PHARMAQ

Environmental Assessment in Support of an Import Tolerance Request for Hexaflumuron in Fin Fish

PHARMAQ AS
Part of Zoetis

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zoetis

Approved

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List of Abbreviations

Abbreviation	Explanation
bw	Body weight
Log K_{ow}	n-octanol/water partition coefficient
WWTP	Wastewater treatment plant

List of Units

Unit	Explanation
kg	Kilogram
g	Gram
mg	Milligram
µg	Microgram
L	Liter
mL	Milliliter
µL	Microliter
ppm	Parts per million (e.g. mg/L)
°C	Degrees Celsius
°K	Degrees Kelvin
mol	Moles
Pa	Pascal
h	Hour

1. General information

Sponsor: PHARMAQ AS a part of Zoetis
Harbitzalléen 2A,
P.O.Box 267 Skøyen,
N-0213 Oslo, Norway

Established Name: Hexaflumuron

2. Purpose and need for the proposed action

Hexaflumuron is the active pharmaceutical ingredient (API) in ALPHA FLUX® 100 mg/mL, Concentrate for Solution for immersion of salmonids to treat sea lice infestations. It is currently approved for use in Chile. Hexaflumuron is indicated for the treatment and prevention of infestations with juvenile stages of sea lice (*Caligus rogercresseyi*) in salmonids. It is diluted to 2 ppm in water administered by immersion bath in closed units.

Hexaflumuron is not currently approved or conditionally approved in the United States (U.S.) as a drug substance for use in or on any fish species, or registered for use in food commodities in the U.S. Therefore, PHARMAQ is requesting the establishment of an import tolerance for hexaflumuron for the purpose of importation of treated finfish for human consumption in the U.S. Establishment of an import tolerance is an agency action by the U.S. Food and Drug Administration (FDA) that requires preparation of an environmental assessment (EA) unless that action meets the criteria for categorical exclusion under FDA regulations at 21 CFR Part 25, Subpart C. Because there are currently no categorical exclusions that apply for the proposed agency action (i.e., establishment of an import tolerance), this EA has been prepared to address and evaluate the potential direct and indirect environmental impacts in the U.S. should the FDA establish an import tolerance for residues of hexaflumuron in salmonids.

This document presents relevant environmental fate data and physical-chemical characteristics of hexaflumuron as well as an assessment of possible risks to the U.S. environment following potential exposure pathways.

3. Identification of the substance

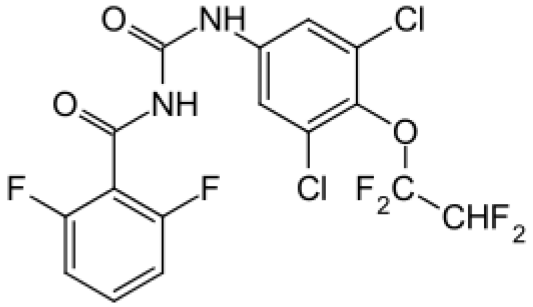
Hexaflumuron is a chitin synthesis inhibitor belonging to the class of benzoylureas. Hexaflumuron is closely related to teflubenzuron and lufenuron.

Hexaflumuron is not licensed for use in food animals in the U.S.

Hexaflumuron is registered for use in non-food products as an insecticide/termiticide in the U.S.

The identity and physicochemical properties of hexaflumuron are summarized in Table 1 below.

Table 1. Identity and physicochemical properties of hexaflumuron.

Item	Description
International Nonproprietary Name (INN)	Hexaflumuron
International Union of Pure and Applied Chemistry (IUPAC) Name	1-(3,5-dichloro-4-(1,1,2,2-tetrafluroethoxy)-phenyl)-3-(2,6-difluorobenzoyl)-urea
Chemical Abstracts (CA) Name	N-(((3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)-phenyl)-amino)-carbonyl)-2,6-difluorobenzamide
Chemical Abstracts Service (CAS) Number	86479-06-3
Structure	
Molecular formula	$C_{16}H_8Cl_2F_6N_2O_3$
Molecular weight	461.14 g/mol
Vapor pressure (Pa at 25°C)	5.87×10^{-9} Pa [1]
Melting point/ melting range	202 – 205°C [2]
n-octanol / water partition coefficient (Log K_{ow})	5.68 at 20°C [1] 5.46 at 24°C [2]
Water solubility	27 µg/L at 18°C [1]

Summaries of proprietary studies cited above are included in 12.2.

4. Sites of introduction and exposure pathways

There are two possible pathways for hexaflumuron entering the U.S. environment that could potentially exist due to the establishment of an import tolerance for use in fin fish:

1) Residues released from imported food containing treated fish.

2) Hexaflumuron released from treatment of finfish in neighboring countries where use could be authorized.

Release of hexaflumuron into the U.S. environment (e.g., soil, surface water, air) could potentially occur through points of introduction to the following ecosystems: (a) ecosystems where the residue of hexaflumuron from unconsumed salmonids products, waste from fish processing plants, or sludge from wastewater treatment plants (WWTPs) might be introduced through landfilling; (b) ecosystems where the residues of hexaflumuron from consumed salmonids products might be introduced into surface water through wastewater from WWTPs; and (c) ecosystems where biosolids from WWTPs are applied to soil.

In addition, hexaflumuron could potentially enter the U.S. environment via water flow from neighboring countries such as Canada where salmonids are produced. However, hexaflumuron is not currently licensed for use in fish treatment in any countries adjoining the U.S.

The environmental exposure and likelihood of hexaflumuron to cause impacts on U.S. ecosystems at the sites of introduction are evaluated in Section 5.

5. Analysis of exposure and risk

5.1 Analysis of environmental risk from potential pathways arising from the release of drug residues, if present, from imported food derived from treated fish

As discussed previously, there are three theoretically possible pathways to the environment at large for hexaflumuron originating in imported food (e.g., fish steaks and fillets):

- ecosystems where the residue of hexaflumuron from unconsumed salmonids products, waste from fish processing plants, or sludge from WWTPs might be introduced through landfilling
- ecosystems where the residues of hexaflumuron from consumed salmonids products might be introduced into surface water through wastewater from WWTPs
- ecosystems where biosolids from WWTPs are applied to soil

The potential for impacts to the U.S. environment through these three exposure pathways is evaluated further below.

5.1.1 Disposal of seized fish and waste from processing of treated fish at U.S. processing plants to landfills

Imported fish which have been treated with hexaflumuron that are processed in the U.S., or that may be seized because of compliance issues may be disposed of in landfills or may be incinerated. This pathway could theoretically lead to hexaflumuron entering the U.S. environment by leaching from landfills. However, the K_{ow}, low water solubility, and molecular structure of hexaflumuron (see Table 1 in Section 3 above) suggest that hexaflumuron will have low mobility in soils and should not leach into deeper layers making transfer to groundwater improbable. In addition, such disposal events are sporadic and rare, and therefore, only a negligible amount of hexaflumuron is expected to be available to potentially leach from salmon products disposed of in landfills.

Furthermore, U.S. landfills are highly regulated by local, state and federal authorities to prevent environmental contamination. For example, most landfills are required to have caps and liners of clay or impermeable membranes to prevent leaching of water or fluids therein (and any contaminants they may contain) to groundwater and/or nearby surface waters (e.g., rivers and lakes). As a result of these controls, there is expected to be minimal or no movement of hexaflumuron out of U.S. landfills and into the adjacent U.S. environment (groundwater or surface water). In addition, because hexaflumuron has a low vapor pressure (5.87×10^{-9} Pa at 25°C, see Table 1 in Section 3 above) it is not expected to volatilize from landfills or enter air to any significant extent. Therefore, based on lack of exposure, significant environmental impacts on the terrestrial and aquatic environments are not expected from residues of hexaflumuron in imported food derived from treated salmonid products that are disposed of in U.S. landfills.

5.1.2 Effluent from wastewater treatment

Hexaflumuron might enter WWTPs in low concentrations via excreta from humans having consumed treated fish, or from factories processing treated fish.

When the input is from human consumption of treated fish then excretion will occur slowly over a prolonged period following consumption. Within the WWTPs it can be expected that there will be negligible degradation of hexaflumuron within the transit time through the plant. However, the low concentrations expected in human feces following consumption of treated fish will be further reduced (diluted) by the excreta from other consumers who had not eaten salmon previously treated with hexaflumuron. Additionally, consumption rates of salmon in the U.S. are low compared to those for most other types of meats, and the distribution of the excreted residues, if any, in the U.S. environment will likely be spatially and temporally variable. For both effluent from factories processing fish and human consumption, the partitioning characteristics are such that hexaflumuron will remain largely adsorbed to the organic matter and inorganic filtration matrices of the WWTPs and be disposed of as biosolids to land, landfill, or incineration. Further, dissipation (e.g., adsorption to sediments) and dilution can be expected in the receiving water.

Based on the above, effluent from wastewater treatment is unlikely to pose any risk to the U.S. aquatic environment.

5.1.3 Application of residues from wastewater treatment as fertilizer to soil

There is a potential pathway for hexaflumuron entering the U.S. terrestrial environment via the use of fertilizers produced from biosolids collected in WWTPs. However, the amounts of hexaflumuron entering the terrestrial environment via fertilizers are assumed to be very limited for the reasons described in Section 5.1.2 above (e.g., low concentrations in biosolids because of expected low concentration in wastewater), as well as considerable dilution in the soil. Additionally, biosolids are used on less than 1% of the U.S. agricultural land (U.S. EPA: https://www.epa.gov/biosolids/frequent-questions-about-biosolids) indicating only limited terrestrial exposure. Furthermore, the K_{ow}, low water solubility, and molecular structure of hexaflumuron (see Table 1 in Section 3 above) suggest that hexaflumuron will have low mobility in soils and should not leach into groundwater or be transported via runoff to surface water.

5.2 Water flow from treatment of fish in foreign countries (e.g., Canada) adjoining the U.S.

Hexaflumuron is currently not registered as anti-sea lice pharmaceutical in Canada or any other countries adjoining the U.S. However, it is reasonably foreseeable that it could be approved there in the future because salmon farming is a major industry in Canada. Therefore, for this reason and because of Canada's close proximity to the U.S., the possible impact to the U.S. environment due to discharge in a neighboring country is assessed below.

Treatment with hexaflumuron is conducted by immersion of fish in enclosed treatment units e.g. well boats, or tarped net pens, at 2 mg/L for 2 h. Following treatment, water is discharged to the marine aquatic environment where hexaflumuron will be rapidly diluted and dispersed in the water. In addition, these discharges are regulated and/or permitted by the country of origin. For example, the operation of fish farms in Canada is regulated to prevent adverse impacts on the environment around the farms. Aquaculture facilities and activities in Canada are regulated under a number of acts, laws, and programs related to environmental management and shared use of aquatic resources. Given this, it is unlikely that an animal drug being used on a Canadian farm would enter U.S. waters at concentrations that could have adverse environmental impacts to the U.S. environment.

Due to the physico-chemical characteristics (Table 1 of Section 3 above) of hexaflumuron, it is very unlikely that hexaflumuron discharged after treatment in a neighboring country will pose any significant risk to the U.S. environment. Based on its low water solubility, high lipophilicity and molecular structure, hexaflumuron is expected to rapidly partition to the sediment phase where it will be immobile. Hexaflumuron is expected to settle in sediment with a gradient from the farm; higher sediment concentrations just beneath and close to the farm, with rapidly decreasing concentrations as the distance from the farm increases, thus residues would remain in the country of origin.

Should a discharge of treatment water occur close to the U.S. border, it is theoretically possible that very small amounts of hexaflumuron could potentially enter the U.S. environment via tides and near-shore currents. However, due to rapid dilution and dispersion, and subsequent settling and partitioning into sediment, it is unlikely that these hexaflumuron concentrations will pose any unacceptable risk in U.S. waters.

6 Description of any alternatives to the proposed use

PHARMAQ is proposing to establish an import tolerance for hexaflumuron in fin fish for human consumption. The only alternative to the proposed action is the “no action” alternative, which would be the failure to establish a tolerance for residues of hexaflumuron in salmonid products. However, based on our analysis in this EA, we do not believe that significant environmental impacts will occur from this action; therefore, the “no action” alternative was eliminated from consideration.

7 Conclusion

Based on the available information on the metabolism, environmental fate, and exposure of hexaflumuron, there is expected to be little or no exposure to hexaflumuron residues in the U.S. environment for any of the exposure pathways evaluated. Therefore, it is concluded that the proposed action of establishing an import tolerance for hexaflumuron residues in salmonids will not result in significant environmental impacts in the U.S.

8 Agencies and persons consulted

This EA was prepared with input from members of the Environmental Safety Team in the Office of New Animal Drug Evaluation in the U.S. FDA’s Center for Veterinary Medicine.

9 Author

Chris Van den Eede

Zoetis Inc.

10 Signature

Dated: XXXXXXXX

Signed: See appended electronic signature page
Chris Van den Eede
Zoetis Inc.

11 References

[1] I. Macdonald, D. Howes, M. Douglas og I. Pell, «XRD 473 – Physico-chemical parameters, ready and inherent biodegradability,» Dow Chemical Europe Laboratory Report Code GHE-P 1466, 1986.

[2] T. Jones-Jefferson, «Series 63: Physical and chemical characteristics of the technical grade of active ingredient, hexaflumuron (DE-473),» Dow Elanco Laboratory Report Coode GH-C-2927, 1992.

12 Appendix: Executive study summaries for cited studies that are considered confidential business information

[1]

Reference

Macdonald, IA, et al. 1986. XRD 473 – Physico-chemical parameters, ready and inherent biodegradability. Dow Chemical Europe Laboratory Report Code GHE-P 1466, 1986.

Sponsor

Dow Chemical Company Ltd., Agricultural Products R&D Centre, King's Lynn, Norfolk. PE30 2JD.UK

Test facility

Huntinqdon Research Centre Ltd., Huntingdon, Cambridqeshire. PE18 6ES. UK

Test substance

Hexaflumuron

Guideline

- EEC Directive 79/831, Annex V, Part A, Method A3, and the Health and Safety Commission's Approved Code of Practice, Test 3.
- EEC Directive 79/831, Annex V, Part A, Method A4, and the Health and Safety Commission's Approved Code of Practice, Test 4.
- EEC Directive 79/831, Annex V, Part A, Method A6, and the Health and Safety Commission's Approved Code of Practice, Test 6.
- EEC Directive 83/791, Annex V, Part A, Method A8 and the Health and Safety Commission's Approved Code of Practice, Test 8.
- OECD Guideline Number 301D, Closed bottle test
- OECD Guideline Number 302B, Assessment of inherent biodegradability

GLP compliance

GLP

Summary and conclusions

The EI mass spectrum is consistent with the given structure. Postulated structures of key fragments are shown together with the number of chlorine atoms predicted from the peak height ratios of each ion cluster.

The CI mass spectrum shows an intense $(M+H)^+$ cluster starting at *M/Z* 461 containing two chlorine atoms and so provided further confirmation of the structure. The base peak at *M/Z 158* containing no chlorine is consistent with the fragment ion shown.

The solvent solubilities were determined:

Solvent	Volume solvent analysed (ml)	Weight XRD 473 determined (g)	Solubility (g/l)
Acetone	-	-	>100
Dichloromethane	5	0.07301	14.6
Ethyl acetate	-	-	>100
Methanol	5	0.05668	11.3
Propan-2-ol	100	0.30296	3.0
Toluene	100	0.64207	6.4
Xylene	100	0.51954	5.2

The relative density was determined to be 1.680.

The vapor pressure at 298°K • 5.87 x 10^{-9} Pa.

The water solubility was found to be 2.7 x 10^{-5} g/L at 18°C.

The n-Octanol/water partition coefficient was determined to be >481,000:1 (log P>5.6821).

XRD 473 attained 76% degradation after 28 days at 20 ± 1°C and may be considered to be readily biodegradable under these test conditions.

[2]

Reference	**Jones-Jefferson, TJ. 1992.** Series 63: Physical and chemical characteristics of the technical grade of active ingredient, hexaflumuron (DE-473). Dow Elanco Laboratory Report Code GH-C-2927, 1992.
Sponsor	DowElanco, 4040 Vincennes Circle, Indianapolis, Indiana 46268-3030, USA DowChemicla Company Ltd., Agricultural R&D Department, Chemical Development, King's Lynn, Norfolk, PE30 2JD, UK
Test facility	DowElanco, Formulation and Science & Technology, 9550 Zionsville Road, Indianapolis, Indiana 46268, USA Department of Physical Chemistry Leeds University, Leeds, UK Huntigdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, UK
Test substance	Hexaflumuron
Guidelines	• OECD Guidelines for Testing of Chemicals, Number 102, Metal Block Method • OECD Guidelines for Testing of Chemicals, Number 109, Pycnometer Method • OECD Guidelines for Testing of Chemicals, Number 105, Column Elution Method • OECD Guidelines for Testing of Chemicals, Number 104, Vapor Pressure Balance Method • OECD Guidelines for Testing of Chemicals, Number 107, Shake Flask Method • ASTM E70-77 • CIPAC MT 46
GLP compliance	GLP
Summary	Hexaflumuron is an experimental insect management compound proposed to be used for the control of termites. Hexaflumuron is also referred to as DE-473, XDE-473 and XRD 473. The physical and chemical characteristics of this compound have been determined in accordance with 40 CFR § 158.190. This report includes data on the physical and chemical parameters of the solid technical grade of active ingredient (TGAI) which are color, physical state, odor, melting point, density, solubility, vapor pressure, dissociation constant, octanol/water partition coefficient, pH and stability. No statistical methods other than arithmetic means, standard deviations and relative standard deviations were used in this study. Four grams of hexaflumuron were weighted into each of two 4 oz. glass bottles, one for storage under ambient conditions and the other for storage at 122°F and placed in the monitored rooms. Fifteen grams each of hexaflumuron was also placed into 8oz. bottles with the appropriate metal coupons or ions and store in the monitored 122°F room for 28 days. After 28 days, all bottles were analyzed using DOWM 100273 for weight percent hexaflumuron and compared with an initial assay.

PROPERTY		VALUE	
63-2	Color	White	
63-3	Physical State	Powder at 20°C	
63-4	Odor	Odorless	
63-5	Melting Point Range	202°C to 205°C	
63-6	Boiling Point	Not applicable for a solid	
63-7	Density	Relative density is 1.680 at 20°C	
63-8	Solubility (at 20°C)	Solvents:	(g/100 mL):
		Water	2.7×10^{-6}
		Acetone	>1.0
		Acetonitrile	1.5
		Dichloromethane	1.3
		Ethyl acetate	>1.0
		Hexane	7×10^{-4}
		Methanol	1.1
		Propan-2-ol	0.30
		1-Octanol	0.2
		Toluene	0.64
		Xylene	0.52
63-9	Vapor Pressure	5.9×10^{-9} Pa at 25°C	
63-10	Dissociation Constant	Not applicable due to the low water solubility of DE-473.	
63-11	Octanol/Water Partition Coefficient	log Kow = 5.462	
63-12	pH	pH = 3.66 for a 10% slurry of Hexaflumuron (DE-473) in water.	
63-13	Stability	Hexaflumuron (DE-473) was found to be stable after 28 days at ambient, 122°F and in contact with stainless steel, pail steel, brass and ferric chloride (metal ions). No absorbance in the wavelength range of sunlight was observed.	

Conclusions

Physical and chemical characteristics of the technical grade of active ingredient, DE-473 have been determined. DE-473 is a white, odorless powder with a melting point range of 202 to 205°C and a relative density of 1.680 at 20°C. The solubility of DE-473 in organic solvents and water was determined and the vapor pressure of DE-473 was found to be 5.9 x 10-9 Pa at 25°C. The octanol/water partition coefficient was determined to be Log K_{ow} = 5.462. DE-473 was found to be chemically stable under the conditions tested.

Electronic Signature for Zoetis Document Number ZRD-STU-085798 (1.0)
VMF 006-294 Hexaflumuron Import Tolerance Environmental Assessment

Chris Van den Eede Approver	12-May-2020 21:26:34 GMT+0000

This is a representation of a Zoetis electronic record that was signed electronically and this page is the manifestation of the electronic signature.

Approved

PACKAGE INSERT

1. Product name

Alpha Flux®
Hexaflumuron100 mg/mL
External Solution

2. Content of the container

2.5 L
10 L
25 L

3. Composition

Each mL of the solution contains:
Hexaflumuron 100 mg
Excipients Q.S. 1 mL

4. Target species

Salmonids

5. Indications of use

For the treatment and prevention of infestations in all juvenile stages of sea lice (*Caligus rogercresseyi*) in salmonids.

6. Dose

Treatment dose: 20 mL of Alpha Flux® per m^3 (1000 L) water in the treatment unit. This corresponds to 2 mg hexaflumuron/liter water (2 ppm).
Treatment period: 2 hours.

7. Route(s) of administration and directions

The product is indicated for bath or immersion treatment in marine waters and it could be administered in fish up tp approximately 800 g.
The treatment should be performed in a closed system such as a well boat or in a sea cage where fish are enclosed by a tarpaulin. Well boat treatment should not be carried out outside the sea site or while the well boat is in transit. This is to ensure proper control of the treatment volume and the treatment dosage, in addition to reducing the amount of product used and environmental exposure. Calculate the water volume as precisely as possible to ensure correct dosing.

Directions:
Calculate the volume in the treatment unit and the product volume to be used. The product can be added directly into the treatment unit or it can be pre-diluted immediately before adding it to the treatment unit. Ensure rapid, but gradual dispersal in the whole water body. This can be achieved, for example, by adding the product slowly into the water aeration system outflow, or through pierced hoses in the treatment unit. Do not disperse under high pressure as this may cause foaming.
Fish density in a tarpaulin can be up to 40 kg/m^3 and up to 90 kg/m^3 in a well boat during treatment.

8. Warnings, interactions and special precautions of use

Ensure that the oxygen level in the water is monitored and kept between 80-110% saturation during the entire treatment.
If treatment of adult stages is required, other products must be used.
Lack of efficacy and reduced sensitivity to hexaflumuron may develop over time.
When applying the treatment, avoid conditions that could diminish product efficacy, such as dirty nets, fecal material or other particles in the water.
Fish with gill disease are especially vulnerable.

Other precautions:
Hexaflumuron demonstrates high affinity to organic matter and particles in the water column and in sediments. Hexaflumuron is relatively stable and slowly degradable when bound to sediments.

The substance affects moulting of crustaceans and should not be released where crabs or lobsters are kept in the vicinity.

Macrofauna monitoring at a low energy site fully treated with hexaflumuron indicated that the overall macrofauna, abundance and diversity, was not affected after treatment. At the same site, hexaflumuron concentrations below the predicted no-effect concentration for crustaceans (*Monocorophium insidiosum*) were measured in sediment. Macrofauna and sediment monitoring was performed 0-1000 m from the cages.

To reduce the risk of bioaccumulation, a single bath should be carried out during the productive cycle of the sea site, that is, during the period that the sea site is operational.

9. Contraindications

Do not use on fish during outbreak of infectious diseases, as treatment procedures may aggravate clinical signs and increase mortality. In clinical trials where fish have been healthy and oxygen levels have been adequate, only temporary behavioral effects should be observed in treated fish.
Fish with skin lesions should not be treated.

Do not use more than once during a production cycle at the farm.

10. Precautions for the administrator

Personal protective equipment consisting of protective clothing (cotton overalls, nitrile or neoprene gloves (0.3 mm thick), eye protection and a disposable face mask) should be worn when handling the veterinary medicinal product. This product may cause skin and eye irritation, and it may cause dermatitis in sensitized individuals. If the product comes into contact with eyes or skin, rinse immediately with plenty of water
People with known hypersensitivity to hexaflumuron should avoid contact with the veterinary medicinal product.

11. Storage conditions

Store between 15°C and 30°C.
Once opened use within 24 months.
The diluted product should be used immediately.

12. Special precautions for the disposal of the unused product or waste material, including the primary container and its content

Do not drop empty containers or containers with remaining concentrated product in soil, water flows or together with domestic waste. All unused product or waste material must be disposed through companies authorized to perform that service safely.

13. Name and address of manufacturer, importer and licensing company

Manufactured by:
Bela-Pharm GmbH & Co. KG
Lohner Straße 19
D-49377 Vechta, Germany

Imported and distributed by:
PHARMAQ Chile Ltda.,
Bernardino # 1981, oficina 202
Parque Empresarial San Andrés
Puerto Montt, Chile

Under License of: PHARMAQ AS, Norway

14. Withdrawal period

Salmonids: 1923 degree days.

15. Label "VETERINARY USE"

VETERINARY USE

16. Sales conditions

Sell under retained veterinary prescription.

17. SAG License Nº

SAG Nº 2411

Keep out of reach of children.

Note of the translator:
I, Natalia Sáez S., Managing Director of Traduc Ltda., hereby certify that this is a true translation of the original Spanish document.
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