CV 247 - Information for doctors

There is no marketing authorisation for the combination of the ingredients in CV247, which is still under development.

CV247 is only available for named patients as a special.

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 (humans) and appendix 2 (animals).

Three formal studies in humans have been undertaken, a phase II study was completed with the analysis of 37 patients with progressive malignancy by Dr Robert Thomas, Consultant Oncologist at Bedford Hospital and Addenbrokesôs Hospitals, a study on 110 patients early progressive prostate cancer was conducted over a 3 year period under the investigational directorship of Dr Robert Thomas and an open prospective Phase II study on 36 patients under the medical directorship of Dr Ros Taylor at the Hospice of St Francis in Berkhamsted, and a private clinic in Harrow, Middlesex.

The studies on humans and animals show the anti-tumour effect of the treatment as well as its beneficial effect on the quality of life of patients 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 had over 20 yearsô experience of the treatment.

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 bodyôs 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. Asprin is considered to be an effective substitute for sodium salicylate in CV247.

Prescription of CV247

CV247 is does not have a marketing authorisation in the UK and can only be prescribed by a doctor on a named patient basis. Treatment is often prescribed in circumstances where the alternative is palliative treatment. 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. CV247 can only be prescribed for an individual for whom no similar medicine is available and only after the prescribing doctor is satisfied that CV247 may be of benefit. It should not be passed onto others.

Obtaining CV247

CV247 can be obtained by prescription from Lexon UK Ltd. Either order online at www.lexonspecials.co.uk or call free on 0800 1383117 or fax free on 0800 1382032.

Precautions

CV 247 should not be prescribed if the patient may be allergic to any of the ingredients, or suffer from hepatobilary disease. CV 247 should not be prescribed to pregnant patients.

Salicylic acid, the principle metabolite, of sodium salicylate, is a substrate of the liver enzyme CYP 2E1, and has the potential for interacting with other highly protein bound drugs and, when co-administered with other NSAIDs such as flurbiprofen, ibuprofen and naproxen, can lead to these drugs being displaced by salicylic acid. Interaction with other drugs that are extensively protein bound, may lead to the displacement of methotrexate, penicillin, phenytoin and warfarin for examples. Hence salicylates should only be co-administered with anti-coagulant drugs with caution.

It is not considered that there is a narrow therapeutic margin with CV247, nor does it present a significant toxicological risk as important adverse events with the components have only been observed in experimental animals following chronic parenteral administration of very high doses of the components.

Dosing recommendations are based upon weight, and the risk of repeated overdosing is considered to be unlikely.

There are no documented symptoms associated with an overdose.

How CV247 should be taken

CV 247 should only be taken as prescribed.

.The dose prescribed will depend upon the patientôs weight.

CV 247 is supplied in 300ml bottles.

The usual dose for adults and adolescents (13 years or more) is 10ml if the patientôs weight is 50kg or less, 20ml if between 50 and 75 kg, and 30ml if over 75 kg.

For each 10ml dose, 400mg vitamin C should be added. The whole may be diluted with fruit juice to disguise the slightly metallic taste associated with CV 247.

CV 247 should be taken within 90 min of preparation.

CV 247 should only be taken for the time period prescribed.

A double dose should not be taken to make up for forgotten individual doses.

POSSIBLE SIDE EFFECTS

Like all medicines, CV 247.can have side effects Experiences from studies in man have demonstrated that adverse events are occasionally reported, predominantly relating to mild gastro-intestinal events such as gastric irritation, abdominal; pain and bloatedness. No serious or severe reactions have been reported. Monitoring of copper and manganese levels, which are toxic if taken at very high doses for long periods, has not revealed any unexpectedly high plasma concentrations, and routine clinical pathology screens have been within clinically normal ranges, except where the underlying disease has impaired organ function.

STORING CV 247

After opening, CV 247 should be stored in a refrigerator and used within 28 days. It should be kept it in its original container.

CV 247 should be kept out of reach and sight of children, and not used after the expiry date on the label.

Appendix 1

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 Addenbrokesõs 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.ò

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 Addenbrokes Hospital, Cambridge. Half of the patients were treated with CV247 and the other half were treated with sodium salycilate 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 ñwatch and waitò 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 ñfailuresò 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 ñopenò 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 ñfeeling of bloatednessò, one due to constipation, 3 because of indigestion and one reported ñfeeling drowsyò. 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, colormetric 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 2

Studies in Dogs

Two open studies on dogs were monitored independently by Professor Sebesteny. The first study on 51 dogs entitled ñAn open clinical assessment of CV247 for the treatment of cancer in dogsò 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 ñA Clinical Study for the Treatment of Cancer in Dogsò 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 ñSubstance with Therapeutic Effectò 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 Semmelweiss 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 (ñrancidificationò) 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 formulationôs 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 3

Summary of Professor Andor Sebesteny MRCVS

Background: Beside my 44 yearsô 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, <u>or</u> 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 Regenerál**ò has received registration as a ĂFood Supplementò in Hungary.

<u>Cell cultures</u> <u>of human</u> 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 individal components. With flow cytometry, ATP-TCA luminometry, sulpho-rhodamine 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 salicilate 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 Semmelweiss 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** (Ărancidificationò) 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 sate of health*.

The mechanism of the effects of components:

Manganese and copper: are importent 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 salicilate

Inhibits the effect of *oxidising enzymes* (such as cyclooxigenase, 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 distruction 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 be given** with anticoagulants and **only with caution** with other NSAID-**s**