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(54) **Title**: SYSTEMIC USE OF COMPOUNDS IN HUMANS THAT KILL FREE-LIVING BLOOD-FEEDING ECTOPARASITES

(57) **Abstract**: It is disclosed a composition of one or more active compounds belonging to the group of neonicotinoids suitable to be administered to humans and used to kill free-living blood feeding ectoparasites including ectoparasitic arthropods. The group of neonicotinoids includes imidacloprid, thiacloprid, acetamiprid, thiamethoxam, nitenpyram, and/or its subgroups e.g. nitroguanidines such as clothianidine. Neonicotinoids comprising compositions can be used to kill free-living blood feeding ectoparasites, shortly after feeding on a human host, and in this way prevent such ectoparasites from surviving to pass on pathogens to other humans or pathogen reservoir hosts.

SYSTEMIC USE OF COMPOUNDS IN HUMANS THAT KILL FREE-LIVING BLOOD-FEEDING ECTOPARASITES

INTRODUCTION

The present invention relates to compositions comprising neonicotinoids (as active ingredient(s)), and specifically their systemic use in humans against free-living ectoparasites. Importantly, although such compounds have been used in and on companion animals against temporary and permanent ectoparasites in the veterinary and plant-breeding sectors, the present invention relates to the surprising findings of their hitherto unexplored application in humans for the control of free-living ectoparasites and the diseases they transmit.

Free-living ectoparasites visit their blood hosts for the duration of blood feeding only and live elsewhere in the environment outside this activity (e.g. mosquitoes). Temporary ectoparasites stay significantly longer on their hosts, (i.e. several) days (e.g. fleas and ticks), whereas permanent ectoparasites complete their entire life-cycle on the host, never leaving it (e.g. head lice).

Beyond the novel application in humans against free-living ectoparasites the present invention is also the first to demonstrate that single neonicotinoids are effective killing agents for free-living ectoparasites when present in the bloodstream of humans. The invention therefore creates multiple opportunities for systemic use in humans to interfere with the transmission, by free-living ectoparasites, of disease-causing pathogens. Given the huge public health burden caused by diseases like malaria (300 million cases per annum, with 800.000 deaths)

and dengue (50-100 million cases per annum), as reported by the World Health Organization, such novel application has high significance for alleviating human suffering, particularly in developing countries.

BACKGROUND

Neonicotinoids are an important class of synthetic insecticides (Tomizawa and Casida, 2003), with a common mode of action that affects the central nervous system of arthropods, initially causing paralysis followed by death. Compounds of this class of insecticides act on the central nervous system of insects by binding at a specific site, the postsynaptic nicotinic acetylcholine receptor channels (nAChRs).

In blocking this specific neural pathway, which is more common in arthropods than in warm-blooded animals, toxicity is far more pronounced in the former than the latter group of organisms, rendering WHO/EPA classification of these compounds in toxicity class II or III.

Advantageously neonicotionids may, through their unique mode of action that differs from that of classical insecticides used in arthropod pest control, like organochlorines, organophosphates, carbamates, and synthetic pyrethroids, be used to manage pests that have developed (physiological) resistance to these classes of insecticides. Neonicotinoids have a fast mode of action. Moreover, their low mammalian toxicity (see below) offers unique prospects for systemic use beyond plants or animals, i.e. in humans, which forms part of the current invention.

Uses of neonicotinoids are reported from both the veterinary and plant breeding sectors, whereby use of the compounds in the environment (e.g. through spraying or soaking) as well as systemic uptake (in plant nutrient substrates) or topical and oral administration (in companion animals, notably cats and dogs) in different combinations is practiced. For instance, oral application of a single dose (at recommended levels of 1 mg/kg bodyweight) of nitenpyram provides 100% kill of flea infestations on cats for up to 48 hours (Rust et al., 2003); see also WO 00/21371. Oral use in tablet form of 11.4 mg can be used in animals of 2 pounds bodyweight, essentially extending the dose range from 1 – 10 mg/kg bodyweight (Novartis, 2011).

Additional uses are described in:

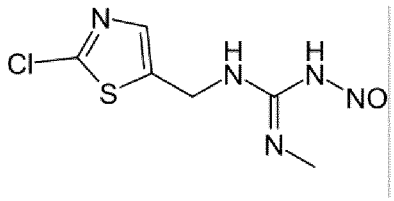
US5750548: 1-[N-(halo-3-pyridylmethyl)]-N-methylamino-1-alklamino-2-nitroethylene derivatives for controlling fleas in domestic animals;
WO2008062821: Composition for controlling plant disease and insect damage and method for preventing plant disease and insect damage;

For example nitenpyram (N-((6-chloro-3-pyridinyl)methyl)-N ethyl-N'-methyl-2-nitro-1,1-ethenediamine), is a neonicotinoid that acts as an agonist of nAChRs and is used as a systemic flea control drug for companion animals. Nitenpyram does not inhibit acetylcholinesterase. Nitenpyram, when administered orally to cats/dogs, acts within 30 min, and kills 90% of fleas within 4-6 hours. Oral (ORL) and dermal (SKN) toxicity of nitenpyram is low, ORL-Rat (male) LD_{50} 1680 mg kg^{-1}, ORL-Rat (female) LD_{50} 1575 mg kg^{-1}, SKN-Rat LD_{50} > 2000 mg kg^{-1}

(MSDS, 2006). A summary of safety and dose-effectiveness trials with nitenpyram is available (FDA).

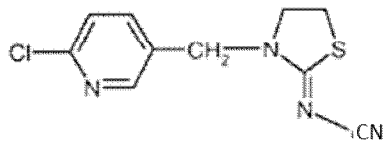
There are seven neonicotinoid insecticides currently on the market: three cyclic compounds, that is, neonicotinoids with five-membered ring systems such as imidacloprid and thiacloprid (Bayer CropScience) and the six-membered neonicotinoid thiamethoxam (Syngenta), and four noncyclic compounds, that is, nitenpyram (Sumitomo Chemical Takeda Agro Co.), acetamiprid (Nippon Soda), clothianidin (Sumitomo Chemical Takeda Agro Co./Bayer CropScience), and dinotefuran (Mitsui Chemicals).

Clothianidin (i) is known for the publication EP 0376279 A2:



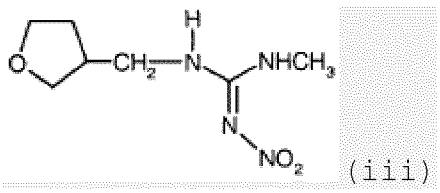
(i)

Thiacloprid (ii) is known for the publication EP 0235725 A2.



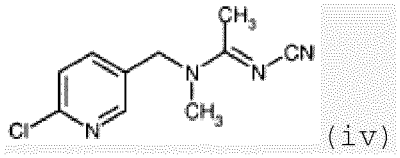
(ii)

Dinotefuran (iii) is known for the publication EP 0649845 A1.

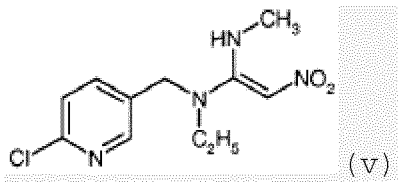


(iii)

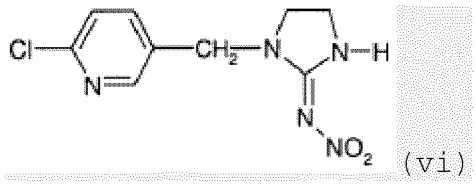
Acetamiprid (iv) is known for the publication WO 91/0465 A1.


(iv)

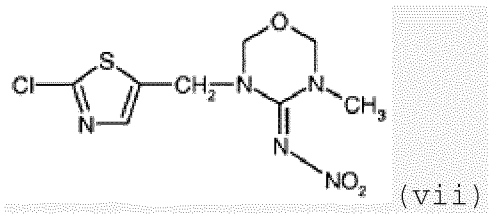
Nitenpyram (v) is known for the publication EP 0302389 A2.


(v)

Imidacloprid (vi)is known for the publication EP 0192060 A1.


(vi)

And Thiamethoxam (vii)is known for the publication EP 0580553 A2.


(vii)

There are several ways to subdivide the seven commercially available neonicotinoids into different groups.

They can be classified by their pharmacophore moieties [-N—C(E)dX—Y] (see Fig.1: part ii), as N-nitroguanidines (imidacloprid, thiamethoxam, clothianidin, and dinotefuran), nitromethylenes (nitenpyram), and N-cyanoamidines (acetamiprid and thiacloprid).

Another way to subdivide them is via their different nicotyl groups. This method subdivides them into chloronicotinyl (imidacloprid, nitenpyram, acetamiprid and thiacloprid), thianicotinyl (thiamethoxam and clothianidin) and furanicotinyl (dinotefuran) molecules.

A more general way to subdivide the neonicotinoids is division into ring systems (imidacloprid, thiacloprid and thiamethoxam) and non-cyclic compounds (Nitenpyram, Acetamiprid, Clothianidin and Dinotefuran). The overall chemical structure of both rings systems and non-cyclic compounds consists of three segments (see Fig.1):

i. for five and six-membered ring systems the bridging fragment -Z- between R^1 and R^2 including the two substituents and
for noncyclic neonicotinoids the separate substituents (R1, R2).

ii. the hetarylmethyl or heterocyclylmethyl group R

iii. the functional group [= X-Y] as part of the dif-

ferent pharmacophore types [-N-C(E) = X-Y].

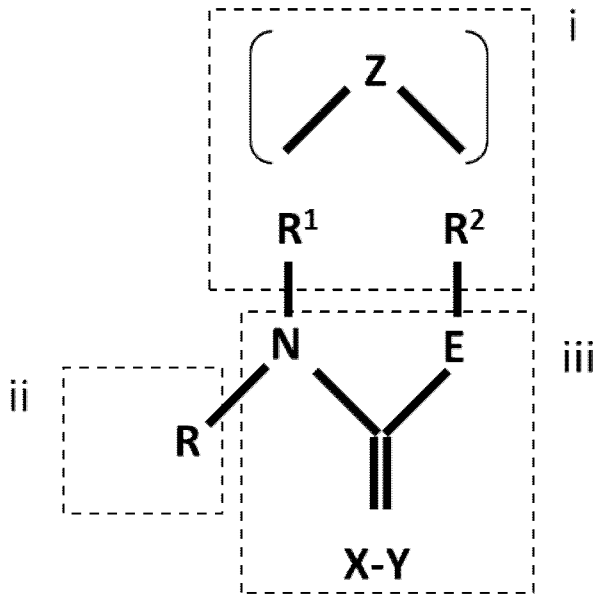


Figure 1: The general chemical structure for neonicotinoids. The different substituents are shown in Table 1.

Table 1: Different known chemical structures belonging to the neonicotinoids

Noncyclic neonicotinoids

Commercial names	R	R^1	X-Y	E	R^2
	6-chloro-pyrid-3-ylmethyl (CPM)	H	$CHNO_2$	NH_2	\
	6-chloro-pyrid-3-ylmethyl (CPM)	H	$CHNO_2$	NH	$N(CH_3)_2$
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_3 (=Me)	$CHNO_2$	NH	CH_3
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_3	$CHNO_2$	NH	CH_2CH_3
Nitenpyram	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2CH_3 (=Et)	$CHNO_2$	NH	CH_3
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2CH_3	$CHNO_2$	NH	CH_2CH_3
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2CH_3	$CHNO_2$	NCH_2CH_3	CH_2CH_3
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2CH_3	$CHNO_2$	NH	cyclopropyl
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2CH_3	$CHNO_2$	$N(CH_2)_4$	\
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2CH_2F	$CHNO_2$	NH_2	\
	6-chloro-pyrid-3-ylmethyl (CPM)	$CH_2CH_2CH_3$	$CHNO_2$	NH_2	\
	6-chloro-pyrid-3-ylmethyl (CPM)	$CH(CH_3)_2$	$CHNO_2$	NH	CH_3
Acetamiprid	6-chloro-pyrid-3-ylmethyl (CPM)	CH_3	NCN	CH_3	\
Clothianidin	2-chloro-1,3-thiazol-5-ylmethyl (CTM)	H	NNO_2	NH	CH_3
Dinotefuran	(+/-)-6-tetrahydrofur-3-ylmethyl (TFM)	H	NNO_2	NH	CH_3

Cyclic neonicotinoids

Commercial names	R	R^1	X-Y	E	R^2	Z
	3-Pyridylmethyl	CH_2	$CHNO_2$	NH	0	CH_2
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	$CHNO_2$	NH	0	CH_2
	6-Methyl-pyrid-3-ylmethyl	CH_2	$CHNO_2$	NH	0	CH_2
	6-chloro-pyrid-3-yl	CH_2	$CHNO_2$	NH	0	CH_2
	2-(6-chloro-3-pyridyl)ethyl	CH_2	$CHNO_2$	NH	0	CH_2
	2-Pyridylmethyl	CH_2	$CHNO_2$	NH	0	CH_2
	4-Pyridylmethyl	CH_2	$CHNO_2$	NH	0	CH_2
	Benzyl	CH_2	$CHNO_2$	NH	0	CH_2
	4-chloro-benzyl	CH_2	$CHNO_2$	NH	0	CH_2
	5-(2-Cl-thiazolyl)methyl	CH_2	$CHNO_2$	NH	0	CH_2
	3-Pyridylmethyl	CH_2	NNO_2	NH	0	CH_2
Imidacloprid	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	NNO_2	NH	0	CH_2
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	NNO_2	NCH_3	0	CH_2
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	NCN	NH	0	CH_2
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	CHCN	NH	0	CH_2
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	$CHNO_2$	CH_2	0	CH_2
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	$CHNO_2$	O	0	CH_2
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	$CHNO_2$	S	0	CH_2
	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	$CHNO_2$	NH	CH_2	CH_2
Thiacloprid	6-chloro-pyrid-3-ylmethyl (CPM)	CH_2	NCN	S	0	CH_2
Thiamethoxam	(+/-)-6-tetrahydrofur-3-ylmethyl	CH_2	NNO_2	NCH_3	CH_2	O

DESCRIPTION

The present invention aims at killing free-living blood feeding ectoparasites, in particular the novel use of neonicotinoids for this purpose, shortly after feeding on a human host, and in this way prevent such arthropod ectoparasites from surviving to subsequently pass on pathogens to other humans. Compositions comprising one or more active compounds belonging to the group of neonicotinoids can thereto be made suitable for administration in humans, for instance oral administration.

Surprisingly, we found that systemic use of only nitenpyram without additional compounds in humans, at 1,2 mg/kg bodyweight, results in 100% kill of free-living ectoparasites within 12 hours post blood feeding at 1-24 hours post drug administration (Table 2). Given that pathogen development in free-living ectoparasites (the so-called extrinsic incubation period) exceeds this period of survival, this novel use in humans can therefore be applied to stop transmission of pathogens. Nitenpyram is rapidly excreted from circulation (through the urinary system) and insects feeding on humans after 24 hours survive mostly unscathed.

Table 2. Effect of oral administration of nitenpyram on a free-living blood feeding arthropod (the dengue mosquito *Aedes aegypti*) at various times post-administration.

Period (hours) after oral human use of 1,2 mg/kg bodyweight	Percentage kill of *Aedes aegypti* 24 hours after blood feeding (n=25)
1	100
3	100
6	100
9	100
12	92
15	78
18	84
24	8

Now therefore, neonicotinoids, notably nitenpyram, can be used to kill free-living blood feeding ectoparasites, shortly after feeding on a human host, and in this way prevent such ectoparasites from surviving to pass on pathogens to other humans/livestock. Such free-living ectoparasites are considered to be mosquitoes (*Culicidae*), tsetse flies (*Glossinidae*), deer and horse flies (*Tabanidae*), midges (*Ceratopogonidae*), black flies (*Simuliidae*), stable flies (*Muscidae*), kissing bugs (*Reduviidae*), and sand flies (*Psychodidae*).

The invention specifically focuses on the second medical use of neonicotinoids, notably nitenpyram, as a killing agent in human blood for free living ectoparasites. These compositions can be used for:

1. Altruistic drugs for dengue virus (DENV) transmission control. There is, at present, no specific

medication or vaccination against DENV. Mosquitoes that transmit DENV, notably the Yellow Fever mosquito *Aedes aegypti* L., preferably reside within the premises close to its breeding grounds. Infections with DENV therefore often lead to disease clusters, whereby those living in the immediate vicinity (i.e. within the same household) of a dengue-infected person also become infected.

The period of infectiousness of DENV for mosquitoes (i.e. the period during which humans can pass the virus to mosquitoes) coincides with the period of intense febrile illness in humans (WHO, 2009), when normally medical care will be sought. This infective period typically lasts for 4-8 days. Prescription of neonicotinoids, notably nitenpyram, by health providers during the infective period, with daily administration of 1 mg/kg bodyweight, will result in the killing of all biting potential mosquito vectors within 24 hours, thus completely blocking virus transmission. Although the patient remains ill, he/she will avoid further dissemination of the virus in the environment, hence the term 'altruistic drug'. Alternatively, slow-release formulations can be administered so that a single or few doses will suffice to kill all mosquitoes during the host's infectious period.

Alternatively, if the viremic patient is not capable of taking such drugs, those living in the patient's vicinity may do so to halt the spread of DENV. The option described here does also include use by both the patient and those living nearby.

2. Mass drug administration, in elimination or eradication campaigns of ectoparasite-borne infectious diseases, for example malaria, and particularly for diseases of which the ectoparasites that transmit them have

a strong innate tendency to consume human blood (i.e. anthropophilic arthropods), such as the malaria mosquitoes *Anopheles gambiae sensu stricto* Giles, *An. funestus* Giles, and the arbovirus vectors *Aedes albopictus* Skuse and *Aedes aegypti*. Such mass drug administrations can for instance be integrated with conventional mosquito control strategies, in such manner as to wipe out remaining pockets of infestation.

3. A means to interrupt transmission of diseases like malaria, through prescriptive treatment following recovery from infection with asexual parasites. Such recovery is normally followed by a period in which human hosts are infectious to mosquito vectors. Carriage of infective parasites (so-called gametocytes) often occurs after the patient is sick, and leads to further transmission of the disease to mosquitoes, which can thus be overcome. Most drugs to cure malaria do not affect the infectious stage of the disease (with the exception of primaquine), and nitenpyram thus provides a novel means to stop transmission of malaria.

4. Mass drug administration if an epidemic disease outbreak occurs. Epidemic outbreaks of many ectoparasite-borne diseases are often restricted to so-called hotspots (Bousema *et al.*, 2010). Targeted interventions based on mass drug administration in such hotspots can be used to prevent the epidemic from spreading further. For instance, models have shown that 80% of malaria transmission originates from 20% of the population, thus targeted interventions may have a huge impact on disease prevalence and incidence (Bousema *et al.*, 2010). Similar uses are foreseen for outbreaks of leishmaniasis, (remaining) foci of river blindness (onchocerciasis), and foci of human

sleeping sickness (trypanosomiasis). This latter use may include treatment of livestock as a means to eliminate their role as a parasite reservoir from which human infections may culminate.

5. A means to control intra-domiciliary ectoparasitic arthropods transmitting pathogens, particularly kissing bugs (e.g. *Triatoma infestans*) that spend the vast majority of their lifecycle indoors and transmit the causative parasite of Chagas disease, *Trypanosoma cruzii*.

What is set out in the above for nitenpyram also holds for other members of the group of active neonicotinoid compounds including imidacloprid, thiacloprid, acetamiprid, thiamethoxam, and/or its subgroups e.g. nitroguanidines such as clothianidine.

In the above mentioned compositions the one or more compounds belonging to the group of neonicotinoids may be mixed with pesticides, fungicides and/or insecticides, as long as the thus practically administered composition is not too toxic if administered to humans.

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CLAIMS

1. Composition of one or more compounds belonging to the neonicotinoids for use in humans for the killing of free-living blood-feeding ectoparasites (including ectoparasitic arthropods), thereby preventing the transmission of human disease pathogens.

2. Composition according to claim 1, whereby the group of neonicotinoids includes imidacloprid, thiacloprid, acetamiprid, thiamethoxam, clothianidin, dinotefuran, and nitenpyram, and/or its subgroups as defined according to the chemical structure shown in Fig. 1 and Table 1.

3. Composition according to claim 1 or 2, which compound(s) is (are) may be mixed with pesticides, fungicides and/or insecticides.

4. Composition according to any one of the claims 1-3, wherein free-living ectoparasites are considered, specifically mosquitoes (*Culicidae*), tsetse flies (*Glossinidae*), deer and horse flies (*Tabanidae*), midges (*Ceratopogonidae*), black flies (*Simuliidae*), stable flies (*Muscidae*), kissing bugs (*Reduviidae*), and sand flies (*Psychodidae*).

5. Use of the composition according to any one of the claims 1-4 for killing free-living ectoparasites including ectoparasitic arthropods, whereby said one or more compound(s) is (are) orally administered to humans at a dose of .5 - 10, in particular .75 - 5, more particular 1 - 2 mg/kg bodyweight for every 24 hours of use.

6. Use according to claim 5 whereby the composition can also comprise higher compound doses that are formulated in such manner that slow release of said compound(s) is prolonged relative to the required effective dose.

7. Use according to claim 5 or 6 in humans as a means to kill blood-feeding arthropods capable of transmitting infectious disease pathogens.

8. Use according to any one of the claims 5-7, whereby such use is specifically applied to reduce the nuisance threat of such arthropods through population size reduction.

9. Use according to any one of the claims 5-8 for lowering the population size of blood feeding arthropods, thereby lowering the risk of transmission of arthropod-borne infectious diseases.

10. Use according to any one of the claims 5-9, whereby such use reduces or stops the transmission of pathogens transmitted by the following arthropods: mosquitoes (*Culicidae*), tsetse flies (*Glossinidae*), deer and horse flies (*Tabanidae*), midges (*Ceratopogonidae*), black flies (*Simuliidae*), stable flies (*Muscidae*), kissing bugs (*Reduviidae*), and sand flies (*Psychodidae*).

11. Use according to any one of the claims 5-10, whereby the use is for pathogens that are not mechanically transmitted and require a developmental time inside the arthropod exceeding a time period of at least 24 hours.

12. Use according to any one of the claims 5-11, which said pathogens include parasitic, bacterial, viral, and helminthic pathogens.

13. Use according to any one of the claims 5-12, whereby diseases are targeted for which the control of arthropods and/or pathogens is hindered by insecticide and/or drug resistance, or for arthropod-borne pathogens against which drugs and/or vaccines have not (yet) been developed.

14. Use according to any one of the claims 5-13, used as a means to control and/or eliminate the transmission of malaria, filariasis, heartworm, dengue virus (DENV), Chikungunya virus (CHIKV) and related/other arboviruses, sleeping sickness, Chagas disease, river blindness, and leishmaniasis.

15. Use of the composition according to any one of the claims 1-4 for the manufacture of a medicament for killing free-living blood feeding ectoparasites including ectoparasitic arthropods.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/068172

A. CLASSIFICATION OF SUBJECT MATTER
INV. A01N51/00 A61K31/44 A61P33/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A01N A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Schenker et al: Clinical advances A supplement to compendium on continuing education for the practicing veterinarian , March 2001 (2001-03), pages 1-27, XP002663923, Retrieved from the Internet: URL:http://www.vetcontact.com/downloads/novartis/news10/Clinical-WebII.pdf [retrieved on 2011-11-21] page 4 -----	1-15
X	EP 2 100 505 A1 (MITSUI CHEMICALS AGRO INC [JP]) 16 September 2009 (2009-09-16) claims ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2011	06/12/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Zimmer, Barbara

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/068172

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 201 017 B1 (SEMBO SATOSHI [JP] ET AL) 13 March 2001 (2001-03-13) column 7; claims -----	1-15
X	EP 0 966 961 A1 (SUMITOMO CHEMICAL CO [JP]) 29 December 1999 (1999-12-29) claims -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/068172

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