PRODUCT PROFILE

Product name:	Clomicalm
Procedure No.:	EMEA/V/C/039/01-03
Marketing Authorisation Holder (Name and Address)::	Novartis Tiergesundheit GmbH Industriestraße 30-34 D-65760 Eschborn Deutschland
Manufacturer responsible for batch Release (Name and Address)	Novartis Santé Animale S.A.; Usine de Huningue; 26, rue de la Chapelle; F-68332 Huningue Cedex
Active substance:	Clomipramine
Proposed International Non-proprietary Name:	Clomipramine hydrochloride
Pharmaceutical form:	Tablets
Strength:	5 mg, 20 mg, 80 mg
Target Species:	Dog
Presentation:	30 tablets and one desiccant sachet per bottle
Packaging and package size:	40 ml HDPE bottle with child resistant closure and sealing disk
Withdrawal period:	n/a
Route of administration:	oral use
Product type:	Pharmaceutical
Therapeutic indication:	As an aid in the treatment of separation related disorders manifested by destruction and inappropriate elimination (defecation and urination) and only in combination with behavioural modification techniques.

III SCIENTIFIC DISCUSSION

1. INTRODUCTION

Clomicalm is presented in tablet form containing 5, 20 and 80 mg clomipramine, as the active ingredient for oral administration to dogs. Clomicalm is given as an aid in the treatment of separation related disorders manifested by destruction and inappropriate elimination (defecation and urination) and only in combination with behavioural modification techniques.

Clomicalm is a broad-spectrum tertiary tricyclic antidepressant drug developed for veterinary use. Clomipramine is a substance inhibiting the neuronal reuptake of serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline.

30 tablets of Clomicalm and one silicia gel desiccant sachet are presented one 40 ml bottle consisting of high density polyethylene with child resistant closure and sealing disc. The bottles are packed in individual cartons.

Clomicalm was presented for an entirely new indication, which is of significant therapeutic interest as provided for under Part B of the Annex to Council Regulation (EEC) No 2309/93. The product was therefore considered eligible for the granting of a Community marketing authorisation via the centralised procedure.

2. OVERVIEW OF PART II OF THE DOSSIER: ANALYTICAL ASPECTS

2.1 QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

Clomicalm contains clomipramine hydrochloride as active ingredient. The active ingredient and all excipients are in compliance with Ph. Eur. quality standards except artificial meat flavour, which is in compliance with in-house standards.

Container:

The container for 30 tablets of Clomicalm is a 40 ml bottle consisting of high density polyethylene with child resistant closure, a silicia gel desiccant sachet and a sealing disc (Integraseal 205 seal). The bottle is packed in individual cartons.

Product Development Studies:

Clomipramine hydrochloride was developed for human use and has been marketed worldwide for many years in different dosage forms. The development of a product for veterinary use was generally based on the composition of these tablets, containing commonly used excipients.

In development studies tablets containing 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 40 mg and 80 mg were manufactured. Results of these studies showed that three tablet strengths of 5 mg, 20 mg and 80 mg were required for the treatment of dogs of different weight. Divisible oblong tablets were chosen to allow individual dosing schemes. To increase palatability of the tablets when administered to dogs, 10 % artificial meat flavour was added. As a result of longer disintegration time being observed with this formulation, the content of microcrystalline cellulose was increased and 3 % crospovidone was added as a disintegrate. Scale-up tests indicated that there would be no problems in manufacturing: tablets from direct compression with a rotary press were comparable in quality (uniformity of mass, hardness, disintegration time) to tablets from the formerly used single punch tablet press. The Applicant confirmed that all batches produced for clinical trials and scale up tests complied with

pharmacopoeial requirements for uniformity of mass and content uniformity. In addition uniformity of tablet halves was tested. Differences in individual masses of halved tablets were not more than 10 % for 5 mg tablets and 7.5 % for 20 mg and 80 mg tablets.

In vitro dissolution studies showed that there was no difference between the commercial formulation and the different formulae used during development. Due to the rapid disintegration and the high water solubility of clomipramine hydrochloride, complete dissolution was observed after less than 30 minutes.

2.2 METHOD OF PREPARATION

Manufacturing formula

The manufacturing formula is given for a batch size of 180 kg and 175 kg. This is consistent with approximately 1 500 000 tablets of Clomicalm 5 mg, 1 000 000 tablets of Clomicalm 20 mg or 500 000 tablets of Clomicalm 80 mg. This batch size of 180 kg was later changed into a batch size of 90 kg (Type I No 16 variation).

Manufacturing processes and in processes controls

All ingredients except magnesium stearate are sieved through a 2000 µm sieve and blended for 30 minutes. After addition of magnesium stearate through a 850 µm sieve blending is continued for 3 minutes. The mixture is directly compressed into tablets. During the compression process, periodic controls on appearance, dimensions, weight, disintegration time, hardness and friability are performed. 30 tablets are packed into one 40 ml HDPE bottle with child resistant closures, containing a desiccant bag.

No validation data for the manufacturing process from the intended production site were provided in the original application; therefore, the Applicant provided as a post-authorisation commitment validation data of the manufacturing process on the first 3 commercial batches including batch analysis data. The batches were put on stability testing and the results reported on an ongoing basis. Specification limits for content of clomipramine hydrochloride at the end of shelf life were tightened to 95-105% for all tablet strengths.
Data showed that the 20 mg and 80 mg tablets fulfilled the specification at all time points at the recommended storage condition (store below 30 °C), whereas the 5 mg tablets showed some deviation from the specification. Since the VICH guideline allows a higher percentage for unspecified degradation products, in November 2001 the Marketing Authorisation submitted a Type II variation adapting the specification limits for the 5 mg presentation.

The CVMP, therefore, agreed that the stability data provided on the first two commercial batches of Clomicalm confirmed the provisional shelf life of 2 years when stored below 30 °C.

2.3 CONTROL OF STARTING MATERIALS

2.3.1 Active ingredient described in a Pharmacopoeia

The active ingredient, clomipramine hydrochloride, is the subject of a monograph in the European Pharmacopoeia. Complete information on clomipramine hydrochloride is given in the dossier. The routine tests and specification limits, defined in the Applicant's testing instructions, show conformity to the current Ph. Eur. monograph for all test parameters including possible by-products from the route of synthesis (imipramine-HCl, 3-chloro-10,11-dihydro-5H-dibenz[b,f]azepine). Loss on drying limits the quantity of moisture and of residual solvents used in the last stages of synthesis/purification. Checking of particle size by the sieve method is sufficient as content uniformity of the tablets is acceptable and the active ingredient is freely soluble in water.

Manufacture and in process controls

The method of manufacture is a multi-step process involving dissolution of the base in organic solvents followed by crystallisation, washing and drying after which the product is milled. Throughout the process the various components (starting materials, solvents, reagents, etc) are extensively controlled to ensure sufficient purity in the final product.

Impurities

Ten potential by-products originating from the route of synthesis have been identified. HPLC is used for separation, detection and evaluation. Batch analysis data from 2 lots of working standard and 5 further batches show that the main impurity in clomipramine is imipramine, ranging from 0.15 % to 0.3 %. All other potential impurities are present only in trace amounts (<0.1 %), if at all. The total concentration of all by-products varied from 0.2 % to 0.4 %. With these data the limits set in the specification can be considered as justified.

Possible residual solvents from the last two steps of synthesis are tested on 2 lots of working standard after the final crystallisation. In addition, testing results of 5 batches have been provided by the Applicant, showing that the limits for toluene are in accordance with the VICH guideline on residual solvents.

Batch analysis

Certificates of analysis are provided for twelve recent commercial batches as well as for 2 batches of clomipramine hydrochloride used in dose-finding studies and for 2 batches used in pre-clinical and clinical testing. All testing results are in conformity to the specified requirements. In addition certificates of analysis for the primary reference material (batch 901389) and the working standard are provided.

2.3.2 Other ingredients described in a Pharmacopoeia

All other ingredients except artificial meat flavour are of pharmacopoeial quality and meet the requirements of the Ph. Eur. For each substance specifications and test procedures are given.

Potential risk of Bovine Spongiform Encephalopathy (BSE): The Applicant submitted assurances of the manufacturer and of the United States Department of Agriculture that lactose of US origin exposes no risk of transmitting BSE when being used. Furthermore, the marketing authorisation holder confirmed that magnesium stearate is of vegetable origin only. Therefore the product is in compliance with Commission Decision 97/534/EC.

2.3.3 Other ingredients not described in a Pharmacopoeia

Artificial meat flavour is composed of hydrolysed vegetable protein from soyabeans, hydrogenated vegetable oil from soyabeans and desiccated pork liver powder. To eliminate the risk of transferring viruses from pork liver to the target animal, the artificial meat flavour is treated by gamma-irradiation with a minimum dose of 25 kGy. Routine tests and methods of manufacture are described both for artificial meat flavour and for the 3 components. Certificates of analysis are provided.

2.3.4 Packaging material

The packaging material consists of a 40 ml HDPE bottle with child resistant closure, a desiccant bag containing 13.5 g silica gel. The FDA has approved the HDPE used for contact with food. For all components testing specifications and batch analysis data are provided and are in agreement with the requirements of the European Pharmacopoeia.

2.4 CONTROL AT INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

There are no intermediate products and therefore no testing occurs at this stage.

2.5 CONTROL OF THE FINISHED PRODUCT

Tests and specifications described under this section are sufficient to assure constant quality of the finished product. It should be noted that disintegration and friability of the tablets are tested, as in-process controls during manufacture, so these tests are not repeated in the control of the finished product. Testing of dissolution according to the USP method is acceptable, because this method is nearly identical to the method of the European Pharmacopoeia. The requirements for content uniformity of USP and of Ph. Eur. are also equivalent.

Validation of analytical methods

Content of clomipramine hydrochloride in dissolution tests, content uniformity and assay is determined by the same isocratic reversed-phase liquid chromatography. This method is sufficiently validated with respect to accuracy, precision (repeatability and reproducibility), linearity and selectivity. As dissolution differs in sample preparation from content uniformity and assay, two sets of validation data are provided.

For the identity test of clomipramine hydrochloride and the semi-quantitative determination of related substances by TLC specificity has originally been accepted. However, the Applicant changed the test method by using High Performance Liquid Chromatography (HPLC). Since the new HPLC method is more sensitive and selective, the related substance GP 38025 is specified for stability control in the new version H4 of the three analytical monographs BE-221, BE-222 and BE-223. The limits of detection are 0.2 µg for 3-chloroiminodibenzyl and 0.05 µg for imipramine and clomipramine hydrochloride.

The determination of total viable count and the tests for specific microorganisms have been validated for detection limit. A product dilution of 1: 100 is adequate to allow typical growth of micro-organisms in the presence of the product except for Clomicalm 80 mg, where no specific microorganisms can be determined.

The Applicant commented that the detection limits of the tests for microbial purity of Clomicalm tablets given in the validation documents are not consistent to the results given in the batch analysis data, because at the time of release of the batches the validation documents were not yet available. However, the tests with these batches have been repeated and satisfactory certificates of analysis re-issued.

Batch analysis

Certificates of analysis are provided for 3 batches of each tablet strength, with batch sizes representing one third of the intended commercial size. All results are in accordance to the specification and show very high uniformity from batch to batch.

In addition the Applicant provided satisfactory data to confirm adequate quality of Clomicalm tablets:

- homogeneity of the powder mixture before compression,
- test to control the number of tablets per vial,
- certificates of analysis for 2-nitrotoluene, hydrogen and hydrogen chloride gas,
- irradiation process for artificial beef flavour,
- composition of the starting material used for manufacture of hydrolysed vegetable protein,
- conformity of the packaging materials to Ph. Eur. requirements,
- method for friability testing and
- acceptance limits for stability studies of clomipramine hydrochloride tested by HPLC.

2.6 STABILITY

2.6.1 Active ingredient

Under accelerated condition clomipramine hydrochloride proved to be stable at elevated temperature and humidity. Exposure to xenon light caused discoloration and degradation to imipramine and unknown products. In aqueous solutions clomipramine hydrochloride is stable at 50°C/1 week in 0.1 N NaOH and in buffer solutions at pH 7.0 and pH 9.0; in 0.1 N HCl and in buffer solution of pH 3.0 slight degradation is observed. Aqueous solutions are also stable against oxygen.

Long term stability studies at 25°C on 5 batches in amber glass bottles over a period of 60 and 48 months showed no significant changes in content of clomipramine hydrochloride, degradation products or other parameters. The testing procedure is sufficiently validated for selectivity, accuracy and method precision, system precision and linearity. Impurities can be quantitated at levels below 0.1 %.

Additional stability studies on 2 batches of clomipramine hydrochloride in simulated bulk containers (low-density polyethylene (LDPE) bags within tin cans) have been performed. Results show that loss on drying reaches upper limit of specification after 24 months at 25°C/60%RH, therefore, a retest period of 24 months is justified for this packaging.
However, with the data provided, a retest period of 5 years under the general conditions proposed by the Applicant (‘‘protect from wetness, excessive temperature variations and direct sunlight“) is justified when stored in glass bottles.

2.6.2 Stability tests on other ingredient(s)

No significant changes have been observed for artificial meat flavour when stored for 3 years at 25°C (1 lot) and for 3 months at 40°C (3 lots). As the main testing parameters are total content of protein, fat, ash and moisture, it seems questionable whether these tests will be stability indicating. However, as the organoleptic properties are satisfactory, the function as flavouring agent seems ensured. At present, a shelf life of 3 years for these other ingredients is acceptable. To justify this shelf life of 3 years, stability data for a total of 3 lots have been provided. Test results for microbial purity at the end of the storage time are satisfactory.

2.6.3 Finished Product

Stability studies have been carried out with 3 batches of each tablet strength in the commercial package for a storage time of 5 years. Specifications are the same as for the finished product at release. In addition, tests for disintegration time and water content are added. The validated testing instructions are used with slight variations concerning sample preparation, column temperature in HPLC (35°C instead of room temperature) and a different silica layer in TLC.

At present results are available for 24 months (1 batch for each dose) respectively 18 months (2 batches for each dose) at room temperature (approximately 25°C), 30°C and 40°C with ambient humidity and for 6 months at 40-°C/75 % relative humidity. At temperatures below 40°C Clomicalm

tablets are stable and specifications are fulfilled for all parameters tested. At 40°C/ambient humidity the amount of 3-chloroimino dibenzyl and the sum of further related compounds increased, whereas at 40°C/75 % relative humidity swelling and discoloration was observed, hardness and disintegration time decreased and the total amount of related substances increased. In addition to imipramine and 3-chloroiminodibenzyl as third impurity 3-chlorodesipramine is occasionally found during stability studies in amounts of up to 0.2 %. This substance is reported separately as it is the main *in vivo* metabolite of clomipramine hydrochloride.

For Clomicalm tablets a shelf life of 24 months was proposed, when stored protected from heat (below 30°C) and moisture. With the results provided, this shelf life was accepted by the CVMP. Further data provided by the marketing authorisation holder from stability testing of the first 3 production batches confirmed this shelf life .

3. OVERVIEW OF PART III OF THE DOSSIER: TOXICOLOGICAL AND PHARMACOLOGICAL ASPECTS

3.1 Safety

3.1.1 Pharmacodynamics

Clomipramine has been used in the treatment of psychic disorders in humans for over 30 years and the pharmacological profile of the compound is considered to be well established. The majority of experiments reviewed in the pharmacodynamic documentation concerned the introduction of clomipramine into human medicine. The neurochemical properties of the drug and its effects on behavioural parameters in laboratory animals are sufficiently illustrated, although individual animal data were not included in the reports.

In vitro, clomipramine exerted strong inhibition of serotonin uptake into neuronal stores, while its principal metabolite desmethyl clomipramine preferentially inhibited noradrenaline uptake. Both compounds contribute to the inhibitory effect on serotonin and noradrenaline uptake of the drug *in vivo*. Experimental results obtained in mice and rats have linked the inhibitory effect of clomipramine on biogenic amine uptake with behavioural changes, which could simply be described as a decrease in aggressive behaviour and an increase of immobility in behavioural despair situations.

In human patients suffering from psychic disorders, clomipramine has been proven to be effective in the relief of depression, anxiety and obsessive compulsive disorders and has been considered as a potent antidepressant. These disorders are assumed to be correlated with a deficiency of serotonin and catecholamines at specific receptors in the brain. It is assumed that clomipramine is effective by inhibiting the uptake of biogenic amines into neuronal stores and by increasing their concentration in the synaptic cleft.

Little information is provided on the aetiology of behavioural disorders in the target species the dog. Reports regarding the occurrence of obsessive compulsion-like disorders in about 2 % of the dog population have been issued. The effect of clomipramine on the turnover of biogenic amines in normal canine brain has been investigated. The findings suggested a decrease in the ratio serotonin / noradrenaline and dopamine metabolites after administration of a daily oral dose of 3 mg/kg bodyweight given with the evening feeding over a period of 6 weeks. The results of these reports were interpreted as follows:

> "Given that dogs with compulsive disorders respond to clomipramine, the present findings support the notion that affected dogs may have a similar noradrenaline - serotonin dysfunction to humans with obsessive compulsive disorders."

At elevated doses irritability and hyperactivity occurred and seizures were produced in cats and rabbits after intravenous injection. Food and water intake was slightly reduced in rats. This was attributed to the restriction of the uptake of serotonin, which is considered to exert an inhibitory role in food intake. Anticholinergic effects of clomipramine were considered to be responsible for the decreased motility of the gastrointestinal tract. Elevated prolactin levels were measured in male rats after parental doses of 10 to 30 mg/kg bodyweight clomipramine. In contrast, clomipramine did not affect serum prolactin levels in dogs treated with the therapeutic dose and 5 times the therapeutic dose for 14 days.

Several studies were performed in dogs in order to examine the haemodynamic effects of clomipramine. Clomipramine exerted cardiotoxicity and vascular effects as evidenced from a depression of heart rate, myocardial contractility, cardiac output and stroke volume and a decrease of mean arterial pressure. ECG tracings revealed a deformation of the QRS complex, a prolongation of PQ interval and a slight prolongation of atrioventriculair conduction time. Cardiotoxic effects were more pronounced in dogs with experimentally induced ischaemic heart lesions. These effects occurred at elevated oral doses.

Depression of haemodynamic parameters occurred at intravenous doses of 0.5 to 1 mg/kg bodyweight and above. Some dogs died at a dose of 10 mg/kg bodyweight. At lower doses (< 0.5 mg/kg bodyweight) haemodynamic effects were reversed, as clomipramine produced a transient increase in heart rate, myocardial contractility, cardiac output and mean arterial pressure. It was suggested that the cardiotoxic effects of clomipramine be due both to the anticholinergic activity and the direct myocardial depression of the compound.

A study in dogs with single oral doses of 4 or 12 mg/kg bodyweight revealed no significant effects on ECG tracings different from pre-treatment values. It was concluded that the threshold for cardiac effects of clomipramine is above 4 to 12 mg/kg bodyweight.

Clomipramine interacted with other psychotropic drugs. With respect to the envisaged application in dogs the potentiation of narcotics such as barbiturates, neuroleptics and haloperidol appears relevant. Clomipramine potentates the effects of monoaminooxydase (MAO) inhibitors. However, these compounds have not yet been introduced into use in canine medicine.

More information was requested on the causal relationship between behavioural disorders in dogs and neurochemical correlates justifying the treatment with the antidepressant clomipramine. The Applicant responded that a relationship between behavioural diseases and neurochemical processes is impossible to establish. The CVMP conceded the difficulties of neurochemical investigation and therefore, the Clomicalm treatment schedule is primarily based on clinical experience.

Data regarding the possible influence of long term treatment with Clomicalm on lipid metabolism in dogs was requested from the Applicant. It was questioned whether secondary effects, which have been associated with lipid metabolism disturbances in laboratory animals and humans, are also likely to occur in dogs. According to the Applicant, data from tolerance studies in dogs did not give any evidence of lipid metabolism impairment and more intense studies would be of academic interest only. The CVMP conceded this. It was emphasised that interference with lipid metabolism was observed in rats after long term treatment with clomipramine at 20 mg/kg bodyweight and above. This was associated with atrophy of the testes and accessory sex organs and cardiac thrombosis at elevated doses. In humans, hyperlipidaemia, retinopathia and hepatosplenomegalia were related to the administration with clomipramine-like drugs. Cardiac toxicity and testicular atrophy were also noticed in dogs at 50 mg/kg bodyweight but the aetiology of these changes is unknown.

3.1.2 Pharmacokinetics

Data on pharmacokinetics were provided for man, rat, rabbit, mouse and the target species dog. Most of the information provided by the Applicant was published literature. Three genuine studies were available for the target species dog. One of them was conducted with radiolabelled clomipramine while two other studies used either single or multiple dosing of unlabelled clomipramine.

Absorption and excretion

Absorption and excretion of clomipramine was investigated by use of radiolabelled clomipramine in rats, dogs and man following single oral and intravenous doses. Absorption after oral dosing appeared to be rapid and nearly complete.

In rat and dog (5 mg/kg bodyweight), radiolabelled clomipramine was mainly excreted in faeces (ca. 80 % of the dose) and to a lesser extent in urine (up to 20 % of the dose). Excretion was relatively fast and more than 95 % of the dose were recovered *in excreta* within 3-4 days post dosing. The proportions of the dose excreted in urine and faeces were found to be largely independent of the route of administration (oral or intravenous). In rats there was some evidence for enterohepatic circulation. At 14 days after the oral administration excretion was about 70-90 % of the total dose.

Distribution

Blood

Data on blood or plasma concentrations and kinetics of clomipramine and the principal metabolite desmethylclomipramine were provided for man, rats and in the target species dog. Drug concentrations in blood plasma were remarkably low when compared to those in organs and tissues.

In human plasma following single intravenous administration of 25 mg of ^{14}C-clomipramine concentrations of parent clomipramine decreased from 45 µg/l to 20 µg/l between 0.5 and 8 hours after dosing. The concentration of the demethylated metabolite ranged from 17 µg/l to 5 µg/l in that time period. Following an oral dose of 25 mg of ^{14}C-clomipramine the drug reached its maximum level of about 20 µg/l after 2-3 hours post dose and fell to 7 µg/l after 24 h. The metabolite desmethylclomipramine showed values between 8 µg/l and 4 µg/l during this period. The elimination half-life of clomipramine in man following single oral or intramuscular administration of 1 mg/kg bodyweight was found to be relatively long with 20-25 h.

In man, following multiple oral doses (3 x 25 mg/day) steady state plasma levels of clomipramine were reached after 7 days with a mean concentration of 38.6 µg/l. In contrast, mean plasma levels of desmethylclomipramine still increased from 48.9 µg/l at day 7 to 68.7 µg/l at day 28. Plasma levels of the metabolite tended to exceed those of parent compound following multiple oral doses.

In rats following single intravenous treatment of clomipramine at 10 mg/kg bodyweight plasma levels of clomipramine were reported to decline in three phases with a terminal half-life of 10.9 h. The apparent volume of distribution was relatively high (10.3 l/kg) indicating significant tissue uptake.

Repeated treatment of rats with daily intraperitoneal injections of clomipramine at 15 mg/kg bodyweight for 4 weeks resulted in changes in most of the pharmacokinetic parameters. These are a decrease in the time to maximal plasma concentration of desmethylclomipramine; an increase in maximal concentrations of clomipramine and desmethylclomipramine; and a decrease in $t_{1/2}$ of elimination of both clomipramine and desmethylclomipramine.

In the dog, pharmacokinetic data were only available after single intravenous (2 mg/kg bodyweight) and single oral dosing (4 mg/kg bodyweight). Following the intravenous administration clomipramine concentrations were found to decline in 3 distinct phases. The half-life for the terminal elimination phase was 6.4 h for clomipramine. Desmethylclomipramine showed a terminal elimination half-life of 3.8 h. The volumes of distribution were relatively large with 3.8 l/kg for clomipramine and 3.6 l/kg

for the sum of desmethylclomipramine and clomipramine. Maximum concentrations for the principal metabolite desmethylclomipramine were reached after 0.42-1.08 hours post dosing with about 50 nmol/l (15 µg/l).

Clomipramine and its desmethyl metabolite appeared rapidly in plasma after the oral administration of clomipramine to fed and fasted dogs (t_{max} 1-1.5 h). Maximum plasma levels for clomipramine in fed and fasted dogs were 601 nmol/l (189.3 µg/l) and 379 nmol/l (119.4 µg/l), respectively. The plasma profile of the metabolite desmethylclomipramine followed that of clomipramine with a minimal delay. Maximum plasma was 169 nmol/l (50.7 µg/l) for fed dogs and 155 nmol/l (46.5 µg/l) for fasted dogs. The terminal elimination half-life in fed and fasted dogs was about 5-7.5 hours for clomipramine and 2-3 hours for desmethylclomipramine. The relative oral bioavailability determined from plasma data for the sum of clomipramine and the metabolite desmethylclomipramine was 22 -26%.

The oral administration caused statistically significantly higher bioavailability and maximum plasma concentrations in fed as compared to fasted dogs for clomipramine and the sum of clomipramine plus desmethylclomipramine ($p < 0.05$). However, no statistically significant differences were found for $t_{1/2}$ and t_{max} of clomipramine and desmethylclomipramine.

In dogs following multiple oral doses of clomipramine twice daily over 10 days (1 - 4 mg/kg bodyweight) the increase of plasma concentration of both clomipramine and desmethylclomipramine was moderate. Accumulation ratios were 1.2 for clomipramine and 1.6 for desmethylclomipramine at steady state steady state levels were reached after 3 days. The ratio of plasma clomipramine to desmethylclomipramine at steady state was approximately 3:1.

Clomipramine was found to be extensively bound to plasma proteins (>97%).

Tissues

Distribution of clomipramine in the body tissues was studied in mice, rats, rabbits. Information on organ and tissue distribution of clomipramine was not available for dogs. In the species investigated, the compound revealed a markedly high affinity to body tissues. As demonstrated in various experiments, clomipramine penetration from blood into tissues occurred very rapidly following intravenous administration. The pattern of distribution in tissues can be characterised by high to medium (short-term) concentrations especially in lungs, adrenals, heart and brain. Elevated levels were also observed in the excretion organs such as liver (particularly after oral dosing) and kidney.

In rats, dose proportionality of tissue uptake of orally dosed ^{14}C-clomipramine was observed within a dose range of 5-20 mg/kg bodyweight. Approximate steady state levels were reached after about 14 days. The increase in tissue concentrations was about three folds at that time. Continuation of treatment for up to 28 days caused a further but only moderate increase in tissue concentrations. Tissue accumulation was found not to occur to a great extent following oral doses of 5 and 20 mg/kg. However, at higher oral doses of 50 mg/kg bodyweight a different distribution pattern in tissues was observed. In blood, liver, kidney the uptake was approximately dose proportional while in testes, lung, adrenals, spleen, fat an unproportionally high increase of drug concentrations was observed.

Biotransformation

In the laboratory species investigated and in man N-desmethylation appeared to be the major route of biotransformation. However, in *in-vivo* and *in-vitro* experiments several other metabolites have been identified in urine and tissues. They included N-oxides and several compounds derived from benzylic or phenolic hydroxylation of clomipramine. Metabolites were also present in conjugated form.

3.2 Toxicity

A single oral dose of 1 mg/kg bodyweight was the lowest dose tested in the acute toxicity in rats. No behavioural changes and no toxic effects evident at pathology were recorded at this dose level. However, animals in the toxicity studies were only examined for changes from normal appearance but were not subjected to specific behavioural tests.

At 10 mg/kg bodyweight the behaviour of rats was clearly affected as evidenced from the occurrence of exophthalmus, reduced spontaneous motility, ataxia, tail rigidity and alertness. Higher doses produced ventricumbency, hypoventilation, tremor, cyanosis (at 100 mg/kg bodyweight) and tonic convulsions (at 150 mg/kg bodyweight). Elevated mortality rates were recorded at 300 mg/kg bodyweight. Deaths occurred within 1 to 2 days post dosing.

In the repeated oral dose toxicity studies in rats the lowest doses used were 12.5 mg/kg bodyweight in the 52 weeks study and 20 mg/kg bodyweight in the 104 weeks study. Animals were checked daily for changes in their attitude, but treated rats remained comparable throughout the experiments with control groups in this respect. One female dosed with 20 mg/kg bodyweight exhibited convulsions at a single occasion but the relation to treatment is uncertain. Even at higher doses (up to 100 and 125 mg/kg bodyweight) no behavioural changes were recorded, which were regarded as compound related.

The first drug effect noted at the lowest dosage level in the 52 weeks toxicity study (12.5 mg/kg bodyweight) was a reduction of body weight gain. This effect was ascribed to the food consumption lowering effect of the compound and reached significance even at 20 mg/kg bodyweight in the 104 weeks study. In the highest dose group (100 mg/kg bodyweight in the 104 weeks study) depression of body weight gain was very marked and males and females gained approx. 70 % less weight than controls at the end of the 104 weeks treatment period. Reduction of food consumption became apparent 7 to 14 days after beginning of treatment at the 20 mg/kg bodyweight dosage level in the 104 weeks study. In some cases this was accompanied by reduction in water intake. Depression of food consumption showed a clear dose response. In experiments on the pharmacodynamics of clomipramine depression of food intake was frequently observed and has been correlated with the inhibition of serotonin uptake from the synaptic cleft. Serotonin is considered to exert an inhibitory effect on food intake.

At high dosage levels (100 and 125 mg/kg bodyweight) the mortality rates were increased in the course of the 52 weeks study. In the 104 weeks study survival rates appeared to be almost unaffected in male rats at doses up to 100 mg/kg bodyweight and were elevated in females at doses from 40 to 70 mg/kg bodyweight. This was explained by a retarded onset of age related lesions due to reduced body weights gains preferentially in the second treatment year.

Some morphological changes seen at necropsy in the 104 weeks study were attributed to phospholipidosis: foamy macrophages in lungs, lymph nodes and spleen and cytoplasmatic vacuolation in centrilobular hepatocytes, prostate, seminal vesicles and adrenal cortices. These effects were noted at the 20 mg/kg bodyweight dosage level and were more pronounced at higher doses. At 40 mg/kg bodyweight and above the serum concentration of alkaline phosphatase was elevated probably in relation to changes in hepatocytes. Fatty changes of the liver parenchyma were also recorded in the 52 weeks study at 25 mg/kg bodyweight.

Two publications provided by the Applicant discussed drug induced phospholipidosis in more detail. Clomipramine as an amphophilic drug contains hydrophilic and lipophilic molecular sites and is believed to build complexes with phospholipids. The physicochemical properties of the phospholipids are changed in this way and their degradation by lysosomal enzymes is impaired. Abnormal lysosomes known as myeloid bodies occur intracellularly. In the lung and in other tissues this leads to an accumulation of phospholipid-drug-complex storing macrophages, which turn to foam cells. Most frequently affected organs and tissues are the mesenteric lymph nodes, spleen, liver, lung, dorsal root ganglion, and retina and, in some instances, the skeletal muscle. The accumulation of myeloid bodies in cells is believed to decrease their resistance against microbial infections and to increase damage and

death of affected cells. In men, treatment with some amphophilic drugs was associated with retinopathia, hyperlipidemia, hepatosplenomegalia and liver cell necrosis. Administration of the clomipramine related imipramine at a dose of 45 mg/kg bodyweight to male and female Sprague Dawley rats for two years demonstrated that affected cells remained morphologically intact. The number of myeloid bodies decreased after discontinuation of treatment indicating that the effect was reversible.

Testes and accessory sex organs of males showed a dose response with respect to the frequency of atrophy, mineralisation, epithelial vacuolation and hypospermia of the epidymides. Testicular atrophy was already noticed in one male dosed with 25 mg/kg bodyweight in the 52 weeks study, but the level of significance was reached first at higher doses.

Cardiac thrombosis and dilatation was a significant finding in males treated with 100 mg/kg bodyweight. Cardiotoxicity is an unwanted effect of clomipramine, as was evident from pharmacological investigations in dogs and was suggested to be due both to the interaction of clomipramine with neurotransmitters and to direct myocardial toxicity. Cardiac thrombosis, as observed in rats here, was considered to be secondary to phospholipidosis.

In kidneys tubular dilatation and degenerative changes were observed at the dose of 125 mg/kg bodyweight in the 52 weeks study.

The total number of benign and malignant neoplasms was not increased by treatment. In contrast, the number of some neoplasms such as tumours of the pituitary and the mammary gland were decreased at 70 and 100 mg/kg bodyweight. This was suggested to be due to the low food intake and reduced body weights at these dosage levels and was accompanied by a concurrent retardation of age related alteration.

Findings made in mice in the course of carcinogenicity studies were consistent with those obtained in rats with respect to food consumption and body weight gain. Both parameters were dose dependently depressed. This effect was significant in females at 40 mg/kg bodyweight and in males at 80 mg/kg bodyweight. Body weight gains in high dosed mice (80 mg/kg bodyweight) were, however, less markedly reduced than in high dosed rats (100 mg/kg bodyweight) and were little more than 10 % below control gains at the end of the treatment period.

In treated male mice the degree of amyloidosis of the testes was dose dependently elevated. This finding was already made at the lowest dose (20 mg/kg bodyweight) and reached significance at 80 mg/kg bodyweight. In the high dose group absolute weights of testes and epididymides were reduced. Changes in the testes and accessory organs were probably compound related and had been also observed in rats.

The total number of benign and malign neoplasms in mice was not influenced by treatment. However, the incidence of some tumours such as hepatocellular carcinoma and adenoma, and lymphosarcoma in males and of uterine leiomyosarcoma in females was elevated at 80, 40 and 80, and 80 mg/kg bodyweight, respectively. The author did not range these findings as dose related for several reasons, i.e.: no increased frequency of hepatocellular carcinoma and lymphosarcoma was detected in females; no correlation between hepatocellular carcinoma and hepatocellular alterations were established; no significance was determined at the time adjusted analysis; numbers were considered to be within the normal historical control ranges; and, clomipramine was not mutagenic in the dominant lethal test in mice.

Some other findings were reported with a higher incidence in tested animals than in controls: retinal atrophy in female rats treated with doses from 40 to 100 mg/kg bodyweight and phthisis bulbi in male rats treated with doses from 70 and 100 mg/kg bodyweight. Because both lesions were seen in one sex only they were not considered as compound related. Phthisis bulbi was unilateral in most cases and was attributed to bleeding from the orbital sinus. Phthisis was also detected more often in treated mice (males and females) than in controls. Drug relation is uncertain.

The Applicant provided studies in mice, rats and rabbits, although only investigations of the embryotoxic / foetotoxic and teratogenic potential in one animal species are required for compounds intended for treatment of non food producing animals according to Directive 92/18 EEC. All experiments were performed in 1964 to 1975 and do not meet current standards with respect to the number of doses and the dose ranges used and to the number of animals per group and investigations performed in some cases.

Two doses were used in the studies in rats. The doses used produced slight toxic effects in parental animals and it may be argued that they were too low to fully characterise the toxic potential of clomipramine on reproductive function. Degenerative changes of the testes and accessory sex organs were detected in rats in the course of repeated dose toxicity studies and were clearly evident at 50 mg/kg bodyweight. In the pharmacodynamic experiments serum prolactin concentrations were significantly elevated in male rats (not measured in females) after subcutaneous dose of 10 to 30 mg/kg bodyweight. The relevance of theses changes for reproductive function of males and females cannot be derived from these studies.

Higher dosage levels were used in studies in mice, rats and rabbits. Toxic symptoms in parental animals were very slight. In mice and rats treatment covered the period of implantation and organogenesis. Treatment of mice and rats produced significant embryotoxic effects as evidenced from reduced mean foetal weights at 100 mg/kg bodyweight in mice and from elevated embryonic resorption rates and reduced mean foetal weights at 25 and 50 mg/kg bodyweight in rats.

No corresponding results were obtained from the study in rabbits and no specific investigations of the skeleton and the viscera were performed in the offspring of rabbits.

The study in rats did not reveal significant effects on pups. However, the highest dose produced slight adverse effects in dams. Some adverse findings in pups such as cold body surface after delivery and hunched position and thin appearance during nursing were more frequently seen in the offspring from high dosed dams (30 mg/kg bodyweight) than in controls. Furthermore, mean body weights of these pups were slightly, not significantly, reduced at weaning. The doses used might have been too low to produce clear compound related effect.

The mutagenic potential of clomipramine was investigated in test systems allowing for the detection of gene mutations in prokaryotes and eukaryotes and for chromosomal aberration *in vitro* and *in vivo*. With the exception of the dominant lethal test in mice, which was performed in 1972, all studies were carried out according to international standards during 1995. There was no evidence for a mutagenic potency of clomipramine in any of the tests.

3.3 Studies on other effects

Immunotoxicity

No specific investigations were performed.

Observation in humans

Clomipramine produced side effects such as dry mouth, bitter taste, sweating, accommodation disturbances, glaucoma, nausea, vomiting, obstipation (diarrhoea), urinary retention and sometimes frequent urination caused by the anticholinergic properties of the compound. Central-nervous effects of clomipramine consisted of tremor and ataxia at elevated doses and convulsions were provoked in some patients. Psychiatric effects are described as hypomanic over-swing in depressed persons, hallucinations, memory deficits, depersonalisation, de-realisation. After oral administration clomipramine can provoke aggressiveness, irritability and agitated behaviour at elevated doses. There is an increased suicidal risk in susceptible persons. Intravenous injection of clomipramine is followed by sedation and most patients fall asleep at infusion. This was believed to be related to a different metabolism of clomipramine when administered by this route. Clomipramine was considered to be a

potential lethal drug and doses above 500 µg / person (approx. 10 mg/kg bodyweight) are considered as risk doses.

It is noted that children are more sensitive to overdose with tricyclic antidepressants or clomipramine. In several countries the use of clomipramine is only recommended in children over the age of 5 - 6 years. Although clomipramine is not specifically named, fatalities in children have been reported with tricyclic antidepressants. Therefore, an appropriate warning has been included in the SPC and the labelling under special warnings.

Cardiovascular complications were rarely recorded in healthy patients, but clomipramine should not be administered to patients with recent myocardial infarction or with pre- existing heart diseases. At overdoses clomipramine can provoke cardiac conduction disorders and cardiac arrest. Clomipramine depressed sexual activity and produce testicular changes at high doses. It is uncertain whether effects on spermatogenesis and male fertility occur at normal doses in patients. Clomipramine affects prolactin levels but the significance of his effect is not known. Galactorroe has been reported in some patients.

Weight gain under prolonged treatment with clomipramine has been reported. Serum transaminase elevations were frequently seen at the beginning of treatment, but severe hepatotoxicity was rarely reported. However, clomipramine should not be administered in patients with liver damage.

3.4 Ecotoxicity

Clomicalm is intended for treatment of a low number of individual dogs. Therefore, it is concluded that the impact of faecal or urinary contamination to the environment with clomipramine or its metabolites is low.

4. OVERVIEW OF PART IV OF THE DOSSIER: CLINICAL ASPECTS

4.1 Pre-clinical studies:

In vitro clomipramine is a potent inhibitor of neuronal serotonin and noradrenaline-re-uptake. In addition, clomipramine has anticholinergic activity. In human patients suffering from psychic disorders clomipramine is proven efficacious in the treatment of depression, panic attacks and obsessive-compulsive disorders. A correlation of these disorders is postulated with disturbances in central serotonin and catecholamines activities. Clomipramine is assumed to exert antidepressant and antiobsessional effects by correcting this imbalance. The same hypothesis is proposed for canine grooming stereotypes.

A large number of toxicity studies with clomipramine after single or repeated oral, intramuscular or intravenous administration is presented which were originally conducted to support the application for its therapeutic use in humans. Most of these studies date from the sixties and seventies and do not comply with present GLP standards. The final formulation was not used in any of these studies.

A more recent acute oral toxicity study in dogs (GLP) showed no significant evidence of toxicity after single oral administration of 10 times the recommended maximum daily dose except for transient CNS-stimulation. Macroscopic abnormal findings in the liver and changes in brain and heart weights recorded for treated animals at post mortem examination were not explained.

Reports on withdrawal syndrome in human patients after cessation of clomipramine suggest that Clomicalm in dogs should be withdrawn by decreasing doses step by step. The Applicant differentiates between the acute incidence of side effects after stopping clomipramine therapy (analogous to the withdrawal syndrome in human beings) and the return of behavioural symptoms. The CVMP considered these data and concluded as follows:

i) Regarding the acute incidence of side effects after stopping clomipramine therapy, in all clinical studies the clomipramine dose was not tapered at study termination. Only 1-2 cases treated with the low clomipramine dose were reported in the follow-up investigations that could be interpreted as being a withdrawal syndrome. In the 6 month-tolerance study in dogs in which clomipramine dose in half of the dogs was tapered at the end of the study and stopped abruptly in the remainders, no adverse effects were recorded.

ii) The return of behavioural symptoms after approximately 4 to 39 weeks following study termination was reported. In 6 of 9 cases, the end of trial achieved no control of signs and in 3 cases complete control of signs was achieved by study termination. It is not possible to determine from the available data if these cases represent a relapse of the original problem or were new cases induced by changes in the management of the dog. Even in the event of relapse, it is not possible to know to what extent the original disorder was cured or if the symptoms were only controlled. The Applicant considers however a worsening rate of only 12 %, 6 to 12 months after study termination acceptable for a condition as serious as separation-related disorder.

4.2 Clinical studies:

In the original submission, the Applicant proposed the following indications: "Treatment of anxieties (generalised anxiety and anxieties associated with separation from the owner) and treatment of stereotypies such as lick dermatitis". The original clinical efficacy claim of clomipramine in the treatment of anxieties and stereotypic disorders such as lick dermatitis was not satisfactorily proven. The Applicant, therefore, agreed to limit the indication to "As an aid in the treatment of separation-related disorders manifested by destruction and inappropriate elimination (defecation and urination) and only in combination with behavioural modification techniques".
Three clinical studies were presented for the demonstration of efficacy of Clomicalm in the treatment of anxiety, in particular separation anxiety with hyperattachment to the owner in dogs. These were two dose titration studies in a total of 139 dogs, and one multicentric dose confirmation/ field trial in a total of 84 dogs. In each trial, treatments with clomipramine were combined with behaviour modification techniques. Dogs receiving behavioural therapy alone served for controls (placebo). The field trial was conducted in accordance with European and U.S. GCP requirements.

Results of the clinical trials in separation anxiety indicated that the administration of clomipramine in combination with behaviour modification techniques was effective in the relief of symptoms. Statistical analysis of data revealed that treatment with clomipramine at daily doses of 1-2 mg/kg bodyweight *bis in die (bid*) (the highest dose tested) was the most effective, when compared to lower doses or to placebo (behavioural therapy only).

A broad spectrum of behavioural symptoms related to separation anxiety, to general anxiety as well as signs of hyperattachment to the owner were evaluated. The behavioural symptoms were not well defined (e.g. what was considered to be normal, species-related, abnormal, acceptable or unacceptable behaviour). Symptoms of anxiety/ separation anxiety (medical as well as behavioural differential diagnoses) were described, but not well documented. The ratings of behaviours done by the owners, although under supervision of the investigators, are considered of limited value because of their personal involvement in the behavioural abnormalities of their dogs. The statistical analysis of data is not entirely conclusive. Statistically significant differences between groups were achieved at most time points for global scores based on the owners' global assessment, while statistically significant differences for individual parameters were only reached for certain time points due to low and variable number of comparable cases in the groups. A post-observation period was included in only one of the studies (the GCP field trial).

From literature presented it is understood that most behaviour problems in dogs such as those addressed in the clinical studies are learned disorders that arise from conflicts such as limited adequate housing, isolation, social deprivation etc. Most of the behaviour problems are considered usually normal species-specific behaviours that clash with human life-style and occur in a situation or manner

that is unacceptable to the owner, although behaviours may be abnormally intense or frequently repeated. These behaviour problems are candidates for behaviour modification techniques aimed at both the dog and owner. In certain cases, when the unacceptable behaviour is strongly maintained, adjunctive drug therapy may be helpful.

Insufficient clinical studies were submitted for the demonstration of clomipramine in the treatment of stereotypes, such as lick dermatitis.

Since the Applicant no longer proposes the treatment of stereotypic disorders, the recommended therapeutic dose for the treatment of separation-related disorders is the high dose used in the multicentric clinical study (1-2 mg/kg bodyweight *bid* corresponding to a total daily dose of 2-4 mg/kg bodyweight). This study was proven to be efficacious in the treatment of separation-related disorders. A follow-up investigation was made approximately 6 months after study. The CVMP considered that the reliability of these results is limited because the investigations were made after completion of the study and the management of the dogs was not longer standardised. The cause and severity of behavioural signs were not assessed and were not compared to the original problems prior to therapy. Satisfactory data are available for a low number of dogs. The dose determination study in a total of 12 dogs using 3 different dosage regimens versus placebo was presented as an abstract only and did not permit the establishment of an effective therapeutic dose due to the limited animal number. No post observation periods were included in these studies.

The Applicant confines and restricts the claimed indication to the treatment of separation related disorders in combination with behavioural modification techniques. Separation related disorders occur when dogs are separated from their owners. The Applicant mainly refers to the multicentric clinical efficacy trial in France, UK and US, which was a GCP study and where all key parameters as required were met. The methods chosen for monitoring the dogs' behaviours are satisfactorily justified. The scoring schemes chosen are reliable from a statistical point of view but do not subtly differentiate from a clinical point of view. The following conclusions of the multicentric clinical efficacy trial can be drawn:

- Regarding the outcome of therapy, only a small number of dogs were finally rated as cured (e.g. complete control of behaviour problems after study termination). The majority of dogs were rated as not completely controlled and required continuation of therapy.
- Behavioural therapy (placebo) showed considerable effects.
- The medicinal relevance of clinical improvement of symptoms cannot conclusively be assessed.
- The diagnosis of separation-related disorders is mainly based on the presence of at least one sign (destruction, defecation, urination, etc.) occurring in the absence of the owner and stated as being unacceptable to the owner. The frequency and/or severity of behaviour problems were not given. For symptoms (appearance/disappearance, improvement, no change, worsening) no precise information regarding the extent of progression or regression of any symptom throughout therapy was given.
- Many cases of behaviour problems arose at the age of 3-6 months (an age where such signs are considered normal puppy behaviours). The fact that owners contribute to behaviour problems of their dogs by themselves (e.g. by insufficient training, inappropriate housing or management) was not addressed. Under practical field conditions and according to good veterinary practice, the knowledge of housing and management of the dog is necessary in order to choose an adequate and causative treatment regime.
- The most frequent side effects occurring during clomipramine therapy were mild intermittent vomiting, diarrhoea, increased or decreased appetite, and lethargy.

At the CVMP oral hearing in July the Applicant emphasised particularly that separation-related disorders are not induced by loneliness or bad housing or management conditions as assumed by many people. Moreover, the Applicant considered caging as an inadequate and not an acceptable method to treat separation-related disorders. Since the diagnosis of separation-related anxiety as defined by the Applicant does not apply to crated or otherwise confined dogs, at least those cases in which caging or signs of caging were mentioned should have been excluded from efficacy evaluation. However, since no valid information on individual housing and management conditions was available and caging or

crating was used by two investigators in the US to treat separation-related anxiety, therefore, some of the data in this report may be only of limited value for the efficacy evaluation.

The most frequent types of aggression in dogs are dominance aggression and fear-related aggression of which may occur in combination with separation-related disorders. There was no evidence of clomipramine inducing or worsening aggressive behaviour in ten clinical efficacy trials submitted.

Furthermore, the Applicant was asked to discuss the benefit of Clomicalm in combination with behavioural therapy in the treatment of behavioural disorders such as anxieties and stereotypes in dogs, when compared to behavioural therapy alone. However, the Applicant has now proposed the term separation-related disorders or separation-related problems because the pathogenesis is probably multifactorial and includes elements of panic and changes in arousal as well as anxiety. There is no consistency in expert opinions on the relative importance of behavioural therapy and drug therapy to treat behavioural disorders in animals. To the Applicant's knowledge there is no controlled study demonstrating that behavioural therapy alone is effective in behavioural disorders including separation-related disorders. Some behavioural therapies such as tethering or confining dogs into cages in the absence of the owners or the use of electro shock collars are considered simply inhumane. In the clinical trials a reasonable but inadequate response was obtained in the placebo group (behavioural therapy alone). In the view of the Applicant behavioural therapy alone cannot be recommended to treat separation-related disorders for the following grounds:

i) It takes too long a time to achieve the effect (3-6 months) while the conditions require rapid control as owners and neighbours cannot wait so long for the dog e.g. to stop barking during the day.
ii) Behavioural therapy can increase anxiety of the dog in the first days of treatment and this effect is countered by application of a drug, which reduces anxiety. The optimum therapy for separation-related disorders is therefore the combination of clomipramine plus behavioural therapy.

As stated already by the Applicant, no reliable controlled studies of the efficacy of behavioural therapy alone or in combination with medication are available from literature. Treatment of behavioural disorders in dogs is a very new field in veterinary medicine and is not established as in human medicine. Although treatment with clomipramine in combination with behaviour therapy has been shown to be efficacious, the CVMP considers that the efficacy data obtained in the pivotal multicentric clinical study are only partly satisfactory, because:

- Information provided in the individual clinical report forms with regard to frequency and severity of symptoms, individual housing and management conditions of dogs by their owners to compensate for the above mentioned shortcomings is of limited value. The cause and severity of symptoms present prior to treatment initiation and finally the extent of improvement of symptoms during therapy can be assessed only partly.
- A synergistic effect of the drug, as stated by the Applicant, in order to get a rapid control of the problems permitting the behavioural therapy is weakly supported by the data.
- Results obtained show that statistically significant differences between groups were not reached at every time point for each parameter. The statistical analysis of data is confusing and allows a limited assessment of the overall efficacy.
- The assumption that treatment with clomipramine could be helpful in severe cases in which behaviour therapy alone is not sufficient, is not satisfactorily proven on the submitted data basis, because no exact identification of severe or less severe cases of separation-related disorders has been made.
- The individual clinical report forms submitted do not provide sufficient information on the progression or regression of behavioural symptoms in dogs throughout therapy.
- The US clinical studies, including a total of 37 dogs, are not reliable since caging or crating or similar confinement of dogs was used by the investigators to treat behavioural disorders.

The CVMP agrees with the Applicant that behavioural therapy alone can take too long a time to achieve effects in dogs with severe behavioural problems such as excessive barking or destruction in-house that cause problems to owners and their neighbours which require rapid control. It is reasonable

to combine, in such cases, behavioural therapy with drugs in order to control problems more rapidly and to make the dog easier to handle and receptive to behavioural training. The CVMP emphasised that clomipramine has no sedative or otherwise depressant activity when compared to other drugs used in veterinary medicine and does not impair the dog's ability to learn.

5. RISK-BENEFIT ASSESSMENT AND CONCLUSION

The Applicant has supported the quality of the product satisfactorily by submitting reliable data in part two of the dossier.

Information on pharmacokinetics of clomipramine has been provided for several animal species, including dog, and for humans. A comprehensive overview of the inhibitory properties on serotonin and noradrenaline re-uptake and anticholinergic properties of the product in laboratory animals has been provided by the Applicant without information on behavioural problems and their neurochemical correlates in dogs.

Clomipramine produces adverse effects in several animal species and in human beings, which are been addressed in the SPCan(section "Special precautions for use").

The Applicant has restricted the claimed indications as requested by the CVMP and now mainly refers to submitted multicentric, placebo controlled, GCP studies which demonstrate satisfactorily the efficacy of the product in the treatment of separation related disorders in combination with behavioural modification techniques. Furthermore, the treatment with this product offers an acceptable level of safety.

A minority of 4 members of the Committee considered these data to be inconclusive, because in their opinion there was a of lack of proven efficacy in the clinical documentation. Therefore, these members expressed divergent positions which are appended to this report (Appendix I).

Based on the original and complementary data presented, the Committee for Veterinary Medicinal Products concluded by a majority that the quality, the safety and the efficacy of the product were considered to be in accordance with the requirements of Council Directive 81/852/EEC. The Committee therefore supported the claims agreed with the Applicant.

Consequently the Committee recommended on 12 November 1997 that the product be granted a Community Marketing Authorisation.

Appendix I

Divergent opinion

Divergent position of the Swedish and Danish Members of CVMP regarding the opinion on Clomicalm tablets for dogs (EMEA/V/C/039/01-03/0/0)

We are not in agreement with the conclusion of the Committee regarding the efficacy of the product in treating separation related anxiety disorders and find that the originally presented pivotal study on the use of clomipramine in combination with behavioural therapy does not support the indication as stated in the Summary of Product Characteristics. The statistical method used can not be applied for the principal reasons of design and defined endpoints of the clinical trials. The supplied data shows that behavioural therapy alone is equally effective as the combination treatment after completed therapy. As evaluated by the rapporteur, the statistical analysis is not useful since the applicant chose only an arbitrary borderline cut-off value (the mean between no effect and improvement) for the assessment of overall efficacy. The clinical end-point of such a treatment must be disappearance of the symptoms, otherwise it should not be instituted. There were only some advantage for some variables (defecation and destruction behaviour) at some time points, while other variables (urination and vocalisation) did not at any time point show any improvement for the combination therapy compared to behavioural therapy alone. Furthermore, the number of animals in the pivotal study is too low to allow valid conlusions to be drawn.

There is no standardised model described for the behavioural therapy to be used and this further weakens the claimed indication. In addition, the argument put forward by the applicant that the use of clomipramine could change the time course of long-term behavioural therapy is not substantiated by the present documentation as the study period was only 8 weeks with no significant final benefit for the combination of clomipramine and behavioural therapy compared to behavioural therapy alone. The responsibility of the owner for the creation of these symptoms of separation anxiety should also be considered in the therapeutic situation as well as the ethical and animal welfare aspects of giving neuroleptic medication, which has not shown to be of value, to dogs not being responsible for the development of the disorder.

London, 12 November 1997

Jan Luthman
Swedish Member of CVMP

Annika Wennberg
Swedish Member of CVMP

Christian Friis
Danish Member of CVMP

Anne Pii
Danish Member of CVMP