A revolution in the parasite control for cats

Dr Anne Bollart
Merial
Technical & Marketing Manager - Pets Business

Jelgava – 11/09/2014
AGENDA

- The cat endectocide market & Results of an epidemiological survey on cat parasites
- Performances of Broadline®
- An unique formulation
- How to use Broadline®?
- The cat endectocide market
- Results of an epidemiological survey on cat parasites
Drivers of the Cat Endectocide Market

Drivers for growth
- Cat population
- Cat care
- Broader spectrum
- Use in kittens
- 2-in-one (1 gesture)
- POM status (vet)

Limiting factors
- Missing tick and tapeworm claims
- High price positioning in some countries
2012-2013: ONE YEAR ROUND STUDY

- An European multicentric survey on cat parasites
- 9 veterinary faculties from 7 European countries
  - FRANCE: Nantes, Maisons-Alfort
  - ITALY: Napoli, Bari
  - SPAIN: Madrid
  - BELGIUM (Liège)
  - AUSTRIA (Vienna)
  - HUNGARY (Budapest)
  - ROMANIA (Cluj-Napoca)

- **Enrolment criteria**
  - Routine consultation (no acute disease, no parasitic disease)
  - **No anthelmintic treatment for 2 months** prior to inclusion
  - **No ectoparasiticide treatment for 1 month** prior to inclusion

- Random sampling of cats weekly
RESULTS

- Out of 1519 examined cats 50.7% were infested by parasites (external or internal)

  More than the half of the European Cat population carry at least 1 parasite

- 14% of cats are co-infested by external and internal parasites

  Co-infestation is not a rare event in cats
### Ectoparasite Infestation

<table>
<thead>
<tr>
<th></th>
<th>% (nb)</th>
<th>CI&lt;sub&gt;95%&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ectoparasite</td>
<td>29.6% (450)</td>
<td>27.3 - 32</td>
</tr>
<tr>
<td>Fleas</td>
<td>15.5% (236)</td>
<td>13.7 - 17.5</td>
</tr>
<tr>
<td>Ticks</td>
<td>1.18% (18)</td>
<td>0.7 - 1.87</td>
</tr>
<tr>
<td>Otodectes</td>
<td>17.5% (265)</td>
<td>15.6 - 19.5</td>
</tr>
<tr>
<td>Other ectoparasites</td>
<td>1.38% (21)</td>
<td>0.86 - 2.11</td>
</tr>
</tbody>
</table>

Other ectoparasite infestation included:
- *Felicola subrastratus* (13 cats)
- *Cheyletiella blakei* (5 cats)
- *Notoedres cati* (3 cats)
## ENDOPARASITE INFESTATION

<table>
<thead>
<tr>
<th></th>
<th>% (nb)</th>
<th>CI&lt;sub&gt;95%&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall endoparasite</strong></td>
<td>35.1% (533/1519)</td>
<td>[32.7%-35.7%]</td>
</tr>
<tr>
<td><strong>GI helminthes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI nematodes</td>
<td>25.7% (390/1519)</td>
<td>[23.5%-28.0%]</td>
</tr>
<tr>
<td>GI cestodes</td>
<td>20.5% (312/1519)</td>
<td>[19.1%-23.3%]</td>
</tr>
<tr>
<td>7.0% (64/1519)</td>
<td>5.8%-8.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Protozoans</strong></td>
<td>20.6% (182/885)</td>
<td>[18.0%-23.4%]</td>
</tr>
<tr>
<td><strong>Respiratory nematodes</strong></td>
<td>5.4% (60/1115)</td>
<td>[4.1%-6.9%]</td>
</tr>
</tbody>
</table>
### Gastro-intestinal Nematodes

<table>
<thead>
<tr>
<th>Nematode</th>
<th>Prevalence (%)</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Roundworm (Toxocara cati)</strong></td>
<td>19.8% (300)</td>
<td>[17.8%-21.8%]</td>
</tr>
<tr>
<td><strong>Toxascaris leonina</strong></td>
<td>0.33% (5)</td>
<td>[0.11%-0.77%]</td>
</tr>
<tr>
<td><strong>Hookworm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ancylostoma tubaeformae /</td>
<td>1.45% (22)</td>
<td>[0.91%-2.18%]</td>
</tr>
<tr>
<td>Uncinaria stenocephala</td>
<td></td>
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</tr>
</tbody>
</table>

#### Human Risk

- **Kittens can become infected from the milk.**
- **Non-infective eggs**
  - Rodents ingest non-infective eggs.
  - P.H. ingest infective eggs.
  - Faeces
- **Cat roundworm (Toxocara cati)**
GI HELMINTHES - CESTODES

| Gastro-intestinal cestodes | 7.0% (64) | [5.8%-8.5%] |

Under-estimation because of the poor sensibility of coproscopy (5 times more infested cats)

- **D. H.**
  - Cats ingest fleas
  - 1-2 days
  - 2-3 weeks

- **1. Adults** (small intestine)
  - Faeces
  - Proglottid (containing egg packets)
  - Egg packets

- **2. Egg packets**
  - Adult fleas
  - Flea pupal stage

- **3. Hexacanth embryo**

- **4. Cysticercoids**

**Dipylidium tapeworm** (*Dipylidium caninum*)

**Echinococcus multilocularis**

Human risk
DEVELOPMENT OBJECTIVES

- Have a topic formulation easy to administer
- Be innovative with the first use of a new molecule for the cats, against roundworms
**KEY CHALLENGES**

- **Diffusion**
  - Skin translocation – topical activity for ectoparasites
  - Transcutaneous absorption – systemic activity for endoparasites

- **Formulation**
  - Allow the double diffusion
  - Avoid any interaction between the molecules
THE DOUBLE DIFFUSION

Skin translocation and storage in skin lipids
For a long-lasting topical activity: treatment & prevention of arthropod infestations

Transcutaneous absorption before plasmatic diffusion
Rapid metabolization for fast-acting systemic activity: treatment of helminth infestations
Performances of Broadline®
AGAINST EXTERNAL PARASITES

**FLEAS**
Achieve long-lasting efficacy against several strains of adult *C.felis* fleas

**Efficacy > 95%**

**TICKS**
Ensure long-lasting efficacy against *I.reicinus* tick infestation

**Efficacy > 90%**

Prevention of flea development of immature flea stages
AGAINST INTERNAL PARASITES

**ROUNDWORMS**
One application of BROADLINE kills:
- Toxocara cat adult: 97.1-100%
- Toxocara cat L3 and L4 larvae: 100%
- Toxascaris leonina adult: 95.8-98.1%

**VESICAL NEMATODE (BLADDER WORM)**
BROADLINE is the only product licensed for the treatment of bladder worm in cats.
- Capillaria plica: 100%

**HOOKWORMS**
- Ancylostoma tubaeforme adult: 99.1-100%
- Ancylostoma tubaeforme L4: 100%
- Ancylostoma braziliense adult: 90.7-99.5%

**HEARTWORM DISEASE PREVENTION**
One application of BROADLINE kills migrating larvae:
- Dirofilaria immitis L4 larvae: 100%

**TAPEWORMS**
BROADLINE is the only endectocide that kills tapeworms:
- Dipylidium caninum: 97.7-100%
- Taenia taeniaformis: 98.5-100%
- Echinococcus multilocularis: 100%
Broadline®, an unique formulation for the broadest spectrum
4 ACTIVES

**EPRINOMECTIN**
Targets roundworm

**FIPRONIL**
Targets fleas and ticks

**PRAZIQUANTEL**
Targets tapeworm

**(S)-METHOPRENE**
Targets flea eggs and larvae
AN UNIQUE FORMULATION

Key Justification
Well-established integrated flea control
immature and adult fleas

(S)-methoprene
Fipronil + Praziquantel
Eprinomectin

GI Cestodes
Dipylidium caninum
Echinococcus multilocularis
Taenia taeniformis

GI Nematodes
Toxocara cati
Ancylostoma sp.

Other spectrum
Flea Allergy Dermatitis

Tick control + Heartworm prevention
Based on geography

Vesical worms
bladderworm
The broadest spectrum

<table>
<thead>
<tr>
<th></th>
<th>Fipronil</th>
<th>(S)-méthoprène</th>
<th>Eprinomectine</th>
<th>Praziquantel</th>
<th>BROADLINE</th>
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<tbody>
<tr>
<td>T. cati</td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td>T. cati L3</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>T. cati L4</td>
<td></td>
<td>✔</td>
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<tr>
<td>A. tubaeforme</td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td>A. tubaeforme L4</td>
<td></td>
<td>✔</td>
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<tr>
<td>A. braziliense</td>
<td>✔</td>
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<tr>
<td>T. leonina</td>
<td>✔</td>
<td></td>
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<tr>
<td>D. Immitis larvae</td>
<td>✔</td>
<td></td>
<td>✔</td>
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<tr>
<td>D. caninum</td>
<td></td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td>T. taenaeformis</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>E. multilocularis</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>C. felis adultes</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>C. felis oeufs/larves</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>I. ricinus</td>
<td>✔</td>
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<td>✔</td>
<td>✔</td>
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</table>
How to use Broadline®?
A PREMIUM TECHNOLOGY

An innovative applicator for an improved compliance

1 • PROFESSIONAL
A high value device bringing veterinary expertise to home users

2 • PRECISE, ANIMAL-FRIENDLY
Round shaped nozzle
Due to special solvent base, no “freezing effect” during the application

3 • ACCURATE DOSAGE
By pumping just once, the right dose is delivered to the cat

4 • SWIFT AND SIMPLE
Fully emptied in one motion

5 • KEEP HANDS CLEAN
No contact with the treated skin, no leakage
2 PRESENTATIONS

- CATS < 2,5 KG
- CATS 2,5 TO 7,5 KG
USE RECOMMENDATIONS

- SAFE AND WELL-TOLERATED
- IN BOTH CATS AND KITTENS FROM 7 WEEKS

<table>
<thead>
<tr>
<th>Kittens</th>
<th>High risk of co-infestation by GI worms and ectoparasites</th>
<th>According to guidelines, monthly treatment between 7 weeks and 6 months is recommended.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(7 weeks - 6 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult cats &gt; 6 months</td>
<td>Variable risk based on cat's habits and local epidemiological situation</td>
<td>Frequency is defined by the veterinarian, depending on the individual situation. Monthly treatment may safely be indicated when there is a continuous risk of co-infestation.</td>
</tr>
</tbody>
</table>
Broadline, first all-in-one

- The broadest spectrum for cats
  - Broad internal worm control (includes tapeworms)
  - Unique external protection (includes ticks)

- An innovative applicator

- A full treatment in one motion
Thanks for your attention
Do you know the tasty innovation that kills fleas & ticks?
Vet Congress Varna 2014

AGENDA

- The oral market of antiparasites
- Afoxolaner, a new molecule
- Nexgard®, a fast & long-lasting flea and tick control
- The safety of Nexgard®
- Nexgard®, an amazing palatability
The oral market of antiparasites
## THE ORAL MARKET

<table>
<thead>
<tr>
<th>DRIVERS</th>
<th>LIMITING FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleas Speed of kill / visible efficacy</td>
<td>Low palatability</td>
</tr>
<tr>
<td>Increased awareness among pet-owners</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Ease of giving</td>
<td>Lack of tick control</td>
</tr>
<tr>
<td>No water impact</td>
<td>Pet owner awareness</td>
</tr>
<tr>
<td>POM</td>
<td></td>
</tr>
</tbody>
</table>
In Europe, 1 vet in 2 agrees that oral segment is set to grow
LEVEL OF INTEREST FOR A NEW ORAL PRODUCT

Owners who talked about their dog

- **Czech Republic (CZ):**
  - Not at all interesting: 6%
  - Not very interesting: 34%
  - Quite interesting: 41%
  - Very Interesting: 19%
  - Total: 60%

- **Poland (PL):**
  - Not at all interesting: 3%
  - Not very interesting: 17%
  - Quite interesting: 54%
  - Very Interesting: 26%
  - Total: 80%

- **Hungary (HG):**
  - Not at all interesting: 6%
  - Not very interesting: 19%
  - Quite interesting: 46%
  - Very Interesting: 29%
  - Total: 75%

*Sample:* Owners who talked about their dog(s) CZ n=307, PL n=328, HG n=328
Afoxolaner
New generation molecule
For a greater efficacy
ISOXAZOLINE FAMILY

- A new class of potent insecticides/acaricides
- Induction of neuron hyperexcitation due to the inhibition of GABA-gated chloride channels
PHARMACOKINETIC

- Rapidly absorbed after oral administration: peak in 2-4 hours
- Highly bound to plasmatic proteins
- Half-life after oral administration: 14 days
MODE OF ACTION
A NEURO-MUSCULAR ACTIVITY

Induction of rapid death of arthropods by hyperexcitation

1. Fixation of afoxolaner on its unique specific receptor site on GABA gated chloride ions channels
2. Inhibition of the opening of the channels No entry of Cl-
3. Increase of the electric potential hyperexcitation and death
A LONG-LASTING PLASMATIC DIFFUSION

Effective concentration for 1 month
No significant impact of the prandial state on the pharmacokinetic
Fast & long lasting flea and tick control
ADULT FLEA CONTROL WITHIN 12 HOURS!

A very fast action of NEXGARD® against fleas
NO MORE NEED OF IGR WITH

NEXGARD

NO EGG LAYING,
NO EGG,
NO LARVAE,
NO PUPAE...

No flea emergence from the environment
HOW LONG DOES IT TAKE TO KILL FLEAS?

After 2 and 6 hours infestation on dogs, surviving fleas are collected and placed in an insectarium for observation during 24h
- All of them are killed within 6 hours
- The little afoxolaner dose they were in contact with kill them all

Immediate flea Speed of Kill
The action of afoxolaner starts from 30 minutes after flea infestation and this effect is still significant within 6 hours for a full month.

NexGard® kills fleas within 6h for up to 1 month.
CONTROL OF EUROPEAN TICKS

The diagram illustrates the control of European ticks over several study days. It shows the effectiveness of treatment against three tick species: *Dermacentor reticulatus*, *Ixodes ricinus*, and *Rhipicephalus sanguineus*. The y-axis represents the percentage of control, while the x-axis shows different study days (D2, D9, D16, D23, and D30). The bars indicate the percentage of ticks controlled on each day, with darker shades for higher control rates.
HOW LONG DOES IT TAKE TO KILL TICKS?

SPEED OF KILL (SOK) STUDIES ON TICKS ARE CONDUCTED TO EVALUATE MORTALITY AT 12H

Tick attachment occurs.

But engorgement is not necessary for Afoxolaner to kill the tick

(The presence of Afoxolaner bound to plasmatic proteins in the skin lesion is responsible for tick intoxication.)
WHAT ABOUT THE PREVENTION OF BABESIOSIS?

- 4 tick challenges (D7, 14, 21, 28) + tick removal and count 48h after each infestation (D. reticulatus infected by B. canis)
- Blood collection and blood smear for B. canis detection (PCR, IFA)

All control dogs positive for babesiosis VS no dog in the treated group was positive for babesiosis during the 56 days of the study

No live ticks were found at D28

NEXGARD treatment is regarded to be fully effective in preventing the transmission of babesiosis by infected D. reticulatus
How safe is it?
SAFETY

- Safe for dogs from 8 weeks of age
- Afoxolaner is safe in dogs at up to 80 times the clinical dose (2.5 mg/kg)
- No breed sensibility
- No accumulation
- In case of pregnancy and lactation, the development occurred normally but the safety profile was not demonstrated
An amazing palatability is a delight!
A TASTY SOFT CHEW

• With a flavour beef braised
• It can be given with or without food
A HIGHLY PALATABLE CHEW

Flea & Tick efficacy in a highly palatable soft chew
### 4 PRESENTATIONS

<table>
<thead>
<tr>
<th>NEXGARD®</th>
<th>Chew Size</th>
<th>Afoxolaner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs 2-4 kg</td>
<td>0,5 g</td>
<td>11,3 mg</td>
</tr>
<tr>
<td>Dogs 4-10 kg</td>
<td>1,25 g</td>
<td>28,3 mg</td>
</tr>
<tr>
<td>Dogs 10-25 kg</td>
<td>3 g</td>
<td>68 mg</td>
</tr>
<tr>
<td>Dogs 25-50 kg</td>
<td>6 g</td>
<td>136 mg</td>
</tr>
</tbody>
</table>
Conclusion

• A new molecule dedicated to veterinary medicine
• An oral treatment against fleas and ticks
• A fast and long-lasting flea & tick control
• A very safe product
• A highly palatable soft chew
Thank you for your attention

Any questions?