

CV 247 - Information for veterinary surgeons

Background

CV247 is a treatment for cancer which was developed by the late John Carter, a veterinary surgeon and research scientist. John Carter started development in 1976 and since then CV247 has been used in the treatment of cancer in animals (mainly dogs) and humans. The validity of the treatment has been demonstrated in a number of studies details of which can be found on the website, www.ivymedical.com and are summarised in appendix I (animals) and appendix 2 (humans).

The studies show the anti-tumour effect of the treatment as well as its beneficial effect on the quality of life of animals suffering from cancer. They also show that the treatment has few side effects.

Appendix 3 gives the summary of Professor Sebesteny, formerly of Cancer Research UK and Ludwig Institute of Cancer Research, who has the most experience of the treatment of any living veterinary surgeon.

Composition

CV247 is a patented combination of four well characterised components: Vitamin C, Manganese Gluconate, Copper Gluconate and Sodium Salicylate, the rationale for their inclusion being:

Manganese

Manganese is an essential trace element for normal brain functioning and for many enzymatic reactions, including hexokinase, superoxide dismutase and xanthine oxidase. Superoxide dismutases are part of the defence mechanism against reactive oxygen species, and altered amounts have been implicated in multistage carcinogenesis in both rodents and man

Copper

Copper can adopt distinct states allowing it to play a pivotal role in free radical scavenging. The importance of copper can also be attributed to its role as a co-factor in a number of enzymes that are involved in the defence against oxidative stress, and a deficiency increases cell susceptibility to oxidative DNA damage.

Vitamin C

Vitamin C (ascorbic acid) is regarded as the most important anti-oxidant in mammalian cells. As a strong reducing agent, vitamin C forms a part of the body's antioxidant defences against reactive oxygen species and free radicals. Ascorbic acid is the single nutrient supplement most commonly used by cancer patients .

Sodium salicylate

Sodium salicylate is non-steroidal anti-inflammatory drug .There is much current interest in these compounds as possible chemotherapeutic agents. The salicylates, in general, are known to be able to exert an anti-inflammatory effect, by direct blocking of prostaglandin synthesis, and by virtue of their inhibition of the cyclooxygenase enzymes, which are induced in response to cell activation by tumour promoters. Aspirin is considered to be an effective substitute for sodium salicylate in CV247.

Prescription of CV247

CV247 does not have a marketing license in the UK and can only be prescribed by a veterinary surgeon under the cascade (see appendix 4 about the cascade and appendix 5 about the holding of unlicensed veterinary medicines). Treatment is often prescribed in circumstances where the alternative is palliative treatment or euthanasia. The treatment can also be prescribed as an adjuvant to chemotherapy (see the human cell line experiments which indicate the benefit of CV247 in combination with cisplatin chemotherapy and the rat trial conducted in Budapest which indicates the benefit of CV247 on the kidneys after a dose of cisplatin), radiotherapy and surgery.

Obtaining CV247

CV247 is supplied in capsules and tablets for simultaneous oral administration and can be obtained through Ivy Medical Chemicals plc by sending an email to info@ivymedical.com which includes veterinary qualifications

Instructions for CV247 liquid

The dose is one Essential Minerals / C-vitamin capsule and one tablet of Sodium Salicylate per day for a dog of 10 Kg bodyweight, according to the following Table:

Bodyweight	CV247 daily dosage
5 Kg	half capsule and half tablet once a day
10 Kg	one capsule and one tablet once a day
20 Kg	one capsule and one tablet twice a day
30 Kg	one capsule and one tablet 3 times a day
40 Kg and above	2 capsules and 2 tablets twice a day

When the animal responds to treatment, the frequency and dose of administration may be reduced or modified on the advice of the treating veterinary surgeon who should periodically assess progress. For the prevention of tumour recurrence a lower dosage may be sufficient.

Administration of the capsule and tablet:

1/ If the owner is experienced enough and the dog is placid enough, put them *one by one* onto the base of the tongue and then hold the mouth closed by hand for a while, until the dog swallows them. (for dogs with good appetite they can be offered hidden into a piece of treat!)

2/ ***Open the capsule and crush the tablet***, pour and mix the contents into a small amount of food BEFORE feeding, while still hungry.

3/ Or into a small amount of favourite fluid, juice, syrup, broth etc. and offer it to drink,

4/ Or administer this solution by a 10 cc (or so) syringe or by a spoon directly into the buccal cavity. (the mouth need not even be opened).

5/ Or put into some honey or marmite etc. and spoonfeed (if the dog likes these).

.Diet:

A change of diet is an integral part of CV 247 treatment. Food preparations with reduced energy supply are recommended. Alternatively a home-prepared diet regime may be used made up of the following ingredients.

RECOMMENDED HOME PREPARED DIET:

With the drastic reduction of salt, sugar, fat, colouring, flavouring agents and preservatives, if possible from „organic” ingredients:

:

<i>%</i>	<i>Proportion</i>	<i>Mode of preparation</i>	<i>Type/origin of Food</i>	<i>Examples</i>
20	1/5	Raw	Fibrous plant	carrot, lettuce, apple, pear, banana
20	1/5	Cooked	Fibrous plant	cabbage, cauliflower, broccoli,
20	1/5	Baked	Fibrous plant	oat porridge, muesli, brown bread
20	1/5	Cooked	Starchy Plant	potato, rice, pasta
10	1/10	Cooked	animal	poultry, veal, rabbit
5	1/20	Mildly cooked	animal	egg, boneless fish
5	1/20	Mildly cooked	animal	liver (except goose or duck)

7/ CONTRAINDICATIONS:

CV247 should not be used in animals who are:

- Suffering from gastrointestinal ulceration or bleeding
- Hypersensitive to any component of the formulation
- In pregnant or lactating bitches

8/ SPECIAL WARNINGS, SIDE-EFFECTS :

Manganese and copper are essential trace elements. In the recommended doses of CV247 these trace elements are present in smaller amounts, than what would be harmful, but the recommended dosage should not be exceeded! CV247 should be used with caution for the treatment of dog varieties that could be sensitive to copper, due to hereditary enzyme deficiency, such as Doberman Pinschers and Bedlington Terriers.

Gastric irritation following sodium salicylate administration is less frequent than with other salicylates and no cases have been encountered, where it could be exclusively attributed to it. This has been supported by toxicity tests, where 6 months administration to dogs of daily therapeutic and its doubled doses did not cause any clinical side-effects or abnormal laboratory test results.

CV 247 should not be prescribed if the patient may be allergic to any of the ingredients, or suffer from hepatobiliary disease. Because salicylic acid may enhance the effect of certain drugs, CV247 should be co-administered cautiously with anti-coagulant drugs (such as coumarins) as salicylic acid impedes the binding of these drugs to plasma proteins. It should be given with caution with other NSAID-s, taking into account the total daily NSAID intake.

Appendix 1

Studies in Dogs

Two open studies on dogs were monitored independently by Professor Sebesteny. The first study on 51 dogs entitled "An open clinical assessment of CV247 for the treatment of cancer in dogs" began in 1997 and treatment lasted for up to a maximum of 25 months. In his opinion as an experienced veterinary practitioner the results of this study suggested that tumours regressed in 19 dogs (37.3%), stabilised in a further 18 dogs (35.3%) and failed or was inconclusive in 14 (27.5%). Quality of life was a secondary end point of this study, as determined between treatment initiation and last assessment, and marked improvement was observed.

The second study on 53 dogs, entitled "A Clinical Study for the Treatment of Cancer in Dogs" began in September 2001 and treatment lasted for up to maximum of 30 months. Once again the results of this study suggested regression in 13 dogs (24.5%), stabilisation in 25 dogs (47.2%) and failure or inconclusive result in 15 (28.3%). In addition, opinion considered that quality of life scores indicated a marked improvement in the quality of life as determined between treatment initiation and last assessment.

In a safety study in 2003 in 18 Beagle dogs by Huntingdon Life Sciences, single and double therapeutic doses administered in a toxicological study for six months did not cause side effects, abnormal biochemical results and pathological changes.

In a clinical study carried out in Hungary in 2008 in 21 dogs suffering from histologically proven malignant tumours, CV 247 has received registration as a "Substance with Therapeutic Effect" for marketing without prescription. Apart from the observed improvement in the quality of life and reduction in weight loss of most patients, antitumour effect was observed in malignant mast cell tumours, mammary tumours and melanomas.

Studies in Rats

In a study conducted in rats in 2009 at the Semmelweis University in Budapest the antioxidant effects of CV 247 has been conclusively demonstrated and studied with a number of biochemical methods. The notorious kidney damage caused by a single injected dose of cisplatin (a drug normally used in chemotherapy) on histological evaluation appeared to have considerably decreased when it was followed by CV 247 treatment. The reduction of oxidative damage was accompanied by the significant reduction of the toxic concentrations of lead, platinum and tin normally caused by cisplatin. At the same time its reducing effect on copper levels was offset by CV 247 follow-up treatment was evident in metal content analyses.

In the liver cisplatin induced high levels of iron accumulation (thought to be responsible for free-radical production) were reduced by CV 247 follow-up treatment. Recently developed chemiluminescence method demonstrated a highly significant reduction in the presence of free radicals in the liver and a somewhat less significant reduction in the plasma samples. A non-significant increase in the overall reducing power of cisplatin treated liver samples after

CV 247 follow-up treatment was also seen. The severely reduced unsaturated fatty acid content of the cisplatin treated livers was significantly restored after CV 247 follow-up treatment apparently due the prevention of their peroxidation (rancidification) by cisplatin.

Studies in Mice

Three controlled experiments at the University College of London under Professor Beverley in 1993 using transplantable murine thymoma, lung and mammary tumours demonstrated significant anti-tumour effects.

A study by BioDynamics in 2005 assessed the anti-tumour activity of CV247 and combinations of the formulation's constituents against the highly metastatic and drug resistant Lewis Lung Carcinoma induced in mice. The effect of CV 247 was compared to untreated control animals bearing tumours and positive control animals treated with Gemcitabine. This study demonstrated potential for CV247 to be an anti-tumour agent. The decrease in final tumour weight indicates a mechanism for tumour reduction that is not necessarily related to tumour volume. Speculatively it may be suggested that an immunological process is initiated that results in break down the tumour core, therefore reducing the weight (but not size) of the Lewis lung carcinoma, a cell line that is particularly aggressive, and which may explain why Gemcitabine did not demonstrate significant efficacy in this model.

Appendix 2

Studies in Humans

Formal evaluation of CV247 in humans commenced on 2 March 2001 as a phase II study in patients with progressive cancer

The study was completed with the analysis of 37 patients with progressive malignancy by Dr Robert Thomas, Consultant Oncologist at Bedford Hospital and Addenbrookes Hospitals. 14 had prostate cancer, 2 ovary, 12 colorectal, 2 breast, and 7 miscellaneous.

The investigator commented that the treatment was well tolerated, with enthusiastic dietary compliance. Of the 2 patients with rapidly progressing ovarian cancer, 1 stabilised for 8 months, the other for approximately 36 months.

28 heavily pre-treated patients had no worthwhile response in very severe cancer types, e.g. colo-rectal (52% stabilisation 3.5 months).

Of the 7 patients with progressive early prostate cancer, 6 (86%) had PSA stabilisation and improved quality of life (mean duration 8.3 months).

The study continued with 4 patients continuing for at least 24 months.

The investigator considered the results sufficiently impressive in prostate cancer to justify a planned randomised double blind trial comparing CV247 and diet versus salicylate (one of the components of CV247) alone.

Prostate trial

This more extensive study to evaluate the product in early progressive prostate cancer cases commenced in 2003 primarily at the Primrose Oncology Centre at Bedford Hospital NHS Trust and also at Addenbrookes Hospital, Cambridge. Half of the patients were treated with CV247 and the other half were treated with sodium salicylate alone. For this study 110 patients were recruited, 35 of whom received treatment for more than a year.

The study was conducted over a 3 year period under the investigational directorship of Dr R Thomas, consultant oncologist, at Bedford General Hospital and Addenbrookes Hospital, Cambridge. The study enjoyed the distinction of being endorsed by the National Cancer Research Network (NCRN), and followed an earlier pilot study that found that previously untreated patients with early stage progressive cancer benefited from treatment with CV247.

The objective of this study was to further investigate whether CV247 might be of benefit in the treatment of early stage progressive prostate cancer and to compare its safety and efficacy with sodium salicylate. According to the protocol all patients recruited into the study had evidence of progressive cancer as defined by histological examination, and PSA levels rising

over 20% or more during the 6 month period prior to study entry (40% over 9 months). Such patients would normally be managed by a 'watch and wait' programme and would, according to the investigator, be patients who he would usually expect to demonstrate continuing and often accelerating disease progression, with few spontaneous remissions. The design of the study was to determine the period of disease stabilisation that patients would enjoy when treated with one or other of the 2 test medications assigned randomly. For the purposes of the study stabilisation was defined as an increase of less than 20% in serum PSA levels between any 2 clinic visits spaced 3 months apart. The duration of the study was set at 12 months though patients who were adequately stabilised at the end of this period were entitled to continue with the randomised medication indefinitely.

A total of 110 patients were recruited into the study, the great majority from Bedford general Hospital. The study was terminated on 30/11/06 at the end of which 38 patients (34.5%) had been stabilised for between 12 and 34 months in the double blind phase. 21 (55%) of these patients had been randomised to sodium salicylate and 17 (45%) to CV247. A further 10 patients were stabilised for 10 months (6 on CV247 and 4 on sodium salicylate). At the end of the study 10 patients were still being treated in the double blind phase, 3 of whom had been recruited less than 12 months prior to study completion. It is known that 2 of these patients were also stabilised for 12 or more months, both of whom had also been randomised to sodium salicylate. A total of 13 of the 38 patients stabilised for 12 months or more had an overall decrease in PSA levels during the period of stabilisation (8 on sodium salicylate and 5 on CV247).

Examination of the treatment 'failures' found that 42 patients (38%) were withdrawn after only 4 months or less in the study. However the majority of these (78.6%) had been pre-treated at an earlier stage following diagnosis of prostate cancer including radiotherapy and chemotherapy. Further examination of the difference in periods of stabilisation when comparing pre-treated with non pre-treated patients revealed that the mean treatment period for all patients on CV247 was 7.4 and 11.3 months respectively, whilst the figures were 6.4 and 12.9 months for those patients randomised to sodium salicylate.

The adverse event (AE) profile was similar for both treatments. A total of 39 patients reported 97 AEs whilst being treated with CV247, compared with 37 patients reporting 112 events on sodium salicylate. The majority were mild or moderate in severity (76% of AEs reported by patients on CV247 and 75% for those on sodium salicylate). Only 13 AEs were considered to be probably or definitely related to CV247, and 12 to sodium salicylate. An AE was the cause for patient discontinuation for 4 patients on CV247 and for 7 on sodium salicylate. Dyspepsia and nausea were the most common AEs for both treatments. Increased manganese levels were recorded for 6 patients on CV247 and for 9 on sodium salicylate, which resulted in 1 patient being withdrawn on CV247 and for 4 to be withdrawn on sodium salicylate. The reason for the increase whilst on sodium salicylate is not clear.

There were a total of 26 serious AEs, only one of which, a case of pancreatitis was considered to have a possible relationship to the test medication.

The investigator had the option of putting any patient onto an open phase should the randomised treatment in the blinded phase fail to stabilise the disease progression. In every case this entailed the patient being treated with CV247 regardless of what treatment had been assigned during the blinded phase of the study. A total of 39 patients were entered into the open phase, 17 of whom were on CV247 in the blinded phase, and hence were effectively continuing with the same treatment. Analysis of the period of stabilisation revealed that a further 7 patients were stabilised for 12 or more months, 2 of whom were switched from sodium salicylate but 5 of whom simply, and unbeknown to the investigator, were continuing with CV247.

It is not known whether the success rate of the 2 treatments would have been greater had the patients recruited all been previous treatment naïve, nor whether the trend would have been similar when comparing the 2 treatments. Nonetheless the evidence would strongly suggest that benefit was derived by a significant number of patients with early stage prostate cancer, and that within the limitations of this study design, that similar benefit was derived from both treatment options.

Palliative trial

In addition to the prostate cancer trial an open label palliative care study in terminal cancer patients was undertaken.

A total of 36 patients were recruited into this open prospective Phase II study, during which patients were expected to attend for a monthly clinical and quality of life assessment for a total of 6 months. The study was under the medical directorship of Dr R Taylor and 2 centres were involved, the Hospice of St Francis in Berkhamsted, and a private clinic in Harrow, Middlesex. All patients had a documented history of late stage progressive cancer, which in several cases, notably breast and prostate cancers had metastasized to involve typically the brain or bone. The range of cancers presenting was varied: breast (7), prostate (7), mesothelioma (5), ovarian (3), lung (3), rectal (2) and 1 each of cervical, Non-Hodgkins lymphoma, thymoma, fallopian, bladder, colonic, myeloma, pancreatic, and basal cell.

A total of 12 (33%) patients completed 6 months treatment with CV247, 3 of whom presented with breast cancer, 5 with prostate, and 1 each of the patients with mesothelioma, NH lymphoma, ovarian and thymoma. Seven of the 12 patients have continued treatment for more than 12 months. Withdrawals from treatment were usually after the first assessment (11 patients) and were often because the patient decided for a variety of reasons that treatment with CV247 was not their preferred treatment option. In 7 cases these were patients who presented to the private clinic, who were all highly motivated and were actively investigating a wide variety of alternative treatments available to them. Withdrawal of patients who attended the clinics at least twice was: withdrawal after 1 month (2), 2 months (6), 3 months (4) and 4 months (1). The reasons for withdrawal included:

Adverse events, 6; dislike of medication, 1; non-compliant, 12 (all at the private clinic); referred for further chemo or radiotherapy, 2; symptoms worsened, 1; deceased, 2.

The primary end-point for efficacy was Quality of Life based upon the utilization of a self scored, validated (EORTC) questionnaire. Of the 25 patients who continued after the initial assessment, 12 had no change (+/- 1) in their combined total global health and quality of life scores, 3 had decreased scores and 10 (40%) had an improvement. For the 12 patients who completed the 6 month study, the mean combined score at entry was 10.4 (range 6-14), and after 6 months, 11.3 (range 6-14). Only 1 of the 12 had a score that was worse after 6 months. No statistical analysis has been undertaken. Because of the variety of cancers presenting, clinical examinations and biomarker determinations were of very limited value. In addition the type of highly motivated patient typically presenting, especially at the private clinic, probably gave a false impression of their true health status, particularly on study entry.

There were no serious adverse events. A total of 6 patients withdrew due, at least in part, to the severity of adverse events experienced during the study. One patient withdrew due to a feeling of bloatedness, one due to constipation, 3 because of indigestion and one reported feeling drowsy. Only the cases of indigestion were considered to be possibly related to CV247.

Human Cell lines CV247 alone

Tests on CV247 using invitro tumourous human cell lines are being done at the Research Genetic Cancer Centre in Greece.

The results of the tests so far have found in LoVo (colon) cells that Vitamin C had no effect, sodium salicylate minimal effect, but CV247 had a marked effect both at 24 and 48 hr. With T47D (breast) cells, again Vitamin C had no effect and CV247 had an effect approximately 2.5 times that of sodium salicylate at 48hr. Curiously the reverse was found with the prostate cell line used (one of 3 to be tested) in which Vitamin C had the most effect, whilst sodium salicylate had none. This may suggest cancer specificity for CV247. Whilst not conclusive, these preliminary results are very encouraging in suggesting both the efficacy of CV247 and that the combination of ingredients in CV247 is more efficacious in certain cancers than the key components on their own.

Human Cell lines CV247 and cisplatin chemotherapy

The study was designed to investigate the possible synergistic effect of combining CV 247 with the widely used cytotoxic agent, cisplatin, in a series of human colon and breast cancer cell lines using a range of functional, colorimetric assays over a ten day period.

The results showed a clear apparent synergistic effect when CV 247 was added to a range of cisplatin concentrations, in many of the cell lines, and even where there was no apparent benefit there was no deterioration of effect when compared to cells treated with cisplatin alone. The concentrations of cisplatin used were intended to represent a range of both clinical

and supra-clinical doses. It was evident that on many occasions the maximum level of cell kill was achieved even for the lower cisplatin doses which would disguise any additional benefit of CV 247. Nevertheless when used in combination with lower cisplatin doses, CV 247 often had a marked synergistic effect seemingly enhancing the effect 5 fold. Some of the lower cisplatin doses had a declining cytotoxic effect after 4 or 6 days particularly with the breast cancer cell lines and it was evident that the addition of CV 247 not only increased the cytotoxic effect but extended the effect for the duration of the study.

Appendix 3

Summary of Professor Andor Sebesteny MRCVS

Background: Beside my 44 yearsø long full time work in a London based cancer research institute (ICRF-CRUK) I also consulted from time to time in neighbouring veterinary practices. There, many owners of dogs affected with malignant tumours asked for a **milder alternative therapy** (weary of side-effects or costs) **instead of, or following**, conventional treatment (operative, radio- or chemotherapy).

Consequently with a colleague (late John Carter), whom I worked with since the late 70-s, we have produced therapy CV 247, from simple, well known, well tolerated substances (Vitamic C, salicylate, trace elements), known to have antitumour and antioxidant properties, supported by a suitable diet, for **small animals suffering from malignant tumours**. After my documentation of the case histories of **20** such treated cases, we received a test permit for the official study of this therapy in Britain We carried this out in more than **100 pets** histologically or otherwise proven to be affected with malignant tumours either alone, or in conjunction with other conventional treatments under a set protocol. **It is being used in increasing number of veterinary practices in Britain under the "cascade" prescription system.**

Beside the **observed antitumour effects** such striking improvement was observed in the **quality of life** of the majority of treated animals, that human doctor colleagues became interested. At first on a voluntary (compassionate) basis, later under official testing permit more than 200 **human** cancer patients were treated with CV 247 either alone, or in conjunction with conventional therapy in several controlled studies in Cambridge, Berkhamsted and Harrow, without observing any side effects exclusively attributable to the CV 247 treatment while witnessing an improvement in the quality of many patients' life and in their predicted survival. **It is now being used in cancer sufferers on a "named patient" basis in Britain.** Its variant named as **CV 247 Regeneráló** has received registration as a šFood Supplementö in Hungary.

Cell cultures of human malignant tumours treated with CV247 showed signs of antitumour effect. In Greece at RGCC-Genlab 12 such cell lines were studied after exposure to CV 247 and its individual components. With flow cytometry, ATP-TCA luminometry, sulphorhodamine B assay and Crystal Violet assay, most exhibited an increase in dead cells and cells apparently halted in the G2 phase of mitosis. This was in contrast to their controls, indicating a cytotoxic effect of a more gradual and sustained type than seen with traditional cytotoxic drugs. This was particularly marked in LoVo colonic cancer and T47D breast cancer cell lines where CV 247 was considerably more active than Na salicylate alone, and least marked in prostatic lines. There, in contrast, the Vitamin C component alone appeared

to be most effective. The exploration of a possible synergism of CV 247 and cytotoxic drugs (such as cisplatin) is being planned in **human tumour tissue cultures and in clinical trials**.

Studies conducted in mice at the University College of London using transplantable murine thymoma, lung and mammary tumours have demonstrated significant antitumour effects.

In Beagle dogs in Huntingdon **single and double therapeutic** doses administered in a **toxicological** study for **six months** did not cause side effects, abnormal biochemical results and pathological changes.

In a recent **study conducted in rats** at the Semmelweis University in Budapest the antioxidant effects of CV 247 has been conclusively demonstrated and studied with a number of *biochemical* methods. The notorious **kidney** damage caused by a single injected dose of cisplatin (a drug normally used in chemotherapy) on *histological* evaluation appeared to have considerably decreased when it was followed by CV 247 treatment. The **reduction of oxidative damage** was accompanied by the significant reduction of the toxic concentrations of lead, platinum and tin normally caused by cisplatin. At the same time its reducing effect on copper levels was offset by CV 247 follow-up treatment according to *metal content analyses*.

In the **liver** cisplatin induced high levels of iron accumulation (thought to be responsible for **free-radical** production) were reduced by CV 247 follow-up treatment. Recently developed chemiluminescence method demonstrated a highly significant reduction in the presence of free radicals in the liver and a somewhat less significant reduction in the plasma samples. A non-significant increase in the overall **reducing power** of cisplatin treated liver samples after CV 247 follow-up treatment was also seen. The severely reduced unsaturated fatty acid content of the cisplatin treated livers was significantly restored after CV 247 follow-up treatment apparently due the **prevention of their peroxidation** (šrancidificationö) by cisplatin.

In the course of the evaluation of the clinical and antitumour parameters in a recent sponsored clinical study carried out in Hungary in 21 dogs suffering from histologically proven malignant tumours, CV 247 has received registration as a „Substance with Therapeutic Effect” for marketing without prescription. Apart from the observed improvement in the quality of life and reduction in weight loss of most patients, antitumour effect was observed in malignant **mast cell** tumours, **mammary** tumours and **melanomas**. Nevertheless for a statistically significant proof of antitumour effects more such case reports are needed, To this end a **sponsored protocol aiming at the study of 80 cases is being started, for which veterinary surgeons are invited to join.**

The treatment is recommended

- When conventional (operative, chemo- or radio-) therapy is not wanted or not advised.
- As an adjuvant treatment for conventional therapy for maintaining the quality of life.
- For the countering of side effects of conventional (e.g. cisplatin) treatment.
- For the prevention or delaying of regrowth of tumours treated surgically.
- For the prevention or delaying of regrowth of tumours treated by radio- or chemotherapy.
- General roborant in poor state of health.

The mechanism of the effects of components:

Manganese and copper: are important trace elements in the active centres of several enzymes for example for the effect of superoxide-dismutase (SOD) enzyme against the free radicals and reactive oxygen species (ROS).

Vitamin-C: its antioxidant, immunestimulant, DNA repair ability and antitumour effects are well known.

Sodium salicylate

Inhibits the effect of *oxidising enzymes* (such as cyclooxygenase, COX 1 and 2) and the production of inflammation stimulating *prostaglandins*, which apart from causing *ill feeling*, promote the *proliferation of malignant tumour cells* and their *blood supply, the spread of tumour cells* (metastasis) and the *development of resistance* against chemo- or radio-therapy.

Promotes the spontaneous death of tumour cells (*apoptosis*) and their destruction by specialised immune cells (killer cells), the *decrease of pain* and the *improvement of well-being*.

Drug interactions:

- **may be given,** in fact may positively interact with methyl donor, flavonoid and other antitumour natural or chemotherapeutic agents and with radio-therapy.
- **may not be given** with anticoagulants and **only with caution** with other NSAID-s

Appendix 4

Extract from “Veterinary Medicines Guidance Note 15” published by the Veterinary Medicines Directorate

THE PRESCRIBING CASCADE 6 NON-FOOD ANIMALS

7. The prescribing cascade provisions are set out in the Regulations. They are available only to veterinary surgeons who have responsibility for the treatment of the animals concerned.

8. If there is no medicine authorised in the UK for a condition affecting a non food-producing species, the veterinary surgeon responsible for treating the animal(s) may, in particular to avoid unacceptable suffering, treat the animal(s) in accordance with the following sequence:

(a) a veterinary medicine authorised in the UK for use in another animal species or for a different condition in the same species; or, if there is no such product:

(b) either -

(i) a medicine authorised in the UK for human use; or

(ii) in accordance with an import certificate (see VMG Note 7), a medicine authorised for veterinary use in accordance with Directive 2001/82 (as amended) in another Member State; or, if there is no such product:

(c) a medicine prepared extemporaneously, by a veterinary surgeon, a pharmacist or a person holding an appropriate manufacturer’s authorisation, as prescribed by the veterinary surgeon responsible for treating the animal.

9. A medicine prescribed in accordance with the cascade may be administered by the prescribing veterinary surgeon or by a person acting under their direction. Responsibility for the prescription and use of the medicine remains with the prescribing veterinary surgeon.

Extract from The Veterinary Medicines Regulations 2007

Possession of an unauthorised veterinary medicinal product

26. (1) It is an offence to be in possession of an unauthorised veterinary medicinal product.

(2) This regulation **does not** apply to

(a) a veterinary medicinal product imported in accordance with a certificate granted by the Secretary of State under these Regulations;

(b) a product prescribed by a veterinary surgeon under the cascade;

(c) a holder of a wholesaler's authorisation if the possession is for re-export; or

(d) a holder of a manufacturer's authorisation or marketing authorisation if the intention is to manufacture a veterinary medicinal product.

(3) A veterinary surgeon who practises in both the United Kingdom and another member State may hold veterinary medicinal products authorised in the other member State provided that the amount that he holds does not exceed the amount expected to be used in that member State.

(4) It is a defence for a person charged under paragraph (1) to prove that he was in possession of the veterinary medicinal product for the purposes of research or development of a veterinary medicinal product.

(5) A veterinary surgeon may have in his possession an authorised human medicinal product intended for administration to animals under the cascade, but he commits an offence if the amount in his possession exceeds the amount expected to be used under the cascade.

Supply of an unauthorised veterinary medicinal product

27. (1) It is an offence to supply an unauthorised veterinary medicinal product.

(2) This regulation **does not** apply to

(a) a veterinary medicinal product prescribed by a veterinary surgeon under the cascade; or

(b) a product supplied in accordance with a certificate granted by the Secretary of State under these Regulations.

(3) It is a defence for a person charged under paragraph (1) to prove that he supplied the veterinary medicinal product for the purposes of research or development of a veterinary medicinal product.