistant strain with the experimental hut results on the pyrethroid-resistant wild population, the tunnel test was the better predictor of hut mortality than was the cone. The mortality with unwashed Interceptor® G2 was 5% in the cone, 82% in the tunnel and 72% in the hut.

Discriminating dose

Discriminating doses are crucial for the monitoring of the resistance status of mosquito populations in vector control. Researchers at the Liverpool School of Tropical Medicine helped in establishing diagnostic doses for the re-purposed and new insecticides, one of them being chlorfenapyr.

Table 4: Lethal concentration (LC) values for chlorfenapyr at 72 h after 1 h exposure against different susceptible Anopheles strains in CDC bottle assays calculated on Xlstat:

<table>
<thead>
<tr>
<th>LC Values</th>
<th>An. gambiae Concentration (%)</th>
<th>An. funestus Concentration (%)</th>
<th>An. arabiensis Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC50</td>
<td>0.0010</td>
<td>0.0014</td>
<td>0.0018</td>
</tr>
<tr>
<td>LC50</td>
<td>0.0004</td>
<td>0.0020</td>
<td>0.0022</td>
</tr>
<tr>
<td>LC95</td>
<td>0.0045</td>
<td>0.0065</td>
<td>0.0039</td>
</tr>
<tr>
<td>LC99</td>
<td>0.0093</td>
<td>0.0135</td>
<td>0.0057</td>
</tr>
</tbody>
</table>
Why use Interceptor® G2?

Superior technology

The patented textile-finishing process and the polyester net coating ensures that the nets are odorless, soft to the touch and pleasant to sleep under. As the active ingredients are coated on the outside of the fibers it is readily available and no heat induced migration of the active ingredients from the inside of the fiber to the surface is required. The net needs no regeneration time and can be used in less than a day after washing. As no active material is incorporated into the fiber, the fiber preserves its originally designed strength. The patented polymer binder system ensures that no depletion of the active ingredients from the surface takes place due to washing making the net long-lasting. Interceptor® G2 remains effective even after 20 washes.

Safe to use

Chlorfenapyr has been applied for pest control in kitchens and food storage since its launch in 1995. In Interceptor® G2 the pyrethroid component alpha-cypermethrin provides excitorepellency and personal protection whilst the chlorfenapyr component provides insecticidal activity against insecticide resistant mosquitoes.

The assessment of risk to humans of washing and sleeping under the Interceptor® G2 LN following the WHO Generic Risk Assessment Model for insecticide-treated nets on behalf of WHO concluded that when used as instructed, Interceptor® G2 LN is safe.

Effective tool to control insecticide resistant mosquitoes

In contrast to the second-generation mosquito nets containing a combination of a pyrethroid with the synergist PBO, Interceptor® G2 provides the new non-pyrethroid active ingredient chlorfenapyr. A synergist works by enhancing the effect of the pyrethroid by inhibiting the metabolic enzyme defense systems of the mosquito, but at the end uses the same mode of action as a pyrethroid alone. The mode of action of chlorfenapyr is new to the control of mosquitoes. In experimental hut trials Interceptor® G2 restored the control of highly resistant mosquitoes killing them as fast as a pyrethroid-only LN. It is highly effective in areas with high insecticide resistance as for example several West African countries.

Innovative active ingredient system

Interceptor® G2 is coated with an innovative mixture of chlorfenapyr and alpha-cypermethrin. Chlorfenapyr is the first non-pyrethroid active ingredient employed on a long-lasting mosquito net. Chlorfenapyr has a new mode of action in vector control and thus shows no cross resistance to other insecticide classes.

Technical information

Product description

Net material: Polyester fibers (multifilament) coated with two insecticides, consisting of 75 Denier or 100 Denier. For easier identification of the mixture net, dark threads are knitted into the netting in a spacing of 5 cm giving a striped appearance.

Shape: Rectangular or conical

Odor: Odorless

Appearance of insecticides on net: Invisible

Wash resistance: Nets are manufactured to provide sufficient insecticidal efficacy for more than 20 washes.

Storage stability: In storage test, net material contains > 95% of the original a.i. content after 2 weeks at 54°C.

Handling precautions when using: Interceptor® G2 can be repeatedly washed and still retains its efficacy (even after 20 washes) against malaria mosquitoes, if the following instructions are followed:

- Do not wash in a washing machine
- Do not use bleaching agents
- Wash without brushing, in tepid water, in a bowl with a small amount of soap
- Always dry in open air, in the shade
- Do not use an electric tumble dryer
- Do not iron
- Always keep Interceptor® G2 in the shade
- Do only use as bed net
- Do keep away from animals
- Do keep away from water bodies

The active ingredients used to treat this net are safe to use. However, in the unlikely event that someone experiences skin and eye irritation, wash the skin with mild soap and water and flush eyes with copious amounts of water. Wash the net before using it again. Rinse your Interceptor® G2 mosquito net with water before first use to avoid possible skin irritation.

Packaging: Interceptor® G2 nets are individually packed in polyethylene bags with clear product identity indications to avoid confusion with other insecticide-treated nets.

Care tag: A care tag is stitched to each net. This label contains the washing instructions in short form on one side. On the other side information on net descriptors like size, the manufacturing and expiry date as well as an identification number is given. Additionally, three-dimensional barcodes allow to trace back every single net and connect it with the respective quality assurance data.

Quality: The quality and reliability of Interceptor® G2 nets is backed by advanced technology developed by BASF. Interceptor® G2 is an in-line, factory treated net, ensuring consistent quality and is subject to the same rigorous BASF quality control standards to which all products must adhere.

Development, marketing and sales as well as the production sites are ISO certified to comply with the requirements of the International Standard for Quality Management.

Disposal: When the useful life of the net is finished, Interceptor® G2 nets will not require any special handling. They should be disposed of according to protocols established by international organizations and local regulations for all LNs.

Risk assessment: The two active ingredients of Interceptor® G2 LN, chlorfenapyr and alpha-cypermethrin, show different toxic actions on different target organs and are therefore considered to act independently via simple additivity of effects.

BASF evaluated the potential human safety issues of sleeping under Interceptor® G2 nets using the WHO Generic Risk Assessment Model for insecticide-treated nets. This model addresses risk for newborn babies, small children and adults sleeping under treated nets.

Wrong-case criteria were used in conducting the assessment:

- Assumptions: A baby or child sleeps 12 hours under the bed net and would suck continuously on the netting
- A 12-hour continuous contact of skin with the netting via sweat is assumed
- Extraction data from unwashed, newly produced bed nets with artificial saliva were used

The results clearly show that systemic exposure is negligible. It can be concluded that no unacceptable risk occurs for newborn babies, children or adults when sleeping under Interceptor® G2 nets.

Ecotoxicology: Exposure of non-target organisms to chlorfenapyr and alpha-cypermethrin on the nets is highly unlikely when used in accordance to the recommendations. Washing of nets in natural water sources, such as rivers, streams, lakes and dams, should be avoided.
Active ingredients of Interceptor® G2

Chlorfenapyr

IUPAC: 4-Brom-2-(1-chlorophenyl)-1-ethylmethyl-5-trifluoromethyl-pyrrol-3-carbonitrile

Chemical Group: Pyrethroids

IRAC Mode of Action Classification: Group 3 – Uncouplers of oxidative phosphorylation via disruption of proton gradient

Structural formula:

Alpha-Cypermethrin

IUPAC: A racemic mixture of: (S)-a-cyano-3-phenoxybenzyl-1(3R,3)- (2,2-dichlorovinyl)-2,2-dimethylcyclopropylcarboxylate and (R)-a-cyano-3-phenoxybenzyl-(3S,3S)-(2,2-dichlorovinyl)-2,2-dimethylcyclopropylcarboxylate

Chemical Group: Pyrethroids

IRAC Mode of Action Classification: Group 3 – Sodium channel modifiers

Structural formula:

WHO specification: The product fulfils the WHO specification 70/7C

Target dose rate on Interceptor® G2: 200 mg/m²

WHO specification: The product fulfils the WHO specification 454/7C

Target dose rate on Interceptor® G2: 100 mg/m²

1 AMP net mapping project 2017

2 World Malaria Report 2016


14 Tungu, W. Sudi, E. Michael, W. Kinsa, M. Kirby, M. Rowland. An experimental hut study to evaluate the efficacy and wash resistance of Interceptor® G2 in long-lasting insecticidal nets against natural populations of Anopheles funestus and Anopheles gambiae s.l in Muheza, Tanzania. Unpublished results

15 Tungu, W. Sudi, E. Michael, W. Kinsa, M. Kirby, M. Rowland. An experimental hut study to evaluate the efficacy and wash resistance of Interceptor® G2 in long-lasting insecticidal nets against natural populations of Anopheles funestus and Anopheles gambiae s.l in Muheza, Tanzania. Unpublished results


17 M. Kirby, M. Rowland Evaluation of the efficacy and wash resistance of chlorfenapyr-alphacypermethrin bi-treated long-lasting nets in experimental huts in Tanzania. Unpublished results


For further information on BASF’s Public Health business and range of solutions, please visit:
www.publichealth.basf.com

Always read and follow label directions.

Interceptor® and Interceptor® G2 are registered trademarks of BASF.

© 2017 BASF SE
All Rights Reserved.
September 2017