



Product History - CV247

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Product History

CV247 is a combination product comprising of Sodium Salicylate, Copper Gluconate, Manganese Gluconate and Ascorbic Acid (Vitamin C) taken as a solution. The product was conceived and initially developed by Mr John Carter, veterinary surgeon, who also advocated that in combination with the therapy a patient also followed an “organic Diet”.

Mr Carter established the treatment regime after many years of study and empirical research starting in around 1976. The work began after a number of friends and associates as well as many companion animals had succumbed to the effects of cancer. Mr Carter’s hypothesis was that the increasing rate of cancer affecting the human and animal world could have an association with modern food manufacturing methods and the environment. His theory and treatment was aimed at stimulating the individual’s immune system so as to resist the development or progression of cancer. The effect of this theory was repeatedly tested in his Veterinary practice on a compassionate treatment basis. Mr Carter’s interest and the success with the animals he treated led to word of mouth recommendations to tend to other animals suffering from cancer.

CV247 was seen by pet owners to have a notable rate of success on their respective companion animals, and an anecdotal portfolio of satisfied dog owners was compiled. Credibility in the drug and treatment regime increased further when in 1993 Mr Carter was introduced to UCL Ventures, a division of University College London (UCLV). The anecdotal evidence collected persuaded UCLV that the claim should be investigated independently. UCLV agreed to carry out controlled trials and introduced Professor Peter Beverly who at that time was Head of the Tumour Immunology Unit of the Imperial Cancer Fund at University College London. Professor Beverly agreed to undertake a series of controlled experiments on the effect of the treatment on malignant cancers in mice. After gaining the necessary licence to undertake the experiment, the trials were carried out under a formal contract between John Carter and UCL.

Three controlled experiments were carried out. Professor Beverly concluded in his report that the treatment caused a statistically significant reduction in the rate of tumour growth in the treated compared to the untreated groups and that there were no observable side effects attributed to the treatment.

To understand the regulatory requirements in more detail Mr Carter, accompanied by Dr Duffield visited the Veterinary Medicines Directorate. It was suggested that as part of the overall clinical development a veterinary surgeon specialising in cancer research should independently study the treatment in an appropriate number of animals.

Professor Andor Sebesteny, the “Named Veterinary Surgeon” of the Imperial Cancer Research Fund and the Ludwig Institute of Cancer Research, was approached for this task in his personal capacity, as he had not only spent 34 years advising and assisting cancer researchers in animal studies, but had also carried out general practice work throughout, since 1960.

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.

Observations for some of the animals in the above study were considered to be sufficiently impressive to be published as a short article in Veterinary Practice, February 1999, page 14.

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

Studies in humans

The potential in human cancer was initially assessed in an open study in human cancer sufferers following approval of a CTX from the MHRA. The results were published by the investigator Dr Thomas, initially in an abstract (Annals of Oncology, vol 13, page 30, 2002, Clinical Oncology, 2002) and in greater detail (Nutrition and Food Science, vol 35, no 6, 2005) and may be summarised from his publications as follows:

Formal evaluation of CV247 in humans commenced on 2 March 2001 as a phase II study.

Summary of Phase II results

Preliminary 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 Addenbrokes’s 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 Addenbrokes 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.

CV247 is a combination product consisting of sodium salicylate, copper and manganese glutamates and ascorbic acid. The scientific rationale for the inclusion of the compounds is well documented with both copper and manganese being essential elements for life as components of superoxide dismutase, ascorbic acid being an essential vitamin with anti-oxidant properties, combined with the known anti-inflammatory properties of sodium salicylate. All these properties may well be of benefit in the treatment of certain aspects of cancer. Trace element deprivation, for example, could result in increased oxidative stress and altered or impaired immune function, whilst the benefits of ascorbic acid may well include enhancement of the immune system and activation of enzyme systems causing tumour cell death. Aspirin itself has been proposed as a treatment for certain types of cancer, but though sodium salicylate which is a close relative of acetyl salicylic acid, is known to be an effective anti-inflammatory agent with a lower propensity for gastrointestinal side effects, and might well inhibit the production of certain growth factors that promote angiogenesis and tumour progression. It has individual properties which are quite distinct, and its individual role as a treatment in early stage progressive prostate cancer would not be obvious and has consequently not previously been proposed or investigated.

CV247 has been found in open label studies to be of apparent benefit for the improvement of well being particularly in dogs with a wide variety of cancers, and possibly to improve quality of life in some human patients with terminal cancer. In addition as referred to earlier, it was observed in a pilot study to be of possible benefit to certain patients with early progressive prostate cancer.

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

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.

Rat trial on anti-oxidant effect

In Hungary we commissioned a trial on 40 rats to investigate the anti-oxidant effect of CV247. The results of this trial show that the product to have such an effect. In order to induce free radicals in the trial, the chemotherapy drug cisplatin was used. In addition to the anti-oxidant effect, CV247 was seen to protect the kidneys against cisplatin damage which suggests a potential use of the treatment in conjunction with cisplatin chemotherapy. Successful application has been made for EU-conform Hungarian registration as human food supplement form of CV247 ("CV247 Regenerál"), a capsular form which excludes salicylate. It is intended that this will be made available to oncologists in Hungary who could use it under licenced trials in chemotherapy treatment protocols, in conjunction with salicylates from other sources. Production of CV247 Regenerál has been completed, and the product is available for marketing and use.