

# **Evidence-Based Review**

## **Coumarin for lymphoedema following cancer treatment --- effectiveness and safety**

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## **Important Note**

**This evidence-based review summarises information on the effectiveness and safety of using coumarin for lymphoedema following cancer treatment. It is not intended to replace clinical judgement, or be used as a clinical protocol. A reasonable attempt has been made to find and review papers relevant to the focus of this report. It does not claim to be exhaustive. This document has been prepared by staff of the ACC, Evidence Based Healthcare Advisory Group. The content does not necessarily represent the official view of ACC or represent ACC policy.**

## **Executive Summary**

**Background:** Lymphoedema may be defined as the abnormal accumulation of protein rich fluid in soft tissues as a result of the interruption of lymphatic flow or dysfunction of the lymphatic system. It can be classified into primary or secondary lymphoedema. Secondary lymphoedema is more common and has many different causes, e.g. cancer and its treatment, and parasitic infection. Secondary lymphoedema in upper limbs among patients who received radiosurgical treatment for breast cancer is a very common complication in clinical practice. Secondary lymphoedema in lower limbs can be a complication following treatment for melanoma, lower abdominal or pelvic cancers.

Coumarin (1,2-benzopyrone or 5,6-benzo-[alpha]-pyrone) belongs to a class of compounds known as benzopyrones and has been used to treat lymphoedema and other clinical conditions. For lymphoedema, it is considered that benzopyrones stimulate macrophage activities by increasing both their numbers and their proteolysis. As a result, excess stagnant protein in the tissue spaces could be removed. Theoretically, this would reduce colloidal osmotic pressure in the tissues affected and may lead to the improvement of oedema and chronic inflammation caused by the excess stagnant protein.

**Search strategy:** A range of databases including Pre-MEDLINE, MEDLINE, MEDLINE Daily Update, CINAHL, CDSR, ACP Journal Club, DARE, CCTR, EMBASE, International Pharmaceutical Abstracts, and PsycINFO were searched in August 2004 and February 2005 for published papers about coumarin for lymphoedema. A secondary hand search of citations was also conducted.

**Selection criteria:** All randomised studies including randomised crossover studies that aimed at investigating the effectiveness of coumarin were considered in this review.

The safety issue has been a major focus of this review. In most cases of drug induced hepatotoxicity, the toxicity is unlikely to be detected in the clinical trials especially when the patients under study are small in number and the study period is short. The cases of hepatotoxicity are usually reported after marketing when enough numbers of patients are

exposed to the drug. Based on these reasons, both randomised and other types of studies, e.g. surveillance reports, are considered in the analysis of safety issues of coumarin.

**Main results:**

- Five randomised studies were included in the review. All included studies have considerable weakness in methodology including using crossover study design, short treatment period and the heterogeneity of study population.
- There appears to be no consistent results from these studies that compared coumarin with placebo for lymphoedema following cancer treatment.
- Clinical effectiveness of coumarin for lymphoedema following cancer treatment cannot be determined from available randomised studies.
- From a relatively valid study, incident rate of coumarin attributable hepatotoxicity was reported to be 0.37%. This figure appears to be significantly higher than a risk range of 1/10,000 to 1/100,000 for most drugs. The risk of coumarin attributable hepatotoxicity is a major concern for its clinical application.
- No cost effectiveness studies of using coumarin for lymphoedema were found.

**Conclusions:** The available randomised controlled studies do not provide good quality evidence to analyse the effectiveness of coumarin for lymphoedema following cancer treatment. There appear to be no consistent results from randomised controlled studies that compared coumarin with placebo for lymphoedema following cancer treatment. Clinical effectiveness of coumarin cannot be determined from these studies. Coumarin attributable hepatotoxicity appears to be a big concern for its clinical application.

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# **1. Background**

Lymphoedema may be defined as the abnormal accumulation of protein rich fluid in soft tissues as a result of the interruption of lymphatic flow or dysfunction of the lymphatic system<sup>1 2</sup>. It can be classified into primary or secondary lymphoedema. About 3 to 10% of lymphoedema cases are primary, which refers to congenital abnormality, e.g. Milroy's disease<sup>2 3</sup>. Secondary lymphoedema is more common and has many different causes, e.g. cancer and its treatment, parasitic infection<sup>2</sup>.

Secondary lymphoedema in upper limbs among patients who received radiosurgical treatment for breast cancer, is a very common complication in clinical practice.

The detailed mechanisms of developing lymphoedema after breast cancer are not fully known<sup>2 4</sup>. However some risk factors have been reported, including axillary surgery and axillary radiotherapy<sup>2 5 6</sup>. Many studies agree that the incidence and degree of lymphoedema correlate with the extent of axillary dissection. Axillary radiotherapy for the dissected area was a strong predictor of lymphoedema incidence<sup>1 2</sup>. Other risk factors of developing lymphoedema include inadequate nutrition, insufficient muscle contraction, prolonged dependency, venepuncture and postoperative wound complications such as delayed healing, infection, haematoma or skin flap necrosis<sup>4 7 8</sup>.

Secondary lymphoedema in the lower limbs can be a complication following the treatment for lower abdominal or pelvic cancers e.g. melanoma, bowel cancer, prostate cancer in men and cervical and other reproductive cancers in women<sup>3</sup>. Parasitic infection e.g. filariasis is a common cause of lower limb lymphoedema in some developing countries.

Risk of developing lymphoedema could remain throughout the patient's lifetime after cancer treatment. Some lymphoedema occurred 30 years after patients received surgical treatment for breast cancer<sup>9</sup>.

The incidence of lymphoedema is estimated to a range from 6% to 30% among breast cancer patients treated in five Western countries (United States, England, Italy, France and Germany)<sup>7 10</sup>. However, the figures reported in some studies are higher than this range. In a

cohort of breast carcinoma patients (923 cases) treated with mastectomy and complete axillary dissection in a cancer centre in New York, 49% of the survivors (263 patients investigated) reported the sensation of lymphoedema at 20 years after treatment<sup>11</sup>. A New Zealand study reported that 38% of 181 Otago women treated for breast cancer developed arm swelling, 31% of them met the criteria for lymphoedema<sup>12</sup>.

For patients with more than mild lymphoedema, the condition may have a number of impacts on their daily life including loss of sensation and limb function, pain, altered body image, difficulties in household duties, sleep, employment and sport. Some patients can suffer from significant psychosocial morbidity, depression, social inhibition and problems with sexuality<sup>4</sup>.

Lymphoedema is an ongoing condition which cannot be completely cured at present<sup>2 4 5 13</sup>. Therapeutic efforts are focused on minimising the oedema, delaying progression, reversing and restoring the function and cosmetic appearance of the limb and reducing the risk of infection (cellulitis, lymphangitis). The treatments can be difficult<sup>3</sup>, costly and time-consuming<sup>4</sup>. It is generally agreed that better results can be achieved if the treatments are started early<sup>3 14</sup>. Currently, the treatment modalities can basically be divided into non-operative treatment and operative treatment<sup>1 14</sup>.

The non-operative treatment includes physical therapy (e.g. exercise and external support, compression bandaging, massage, manual lymphatic drainage and skin care), drug therapy (e.g. diuretics, benzopyrones and high dose steroids) and psychosocial rehabilitation. Use of ultrasound therapy for lymphoedema has also been reported<sup>9 15</sup>. Manual therapy has emerged as the standard of care over the past decades<sup>1</sup>. Compression therapy and manual lymphatic drainage (MLD, a special massage for the treatment of lymphoedema<sup>16</sup>) may improve established lymphoedema<sup>17</sup>.

It is generally agreed that drug therapy only has a small or very little role in the lymphoedema management due to the lack of effectiveness<sup>4 5 17</sup>.

The operative treatment includes resection, which is performed to remove excess skin and subcutaneous tissue of the lymphoedematous limb, and microsurgical procedures<sup>14</sup>.

## **2. Objectives**

The aims of this work are to review the clinical effectiveness and safety of using coumarin for lymphoedema following cancer treatment, and to provide other relevant information for making a purchasing decisions.

## **3. Health technology**

Coumarin (1,2-benzopyrone or 5,6-benzo-[alpha]-pyrone) belongs to a class of compounds known as benzopyrones. In contrast to the anticoagulants derived from 4-hydroxy-coumarin (e.g. warfarin or coumadin), the coumarin considered in this report has no influence on coagulation and possesses different pharmacological properties from anticoagulants.

Coumarin is a naturally occurring element of many plants and essential oils, including tonka beans, sweet clover, woodruff, oil of cassia, and lavender<sup>18</sup>. It was first isolated and purified by Voleg in 1822, and was later synthesised in 1868 by Perkin. It was classified as a carcinogen and hepatotoxin based on animal (rats and dogs) studies, and banned by the Food and Drug Administration (FDA) in 1954 for its use as a food flavouring agent<sup>18 19</sup>. However, the following studies indicated that the metabolism of coumarin in humans was similar to that in baboons, but different from that in rats<sup>18 19</sup>.

Coumarin has been used to treat lymphoedema and other clinical conditions e.g. melanoma, renal cell carcinoma and chronic intracellular infections<sup>19</sup>. For lymphoedema, it is considered that the drug stimulates macrophage activities by increasing both their numbers and their proteolysis. As a result, excess stagnant protein in the tissue spaces could be removed. Theoretically, this would reduce colloidal osmotic pressure in the tissues affected and may lead to the improvement of oedema and chronic inflammation caused by the excess stagnant protein<sup>2 20-22</sup>.

Coumarin products were marketed as Lodema in Australia, Lysedem in France and Venalot Deport in Belgium in 1980's. It is also marketed as Lympedim (200mg tablet) in India. The Lympedim tablets can be obtained from a pharmacy in New Zealand with prescription<sup>23</sup>.

## **4. Methodology**

### 4.1 Criteria for selecting studies for this review

**Types of Studies:** All randomised studies including randomised crossover studies that aim at investigating the effectiveness of coumarin were considered in this review. Non-randomised studies e.g. case reports and case series were excluded.

From preliminary literature review, we noted that potential hepatotoxicity of coumarin is a major concern of its applications. Therefore, the safety issue has been a major focus of this review. For most drugs, drug induced liver disorder ranges from 1 per 10,000 to 1 per 100,000 users<sup>24</sup>. In most cases the toxicity is unlikely to be detected in the clinical trials especially when the patients under study are small in numbers and the study period is short. The cases of hepatotoxicity are usually reported within 1 to 2 years after starting marketing when there are enough numbers of patients who have been exposed to the new drug<sup>24</sup>. For these reasons, both randomised studies included and other types of studies, e.g. surveillance reports, are considered in the analysis of safety issues of coumarin.

The level of evidence for each quantitative study on effectiveness was determined by a grading system<sup>25</sup>(see Appendix 1) reported by the Scottish Intercollegiate Guidelines Network (SIGN).

**Types of Participants:** Patients who were diagnosed with lymphoedema following cancer treatment and received coumarin are considered in this review. Patients with lymphoedema following radiosurgical treatment of breast cancer are our primary focus since they are likely to count for most cases of lymphoedema in New Zealand. However, lymphoedema following other cancer treatment is also considered. Lymphoedema caused by parasitic infection, e.g. filarial lymphoedema, are not considered in this review since the condition has not been reported in New Zealand and is less likely to be considered for accident compensation.

### 4.2 Search strategy and information sources

The following OVID search strategy was developed to search for studies of using coumarin for lymphoedema in August 2004. The secondary updating literature search was performed in

February 2005 using the same search strategy as originally developed, to ensure recently published material was analysed.

1. coumarin/
2. coumarin\$.mp.
3. benzopyrones.mp.
4. lodema.mp.
5. lodemaR.mp.
6. lysedem.mp.
7. "venalot depot".mp.
8. or/1-7
9. lymphedema/
10. lymphoedema/
11. lymph\$edema.mp.
12. or/9-11
13. adverse effects/
14. "adverse effect\$".mp.
15. "adverse effect\$".tw.
16. "side effect\$".mp.
17. "side effect\$".tw.
18. "undesirable effect\$".tw.
19. "undersirable effect\$".mp.
20. or/13-19
21. 8 and 12
22. 8 and 20
23. exp anticoagulants/
24. 22 not 23
25. 21 or 24
26. remove duplicates from 25
27. limit 26 to human

The databases searched included Pre-MEDLINE, MEDLINE, MEDLINE Daily Update, CINAHL, CDSR, ACP Journal Club, DARE, CCTR, EMBASE, IPA, AMED and PsycINFO.

A secondary hand search of citations of systematic reviews and other relevant reports was also conducted. The terms "coumarin" and "benzopyrones" were used to search for information from internet sources, including the websites of:

- The Lymphoedema Association of Australia (<http://www.lymphoedema.org.au>)
- The Lymphovenous Canada (<http://www.lymphovenous-canada.ca>)
- The Essential Drugs and Medicines Policy in the World Health Organisation (<http://www.who.int>)

### 4.3 Methods of the review

The reports on coumarin were appraised by the investigator using the Scottish Intercollegiate Guidelines Network (SIGN) grading system<sup>25</sup> (see Appendix 1) to determine the levels of evidence:

1. The type of study was determined by appraising the methodological information described in each report.
2. The quality of study was assessed by analysing the information including the methods of distributing study subjects to different study groups, blinding, sample size, outcome measurements, period of follow-up, definition of study population and intervention, criteria of inclusion and exclusion, and potential bias in the studies.
3. The levels of evidence were determined by considering the quality of study according to the SIGN system<sup>25</sup>.
4. An evidence table (Appendix 3) was used to summarise the information of study type, clinical conditions, study population, intervention, outcomes and the level of evidence determined.

### 4.4 Description of Studies

Ten randomised studies<sup>26-35</sup> were found that reported the use of coumarin (or benzopyrone) for lymphoedema.

Among them, the following five studies<sup>26-30</sup>(Appendix 2) were excluded:

Study reported by Lokiec<sup>26</sup> appears to be a randomised controlled study. Twenty three patients previously treated for a breast cancer with a swollen upper limb were randomly assigned to receive two different concentrated solutions (1mg/ml or 2.5mg/ml) of benzopyrones. This study was excluded based on two reasons. Firstly, the report only states that the benzopyrone was used in the study, but which benzopyrone was not reported. It could be coumarin or other drugs of benzopyrones. Secondly, the study was designed to demonstrate the differences between two concentrated forms of the drug, rather than to demonstrate the effectiveness of the drug. The same dose of the drug was used in both arms of the trial.

Burgos's study randomly assigned 77 patients with lymphoedema following treatment of breast cancer into two coumarin treatment groups: Group A received coumarin 90 mg/day while Group B received 135 mg/day. The study was designed to compare effects of two different dosages of coumarin, rather than to demonstrate the effectiveness of coumarin because coumarin was used in both arms of the trial<sup>27</sup>.

Three randomised studies<sup>28-30</sup> reported the use of coumarin on filaritic lymphoedema and elephantiasis. These three studies were not included since results from these studies would not provide direct evidence to analyse the clinical effectiveness of using coumarin for lymphoedema following cancer treatment, which is the main focus of this review.

Five studies<sup>31-35</sup> with appropriate study subjects (patients with lymphoedema following cancer treatment) and designed appropriate control groups, were included in the final analysis. The characteristics of each study included are presented in the Appendix 3.

A number of reports including three evaluation studies<sup>19 36 37</sup> on safety issues of coumarin were also included and discussed in this review.

## **5. Results**

### **5.1 Effectiveness of coumarin for lymphoedema following cancer treatment**

Desprez-Curely reported the use of coumarin tablets (containing trioxyethylrutin TER) for ninety two patients with post mastectomy lymphoedema<sup>32</sup>. During the first phase of study, the patients received either the active drug or placebo. However, the results from the second phase (after 6 months) cannot be used to demonstrate effectiveness, since coumarin was used in both arms after 6 months. The results in favour of coumarin at 6 months were reported in this study. However, the study was poorly reported. Many details of the study remain unknown including methods of randomisation and blinding, dose of coumarin, baseline of the patients and outcome measurement. The level of evidence from this study is graded as “2+” rather than “1-”.

Loprinzi reported a randomised crossover study<sup>33</sup> in which 140 women with chronic lymphoedema after treatment for breast cancer received 200mg of oral coumarin or placebo twice daily for six months and then the other treatment for the following six months. Study results from the first six months can be used to analyse the effectiveness of coumarin by comparing with placebo. Study results reported at crossover point indicated that there were non-statistically significant differences between coumarin and placebo in average volume of the affected arm and subjective symptoms measured.

Randomised crossover study reported by Casley-Smith<sup>34</sup> included 31 patients with unilateral postmastectomy lymphoedema in arms, and another 21 patients with unilateral leg lymphoedema of various causes in the study. Some outcomes from patients with arm lymphoedema were reported before the crossover point at six months: the reduction of oedema (limb volume) in the intervention was 46% (95% CI 44% to 48%) vs 25% (95% CI 25% to 28%) in the placebo. No other data for the patients with arm lymphoedema during the first phase of the study can be extracted.

The results from two other studies<sup>31 35</sup> were also assessed in this report. However, it is necessary to note the diversity of the causes of lymphoedema among patients included in the studies.

The French study<sup>35</sup> only stated that “80 patients with secondary upper limb oedema” were included, and did not provide other details about the patients e.g. gender, age and causes of lymphoedema. Lymphoedema following breast cancer treatment are likely to be included in the study since it is the most common cause of secondary upper limb lymphoedema. The number of patients assigned to each group, actual dose of coumarin and other information regarding study design were not reported in detail. The author reported the study as “randomised” and “double blind crossing over” trial; however, we are unable to find any information related to methods of blinding, randomisation and the point of crossover. The author concluded “coumarin is able to decrease statistically the swelling of secondary arm lymphoedema”<sup>35</sup>. The level of evidence from this study is graded as “2-”.

The randomised controlled study reported by Chang<sup>31</sup> only included a very small proportion of patients (5%, 3 cases) with leg lymphoedema caused by treatment for carcinoma. In the first six months of the study, patients in intervention group received 400mg coumarin a day while those in control group received placebo. The authors reported that there were significant improvements in the volume, circumference, tonometric findings and symptoms in the intervention group during the first six months. The results after six month are difficult to interpret since compressing bandaging and microwave heating were added to both intervention and controls. The value of this study appears to be limited for this review due to the problems in the study population and extra modalities were added after six months. The level of evidence from this study is graded as “2-”.

Characteristics of these five included studies are presented in Appendix 3.

## 5.2 Safety of Coumarin

Four studies<sup>32 33 35 38</sup> reported side effects of dizziness, nausea, pruritis, menstrual flow disturbance, digestive disorders and hepatotoxic effects. One study<sup>31</sup> did not report any information in relation to side effects.

Among five randomised studies included, only one study<sup>33</sup> reported using liver function tests (LFTs) to monitor potential hepatotoxic effects of coumarin. Using serum aminotransferase concentrations that reached two or more times the upper limit of normal as a criterion, hepatotoxic effects were found in nine patients (6%) during treatment with coumarin. One patient developed jaundice and the serum bilirubin concentration rose to 19.3 mg per deciliter (330 ( $\mu$ )mol per liter). The liver function tests became normal after coumarin was stopped<sup>33</sup>.

Three evaluation reports<sup>19 36 37</sup> on hepatotoxic effects of coumarin were found from the literature search.

Cox reported the effects of coumarin on LFTs in a clinical trial conducted in Ireland<sup>19</sup>. Two thousand one hundred and seventy three patients were admitted into a trial to determine the clinical pharmacology and toxicology of coumarin. The patients were treated for conditions of (a) chronic brucellosis (50%); (b) cancer, mainly breast carcinoma and melanoma, and a few cases of advanced renal cell carcinoma and glioma (30%) and (c) chronic infections (including toxoplasmosis and mononucleosis) and chronic fatigue syndrome. The coumarin doses used in this trial ranged from 25 mg/day for chronic infections to 2,000 mg/day for advanced renal cell carcinoma and glioma. The majority of patients received 100mg/day for 1 month, followed by 50 mg/day for 2 years<sup>19</sup>. The results showed:

- 17 of 2,173 patients treated with coumarin developed elevated LFTs of sufficient magnitude (i.e. at least double the normal maximum level). All patients with elevated LFTs were screened for hepatitis A and B antigens.
- Four of the 17 patients had probable causes for their elevated LFTs other than hepatotoxicity. Five patients developed elevated LFTs which returned to normal while still on coumarin. Authors' comments on these five patients were "the significance of this is uncertain. It could represent a mild hepatotoxic effect to which the patients became tolerant, or it could reflect a therapeutic response to the drug"<sup>19</sup>.
- Eight patients developed elevated LFTs that had no obvious cause other than as a result of coumarin administration. The incidence of the adverse hepatotoxic effects was about 0.37% (8/2,137). Among them, histories of seven cases were clearly reported (see **Appendix 4**). None of the patients developed serious permanent liver damage as a result of coumarin therapy.

Andrejak reported a national survey on hepatic reactions reported to the marketing authorisation holder (Knoll France Laboratories) and to the French Pharmacovigilance Regional Centres<sup>36</sup>. All hepatic reactions with an increase of alanine aminotransferase (ALAT) over twice the upper limit of normal and/or a rise in alkaline phosphatase over 1.5 times the upper limit of normal were taken into account. Clinical, biological and pathological data of these cases were reviewed. Results showed:

- Over the 8-year period of 1988 to 1996, 33 cases were considered as coumarin associated hepatotoxicity. Coumarin was given at doses ranging from 45 to 135 mg/day (recommended doses of 90 or 135 mg were used in 24 cases and no patient took excessive doses of the drug) for patients with lymphoedema following breast cancer (9 cases), other lymphoedema (10 cases), other conditions (8 cases) and unknown diagnosis (6 cases)
- Hepatic reaction was diagnosed in two-third of the cases between 2 and 6 months after initiation of the treatment. Fourteen of the 33 patients (42%) were hospitalised
- According to the French method of causality assessment, the drug-effect relationship was evaluated as likely or possible in 15 cases. For 18 other cases, the relationship was judged as dubious, generally because the cases were insufficiently documented
- The hepatic damage progressed to severe liver failure with encephalopathy in three cases, a liver transplantation was performed in one case (with subsequent favourable outcome). A fatal evolution was observed in the two remaining cases
- The reported incidence of notified hepatic reactions was estimated to be at least 2-4/10,000 for a mean duration of treatment of 12 months
- Based on these results, the risk-benefit ratio of coumarin was re-evaluated and judged unfavourable. Coumarin has been withdrawn from the market in France<sup>36</sup>.

Andrejak also reported that “Swiss authorities also received some cases of hepatic reactions occurring at daily doses between 100 to 300mg/day. Fatal outcomes occurring in two cases were not considered definitely related to the drug intake. In two cases, the re-administration of the drug led to the re-occurrence of the hepatic reaction”<sup>36</sup>. However, we are unable to find more detailed information about these adverse events in Switzerland.

Bruppacher<sup>37</sup> analysed suspected adverse drug reactions (ADR) of a combination of coumarin and troxerutin (a mixture of hydroxyethylated rutins) in Germany, and reported:

- From 1971 to 1996, eight reported cases of hepatotoxic events were found in Germany. For these cases, total dosage ranged from 30 to 90 mg per day, treatment duration ranged from 5 days to 15 weeks.
- Using background rate from health insurance data in New England and the authors derived an estimate of 77 cases per 100,000 person years, 24 of these with unexplained aetiology.
- Authors concluded “...the number of spontaneous reports does not exceed expectations from the background rate...”<sup>37</sup>, but still suggested “... careful surveillance of the market by the manufacturer and intensive drug monitoring in ongoing clinical trials” to keep this issue under close attention<sup>37</sup>.

In a 14 month period to May 1995, the Adverse Drug Reactions Advisory Committee in Australia received a total of 10 reports of suspected adverse reactions in connection with the use of coumarin. Six of these described jaundice occurring in patients who had taken coumarin 400 mg orally daily for periods ranging from one to four months. In nine cases, coumarin was the only suspected drug cause. The incidence of hepatotoxicity was estimated to be at least 34 cases per 10,000 users<sup>39 40</sup>.

Casley-Smith also estimated that about 3 per 1,000 may get an idiosyncratic hepatitis. Based on four related deaths reported, the death rate of the adverse effect was estimated as 3 per 10,000<sup>22</sup>.

Possible hepatotoxic effects were also reported in the cases where patients were treated with coumarin for Turner’s syndrome in Denmark<sup>41</sup> and lymphoedema in Australia<sup>42</sup> and the UK<sup>43</sup>.

### 5.3 Cost effectiveness

No study about cost effectiveness of using coumarin on lymphoedema was found.

## 5.4 Other information

Some actions have been taken by drug administration and other authorities to deal with the safety issues of coumarin in different countries:

The secretary of the Australian Department of Health and Family Services cancelled the registration of Lodema “on the grounds that the safety and quality of the product is unacceptable”<sup>44 45</sup>. The Australian Drug Evaluation Committee (ADEC) 178<sup>th</sup> meeting minutes state “there are insufficient data to support the efficacy of topical coumarin preparations (powder or ointment) in the treatment of lymphoedema due to any cause”<sup>44 45</sup>.

The Medical Post in Canada reported the cancellation of a large clinical trial on the effectiveness of Lodema being conducted at Princess Margaret Hospital in Toronto for the treatment of lymphoedema as a result of deaths and liver damage associated with use of the drugs in Australia<sup>44</sup>.

The drug has been suspended or restricted in Australia, France, Belgium and Canada<sup>46</sup>.

## **6. Discussion**

### 6.1 Methodological quality

All randomised studies included have considerable weaknesses in study design. The methodological quality of these studies is discussed as follows:

- **Study design:** Among the five studies<sup>31-35</sup> included to analyse effectiveness of coumarin, three studies<sup>33-35</sup> used crossover study design. The usefulness of using crossover study design to investigate the clinical effectiveness of coumarin for lymphoedema needs to be discussed.

Crossover study design may have some advantages such as to reduce sample size required and to eliminate inter subject variability, order and sequence effects. However, using crossover design to investigate the clinical effectiveness of coumarin for lymphoedema, carryover (or residual) effects need to be considered. For the patients who received coumarin in the first phase of study, the effects of the drug are very likely to continue or carryover to the next phase of placebo, especially as no washout period was used in these

studies. Therefore, study results that included data after the crossover point need to be interpreted with caution. Study results reported by Casley-Smith<sup>34</sup> and Cluzan<sup>35</sup> appear to include data after the crossover point.

Study results observed before or at the crossover point can be treated as those of other randomised controlled trials with parallel groups to analyse the effectiveness of coumarin. However, the results from the first phase of crossover studies are usually based on a relatively short time period. Efficiency of these studies appears to be affected by the crossover study design.

For the two other randomised controlled studies with parallel groups<sup>31 32</sup>, only study results from the first phase of the studies can be considered to analyse the effectiveness of coumarin. In the trial reported by Desprez-Curely<sup>32</sup>, patients in both arms received coumarin after 6 months. In another trial reported by Chang<sup>31</sup>, patients in the both arms received micro heating and compressing bandaging after 6 months. These changes in the second phases of the studies make the results from the second phases and whole study periods difficult to interpret.

- **Intervention:** The dose of coumarin used for the intervention was reported to be 400mg daily in three studies<sup>31 33 34</sup>. The actual dose was not reported in the two other French studies<sup>32 35</sup>. The authors only reported that patients received 6 or 9 tablets daily during the study period. If the tablets were the same as those reported in another French study<sup>36</sup>, the daily dose of coumarin in these two trials<sup>32 35</sup> could be 90mg (6 tablets) or 135mg (9 tablets).

The drug used in the study reported by Desprez-Curely<sup>32</sup> also contained trioxyethylrutin. There is no detailed information which can be used to determine whether a similar formulation was used in another French study<sup>35</sup>.

- **Sample size and statistical analysis:** Four randomised studies included in this review have relatively small sample sizes of less than 100 patients. The biggest trial with 138 patients was reported by Loprinzi in the US<sup>33</sup>. There may be a need for large trials to investigate the effectiveness of coumarin for lymphoedema.

Statistical analysis was conducted in all included studies. However, statistical tests for the comparisons of coumarin and placebo from the first phases of the studies, which are useful to determine the effectiveness of the drug, were only reported in three studies<sup>31-33</sup>.

- **Randomisation and blinded method:** The methods for randomisation were not reported in four included studies<sup>31-33 35</sup> that indicated the study subjects were “randomly assigned” to coumarin or placebo. Only one study clearly stated that the randomisation was based on a random-number table<sup>34</sup>.

Subjective measurements appeared to be used in all studies included. Double blinded method was reported in four included studies<sup>31 32 34 35</sup>. However, only one study provided information that “blinding was performed by the pharmacist”<sup>34</sup>. The blinding procedures in the other three studies<sup>31 32 35</sup> were not reported.

- **Comparison:** Ideally, clinical effectiveness of coumarin can be demonstrated by comparing with other treatment modalities (e.g. physical therapy) and placebo. However, all included studies intended to compare coumarin with placebo. There are no studies that are designed to compare coumarin with other modalities which are currently used in clinical practice. For purchasing decision making, studies comparing coumarin with other modalities may provide more useful information than those compared with placebo. Even though compression bandaging and microwave heating were used in the second phase of Chang’s study<sup>31</sup>, the comparisons between outcomes from coumarin treatment at the first time period and from the placebo plus compression bandaging and microwave heating at the second period were not reported.

- **Study population, inclusion and exclusion criteria:** Primarily, we are interested in the effectiveness of coumarin for lymphoedema following cancer treatment especially lymphoedema following breast cancer treatment. In terms of the causes of lymphoedema, heterogeneity of study subjects in some included studies appears to be significant, for example the different causes of lymphoedema in patients studied by Casley-Smith<sup>34</sup> and Chang<sup>31</sup>. The heterogeneous nature of the patient population may create potential confounding factors in these studies.

Compared with other included studies, inclusion and exclusion criteria were clearly described in the American study reported by Loprinzi<sup>33</sup>. This study also only included patients with arm lymphoedema following breast cancer treatment.

Severity of lymphoedema in study subjects was only reported in two studies<sup>31 33</sup>.

- **Follow-up and study period:** The information about drop-out during the study periods was not reported in two studies<sup>31 32</sup>. Eleven patients (5 with arm lymphoedema and 6 with leg lymphoedema) were excluded after enrolment for reasons “unconnected with the trial” in the study reported by Casley-Smith<sup>34</sup>. It is unclear whether these patients were excluded before or after randomisation. They were not included in the final analysis, impact of the exclusion was not discussed in the report. In the American study<sup>33</sup>, drop-out is about 14% at 6 months and 30% at 12 months.

Among five included studies, study periods ranged from 9 months to 18 months. However, due to multiple phases and crossover study design, treatment periods in which outcomes can be considered to analyse the effectiveness of coumarin appear to be short. The “useful” treatment period in four included studies<sup>31-34</sup> was 6 months. The period is unable to be determined in the study reported by Cluzan<sup>35</sup> since the crossover point was not reported (total study period was 9 months).

As suggested by some authors<sup>34</sup> coumarin does not rapidly reduce chronic forms of oedema such as lymphoedema, so a relatively long period of treatment is recommended. Therefore, well designed and conducted studies with relatively long treatment period are desired to analyse the effectiveness and side effects of using coumarin for lymphoedema.

- **Outcome measures:** A relatively valid method of water displacement was used to measure limb volume in two studies<sup>31 34</sup>. Circumference measurement was used in the other three studies<sup>32 33 35</sup>. Circumference measurement has some disadvantages and may only provide limited information. It can be influenced by a number of factors such as the degree of the tape constricting skin and soft tissue<sup>47</sup>.

## 6.2 Effectiveness of the coumarin for lymphoedema

The available randomised controlled studies do not provide good quality evidence to analyse the effectiveness of coumarin for lymphoedema following cancer treatment. All included studies have considerable weaknesses as discussed in the previous section (6.1).

Based on relatively short treatment periods, three included studies<sup>32 34 35</sup> found a favourable outcome for coumarin compared with placebo. Even though favourable results for coumarin were also found in another study reported by Chang<sup>31</sup>, this study may only provide very limited information for this review since the majority of study subjects were not treated for lymphoedema following cancer treatment.

In contrast, no clinical benefit was found in the study reported by Loprinzi<sup>33</sup>. Compared with other included studies, this study may have some advantages, for example relatively large sample size, clear inclusion and exclusion criteria and homogeneity of study subjects included (arm lymphoedema following breast cancer treatment).

**Overall**, there appears to be no consistent results from randomised controlled studies that compared coumarin with placebo for lymphoedema following cancer treatment. Taking the absence of studies comparing coumarin with other treatment modalities, and significant methodological weaknesses (see section 6.1) of each included study into account, the clinical effectiveness of coumarin cannot be determined from the available randomised controlled studies.

## 6.3 Safety of coumarin treatment

Among the five included randomised studies, coumarin attributable hepatotoxic events were only reported in the American study reported by Loprinzi<sup>33</sup>. The incidence rate of 6% was considerable in the 12 month study period. Unfortunately, more detailed information, e.g. the case histories, were not reported. Validity of this figure cannot be discussed in detail.

Even though hepatotoxic events were not reported in four other included studies, the potential hepatotoxic effects cannot be ruled out for at least two reasons: Firstly, in contrast to the American study LFTs were not designed to monitor the side effects. Secondly, there may be

an insufficient number of patients exposed to coumarin because of the small sample sizes and short treatment period in these studies.

The incidence rates of coumarin attributable hepatotoxic events vary significantly between reports, from 2-4 per 10,000 reported in French surveillance system<sup>36</sup> to 37 per 10,000 in a large clinical trial reported by Cox<sup>19</sup>.

Some aspects of the information need to be considered in determining the validity of reported incidence rates of coumarin attributable hepatotoxicity: the number of drug users (in relation to denominator) and the validity of the diagnosis (in relation to numerator). Special attention may need to be paid to the information around the diagnosis. The diagnosis of drug-induced liver diseases remains difficult because of the absence of specific signs in most cases and mainly relies on the exclusion of other causes<sup>24 48</sup>. In current clinical practice, the diagnosis relies on “chronological and clinical criteria to allow elimination of other causes and to demonstrate the role of the offending drug”<sup>24</sup>.

The incidence rate of 0.37% reported by Cox<sup>19</sup> appears to be more valid than others. The figure is based on a large clinical trial that was designed to determine the effectiveness and potential hepatotoxicity of coumarin for 2,173 patients with different conditions. The coumarin dose used in the trial including treatment period was clearly reported. Compared with other reports on coumarin attributable hepatotoxicity, this report has the following advantages:

- The denominator to calculate incidence rate appears to be reliable since the number comes from actual participants in the clinical trial rather than an estimation
- Under reporting is unlikely to be a concern since all patients had regular liver function tests to detect potential hepatotoxic effects
- The diagnosis of 8 cases of coumarin attributable hepatotoxicity appears to be relatively valid. Case histories of 7 cases are clearly reported (Appendix 4). Other causes (e.g. hepatitis) were ruled out from these cases.
- Five cases present a similar pattern that would meet the chronological criteria: LFTs were found abnormal 4 to 6 months after coumarin treatment, returned toward normal

1 to 3 months after coumarin was stopped; **relapse of liver abnormalities after re-administration of coumarin.**

The incidence rate (0.37%) reported in the Cox study is similar to 34 cases per 10,000 users estimated by the Adverse Drug Reactions Advisory Committee in Australia<sup>39 40</sup>, and 3 per 1,000 users estimated by Dr Casley-Smith<sup>22</sup>. However, no detailed supporting materials can be found for these numbers reported in Australia.

The incidence (2-4 per 10,000 users) calculated in the French survey<sup>36</sup> appears to be significantly lower than the rate reported by Cox<sup>19</sup>. Under reporting of adverse events in the surveillance is a major concern and the incidence rate (2-4 per 10,000 users) is very likely to be underestimated.

An adverse incident rate was not reported by Bruppacher<sup>37</sup>. The authors' conclusions of "the number of spontaneous reports does not exceed expectations from the background rate" are based on a comparison of reported events in Germany and estimated background cases calculated from insurance data in New England. Under reporting and population differences between coumarin users in Germany and people who had health insurance in New England need to be taken into account in interpreting the conclusions. This report appears to provide limited information to consider the incidence of coumarin attributable hepatotoxicity.

For most drugs, the risk of hepatotoxicity ranges from 1/10,000 to 1/100,000<sup>24</sup>. For flucloxacillin, an antibiotic being considered as an important cause of drug associated hepatotoxicity in New Zealand<sup>49</sup>, the risk was reported to be 6.7 per 100,000 users<sup>50</sup> or 7.6 per 100,000 users<sup>51</sup>. The incidence rate of 0.37% (or 370/100,000) reported in a relatively valid study on coumarin<sup>19</sup> appears to be significantly higher than these ranges.

## 6.4 Cost effectiveness

The cost effectiveness of using coumarin for lymphoedema following cancer treatment cannot be directly discussed in this report as no cost effectiveness studies were found.

## 6.5 Limitations of the review

A reasonable attempt, including hand searching of citations, has been made to find published reports from relevant medical literature databases and internet sources, but no attempt was

made to identify unpublished studies and studies published in languages other than English. Authors of the studies included in this review have not been contacted for more detail information on study design and data in relation to study results. Assessment of the quality of studies has solely depended on the information published.

Publication bias has not been discussed in this review.

## **7. Conclusions**

**Implications for practice:** The available randomised controlled studies do not provide good quality evidence to analyse the effectiveness of using coumarin for lymphoedema following cancer treatment. There appear to be no consistent results from randomised controlled studies that compared coumarin with placebo for lymphoedema following cancer treatment. Clinical effectiveness of coumarin cannot be determined from these studies. Coumarin attributable hepatotoxicity appears to be a big concern for the clinical application.

**Implications for research:** There may be a need for well-designed and well-conducted randomised controlled studies, with relatively large sample size, long treatment period and clearly defined study population, to investigate the effectiveness of using coumarin for lymphoedema following cancer treatment. However, these studies could be difficult to get ethical approval for due to the concern of coumarin attributable hepatotoxicity.

**Implications for Purchasing and Policy Decisions:** Clinical effectiveness of coumarin for lymphoedema following cancer treatment cannot be determined from available randomised controlled studies. The purchasing decision needs to take the uncertainty of effectiveness, availabilities of other treatment modalities for lymphoedema and the risk of coumarin attributable hepatotoxicity into account.

## **References**

1. Cheville AL, McGarvey CL, Petrek JA, Russo SA, Taylor ME, Thiadens SRJ. Lymphedema management. *Seminars in Radiation Oncology* 2003;13(3):290-301.
2. Loudon L, Petrek J. Lymphedema in women treated for breast cancer. *Cancer Practice* 2000;8(2):65-71.
3. Piller N, Eaton M. Lymphoedema optimising outcomes. *Medicine Today* 2004;5(4):48-60.
4. Sparaco A, Fentiman IS. Arm lymphoedema following breast cancer treatment. *International Journal of Clinical Practice* 2002;56(2):107-110.
5. Hanley S, Rodgers J. An outline of lymphoedema management. *Cme Bulletin Palliative Medicine* 2000;2(1):21-26.
6. Kissin MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphoedema following the treatment of breast cancer. *British Journal of Surgery* 1986;73(7):580-4.
7. Markowski J, Wilcox JP, Helm PA. Lymphedema incidence after specific postmastectomy therapy. *Archives of Physical Medicine & Rehabilitation* 1981;62(9):449-52.
8. Pezner RD, Patterson MP, Hill LR, Lipsett JA, Desai KR, Vora N, et al. Arm lymphedema in patients treated conservatively for breast cancer: relationship to patient age and axillary node dissection technique. *International Journal of Radiation Oncology, Biology, Physics* 1986;12(12):2079-83.
9. Marcks P. Lymphedema: Pathogenesis, prevention, and treatment. *Cancer Practice* 1997;5(1):32-38.
10. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. *Cancer* 1998;83(12 Suppl American):2776-81.
11. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer* 2001;92(6):1368-77.
12. Clark R, Wasilewska T, Carter J. Lymphoedema: a study of Otago women treated for breast cancer. *Nursing Praxis in New Zealand*. 1997;12(2):4-15.
13. Anonymous. The diagnosis and treatment of peripheral lymphedema. *Lymphology* 1995;28(3):113-117.
14. Anonymous. The diagnosis and treatment of peripheral lymphedema: Consensus Document of the International Society of Lymphology. *Lymphology* 2003;36(2):84-91.
15. Balzarini A, Pirovano C, Diazzi G, Olivieri R, Ferla F, Galperti G, et al. Ultrasound therapy of chronic arm lymphedema after surgical treatment of breast cancer. *Lymphology* 1993;26(3):128-134.

16. Casley-Smith JR, Boris M, Weindorf S, Lasinski B. Treatment for lymphedema of the arm--the Casley-Smith method: a noninvasive method produces continued reduction. *Cancer*. 1998;83(12 Suppl American):2843-60.
17. Kligman L, Wong RKS, Johnston M, Laetsch NS. The treatment of lymphedema related to breast cancer: A systematic review and evidence summary. *Supportive Care in Cancer* 2004;12(6):421-431.
18. Egan D, O'Kennedy R, Moran E, Cox D, Prosser E, Thornes RD. The pharmacology, metabolism, analysis, and applications of coumarin and coumarin-related compounds. *Drug Metabolism Reviews* 1990;22(5):503-529.
19. Cox D, O'Kennedy R, Thornes RD. The rarity of liver toxicity in patients treated with coumarin (1,2-benzopyrone). *Human Toxicology* 1989;8(6):501-506.
20. Piller NB. Macrophage and tissue changes in the developmental phases of secondary lymphoedema and during conservative therapy with benzopyrone. *Archives of Histology & Cytology*. 1990;53(Suppl):209-18.
21. Casley-Smith JR, Jamal S, Piller NB, Morgan RG, Wang CT, Nishi M, et al. The effects of all high-protein oedemas and the reduction of all of them by the benzo-pyrones, with particular emphasis on lymphoedema and elephantiasis. *Progress in lymphology XII: proceedings of the XIIth International Congress of Lymphology. ICS887. Conference: The XIIth International Congress of Lymphology* 1989;27(02):17-22.
22. Casley-Smith JR, Casley-Smith J. The benzo-pyrone drugs in the treatment of lymphoedema (and other high-protein oedemas). On <http://www.lymphoedema.org.au/bp.htm> access Jan 2005.
23. Casley-Smith JR, Casley-Smith J. Suppliers of benzo-pyrones for the treatment of lymphoedema (and other high-protein oedemas). On <http://www.lymphoedema.org.au/bp-suppl.htm> access Jan 2005.
24. Larrey D. Drug-induced liver diseases. *Journal of Hepatology*. 2000;32(1 Suppl):77-88.
25. SIGN. Grading system for recommendations in evidence-based clinical guidelines--report of a review of the system for grading recommendations in SIGN guidelines: Scottish Intercollegiate Guidelines Network (SIGN), 2000.
26. Lokiec F, Pecking A, Santoni J, Cluzan R. Benzopyrone pharmacokinetic parameters: dose-efficacy of two coumarin dosages in patients with secondary upper limb edemas. *Progress in lymphology XII: proceedings of the XIIth International Congress of Lymphology. ICS887* 1990;29(1):453-4.
27. Burgos A, Alcaide A, Alcoba C, Azcona JM, Garrido J, Lorente C, et al. Comparative study of the clinical efficacy of two different coumarin dosages in the management of arm lymphedema after treatment for breast cancer. *Lymphology*. 1999;32(1):3-10.
28. Casley-Smith J, Wang CT, Casley-Smith JR, Zi-hai C. Treatment of filarial lymphoedema and elephantiasis with 5,6-benzo-alpha-pyrone (coumarin). *BMJ* 1993;307(6911):1037-41.

29. Jamal S, Casley-Smith JR. The effects of 5,6 benzo-[a]-pyrone (coumarin) and DEC on filaritic lymphoedema and elephantiasis in India. Preliminary results. *Annals of Tropical Medicine & Parasitology*. 1989;83(3):287-90.
30. Casley-Smith JR, Jamal S. Reduction of filaritic lymphoedema and elephantiasis by 5,6 benzo-alpha-pyrone (coumarin), and the effects of diethylcarbamazine (DEC). *Annals of Tropical Medicine & Parasitology* 1993;87(3):247-258.
31. Chang TS, Gan JL, Fu KD, Huang WY. The use of 5,6 benzo-[alpha]-pyrone (coumarin) and heating by microwaves in the treatment of chronic lymphedema of the legs. *Lymphology*. 1996;29(3):106-11.
32. Desprez-Curely P, Cluzan R, Pecking A. Benzo-pyrones and post-mastectomy lymphedemas, double-blind trial placebo versus sustained release coumarin with trioxyethylrutin (TER). *Progress in lymphology X* 1985:203-5.
33. Loprinzi CL, Kugler JW, Sloan JA, Rooke TW, Quella SK, Novotny P, et al. Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *New England Journal of Medicine*. 1999;340(5):346-50.
34. Casley-Smith JR, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-benzo-[alpha]-pyrone. *New England Journal of Medicine*. 1993;329(16):1158-63.
35. Cluzan R, Pecking A, Nishi M, Uchino S, Yabuki S. Benzopyrone (lysedem) double blind crossing over study in patients with secondary upper limb edemas. *Progress in lymphology XII: proceedings of the XIIth International Congress of Lymphology. Conference: The XIIth International Congress of Lymphology* 1989;27(02):453-454.
36. Andrejak M, Gersberg M, Sgro C, Decocq G, Hamel JD, Morin M, et al. French pharmacovigilance survey evaluating the hepatic toxicity of coumarin. *Pharmacoepidemiology & Drug Safety* 1998;7(SUPPL. 1):S45-S50.
37. Bruppacher R, Rieckemann B, Naser-Hijazi B, Wustenberg P. Evaluation of the safety of a coumarin-troloxerutin combination. *Pharmacoepidemiology & Drug Safety* 1998;7(SUPPL. 1):S37-S40.
38. Casley-Smith J, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-benzo-[alpha]-pyrone. *New England Journal of Medicine* 1993;329(16):1158-63.
39. ADRAC. Loderma and the liver. *Australian Adverse Drug Reaction Bulletin* 1995;14(3).
40. WHO. WHO Pharmaceuticals Newsletter. 1996;3.
41. Faurschou P. Toxic hepatitis due to benzo-pyrone. *Human Toxicology*. 1982;1(2):149-50.
42. Beinssen A. Possible coumarin hepatotoxicity. *Medical Journal of Australia* 1994;161(11-12):725.
43. Morrison L, Welsby PD. Side-effects of coumarin. *Postgraduate Medical Journal*. 1995;71(841):701.

44. Anonymous. Editorial response to "There are many benzo-pyrones for lymphedema". *Lymphology*. 1997;30(1):38-9.
45. WHO. WHO Pharmaceuticals Newsletter. 1996;10.
46. Lymphovenous Canada. Liver toxicity raises doubts about coumarin. On: <http://www.lymphovenous-canada.ca/benzo.htm> 2005.
47. Petrek JA, Pressman PI, Smith RA. Lymphedema: current issues in research and management. *Ca: a Cancer Journal for Clinicians*. 2000;50(5):292-307; quiz 308-11.
48. Chakraborty P, Jain A, Kar P. Drug-induced liver diseases. *Tropical Gastroenterology*. 2003;24(1):8-12.
49. Pillans P. Drug associated hepatic reactions in New Zealand: 21 years experience. *New Zealand Medical Journal*. 1996;109(1028):315-9.
50. Devereaux BM, Crawford DH, Purcell P, Powell LW, Roeser HP. Flucloxacillin associated cholestatic hepatitis. An Australian and Swedish epidemic? *European Journal of Clinical Pharmacology*. 1995;49(1-2):81-5.
51. Derby LE, Jick H, Henry DA, Dean AD. Cholestatic hepatitis associated with flucloxacillin. *Medical Journal of Australia*. 1993;158(9):596-600.

## **Appendix 1. Level of evidence in the SIGN system**

1 <sup>++</sup>	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well conducted meta analyses, systematic reviews, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta analyses, systematic reviews, or RCTs with a high risk of bias
2 <sup>++</sup>	High quality systematic reviews of case-control or cohort studies  High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 <sup>+</sup>	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 <sup>-</sup>	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

## **Appendix 2. Randomised studies excluded in this review**

<b>Study</b>	<b>Title</b>	<b>Reasons for excluding</b>
Lokiec, 1990 <sup>26</sup>	Benzopyrone pharmacokinetic parameters: dose-efficacy of two coumarin dosages in patients with secondary upper limb oedemas	Benzopyrone was used in both arms of the trial: 75 mg orally every day for 4 weeks. Patients were randomly assigned to receive the drug in form A (1 mg/ml) or form B (2.5 mg/ml)
Burgos, 1999 <sup>27</sup>	Comparative study of the clinical efficacy of two different coumarin dosages in the management of arm lymphoedema after treatment for breast cancer	Coumarin was used in both arms of the trial: 90 mg/day (Group A) and 135 mg/day (Group B)
Casley-Smith, 1993 <sup>28</sup>	Treatment of filarial lymphoedema and elephantiasis with 5,6-benzo-alpha-pyrone (coumarin)	Study population: patients with chronic filarial lymphoedema or elephantiasis
Jamal, 1989 <sup>29</sup>	The effects of 5,6 benzo-[a]-pyrone (coumarin) and DEC on filaritic lymphoedema and elephantiasis in India. Preliminary results	Study population: patients with chronic filarial lymphoedema or elephantiasis
Casley-Smith, 1993 <sup>30</sup>	Reduction of filaritic lymphoedema and elephantiasis by 5,6 benzo-alpha-pyrone (coumarin), and the effects of diethylcarbamazine (DEC)	Study population: patients with chronic filarial lymphoedema or elephantiasis

### Appendix 3. Characteristics of included studies

Study	Methods	Participants	Intervention	Outcomes	Comments and Level of Evidence
Desprez-Curely 1985 <sup>32</sup>	Randomised controlled study, only the first phase of the study is considered.	<p>Ninety-two patients with post mastectomy lymphoedema, whatever the duration.</p> <p>No other information about the patients was provided</p> <p>During the first phase of 6 months, the patients were given either the active ingredient or the placebo.</p> <p>From the 6<sup>th</sup> month and up to 18<sup>th</sup>, all patients received coumarin with trioxtethylrutin (TER) in the formulation.</p>	<p><b>Intervention (n=45?):</b> coumarin in a formulation containing TER, 9 tablets for the first 6 months, the actual dose of the tablet was not reported</p> <p><b>Control (n=46?):</b> placebo</p> <p><b>Measurement:</b> wrist, forearm and arm perimeters, subjective symptoms and isotopic lymphography</p>	<p>In terms of arm and wrist perimeters, the group treated with the active drug was above the placebo group at 6 months.</p> <p>“The subjective signs have been much more improved in the first group (the intervention group) at 6<sup>th</sup> month (70.5%) than in the placebo group (51%)”</p> <p>There was no difference in the numbers of patients having had blocking area at starting point (T0). There was a development in favour of intervention group observed by isotopic lymphography at six months.</p> <p>Side effects were observed in 6 patients in the intervention group and 2 in the placebo group. These side effects included dizziness, nausea, pruritis and menstrual flow disturbance.</p>	<p>The methods of randomisation and blind were was not stated</p> <p>One patient who did not complete study was not reported</p> <p>Baseline information and some results were not reported in detail</p> <p>Dose of coumarin was not reported</p> <p>Validity of circumference measurement</p> <p>Long term effect of coumarin cannot be analysed</p> <p>Method of statistical analysis was not reported</p> <p>Evidence level: 2<sup>+</sup></p>

<p>Casley-Smith 1993<sup>34</sup></p> <p>Supported by the Lymphoedema Association of Australia</p> <p>Coumarin and placebo tablets were provided by Hamilton Laboratories (Adelaide, Australia)</p>	<p>Randomised crossover study</p>	<p>Thirty one patients with unilateral postmastectomy arm lymphoedema and 21 patients with unilateral leg lymphoedema of various causes</p> <p>The lymphoedema was a primary condition in 15 patients and developed after surgery or in a setting of extensive inflammation in the other 37</p> <p>The patients were diagnosed by history and physical examination, with computed tomography and venography performed if there was any doubt about the diagnosis</p> <p>In addition to 52 patients reported, 11 patients were enrolled who were later excluded: 5 with postmastectomy lymphoedema and 5 with leg lymphoedema withdrew for reasons unconnected with the trial, and 1 patient with leg oedema was excluded because she seldom returned for follow-up</p> <p>Except for short courses of antibiotics given for attacks of secondary acute inflammation, all other therapy was stopped one month before the trial and during the course.</p>	<p><b>Intervention (n=28 at starting point):</b> patients received 400mg coumarin (two tablets, each containing 200mg of the medicine) orally once a day for six months.</p> <p><b>Control (n=24 at starting point):</b> placebo</p> <p><b>Study period:</b> 12 months</p> <p><b>Measurement:</b> limb volumes, limb circumferences, tissue tonometry and skin temperature.</p>	<p>The active drug was preferred to the placebo by 93% of patients</p> <p>Measurements of limb volume showed that the active drug reduced the mean amount of oedema fluid in the arms from 46% above normal to 26% above normal (<math>p&lt;0.001</math>) and the amount in the legs from 25% to 17% above normal (<math>p&lt;0.001</math>). The circumference of the arms was reduced from 17% to 13% above normal, and the circumference of the legs from 11% to 7% above normal</p> <p>The softness of the limb tissue was increased, and elevated skin temperatures were reduced. There were fewer attacks of secondary acute inflammation. Bursting pain and feelings of hardness were decreased, as were feelings of tightness, tension, swelling, and heaviness; limb mobility also improved</p> <p>Side effects: mild nausea or diarrhoea occurred in 7 patients taking the active drug. None withdrew from the trial, and the side effects disappeared after the first month of therapy.</p>	<p>Diverse causes of lymphoedema</p> <p>Crossover study design, no washout period</p> <p>Impact of the exclusion was not discussed</p> <p>Impact of 11 patients excluded was not discussed</p> <p>Random number table and double blind method were used</p> <p>Evidence level 1<sup>-</sup> /2<sup>++</sup></p>
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<p>Loprinzi 1999<sup>33</sup></p> <p>Coumarin and placebo tablets were provided by Drossapharm Pharmaceuticals (Basel, Switzerland).</p> <p>The project was supported in part by grants from the National Cancer Institute.</p>	<p>Randomised crossover study</p>	<p><b>Inclusion:</b> 140 women aged 33 to 84 years old, with unilateral lymphoedema of the arm attributed to earlier local or regional treatment of breast cancer.</p> <p>In each case, both the woman and her physician had determined that the lymphoedema was sufficiently severe to warrant treatment.</p> <p>The lymphoedema had to have been present for at least one year and was not immediately reversible by elevation or compression of the arm</p> <p><b>Exclusion:</b> women were not eligible for the study if they had taken coumarin previously, were currently undergoing radiation therapy or chemotherapy, had changed their regimen of physical therapy for lymphedema during the preceding month, or had an indwelling venous device; if they had an infection of either arm, had evidence of residual active cancer, had a life expectancy of less than 2 years, or had bilateral oedema of the arms; if they were pregnant or nursing; or if they had a history of hepatitis or evidence of liver dysfunction,</p>	<p><b>Intervention (n=67 at starting point):</b> patients received 400 mg coumarin (two tablets, each containing 100mg of the medicine) orally twice a day for six months. Treatment was stopped if serum aminotransferase concentrations were two or more times the upper limit of normal.</p> <p><b>Control (n=71 at starting point):</b> placebo</p> <p><b>Study period:</b> 12 months</p> <p><b>Measurement:</b> limb volumes calculated from measurements of hand and arm circumference and the answers on a questionnaire completed by the patient about symptoms potentially related to lymphoedema.</p>	<p>After the administration of coumarin or placebo for six months, there were no significant differences from baseline in total or distal oedema; volume of the affected arm; ratio of the volume of the affected arm to that of the normal arm; or circumference of the hand, wrist, or arm at points 30, 40, and 50 cm from the tip of the middle finger.</p> <p>The average volume of the affected arm increased by 21ml with placebo and 58 ml with coumarin (P=0.80)</p> <p>The women's responses to questions about arm swelling, pressure, tightness, heaviness, and loss of mobility were similar for coumarin and placebo during both period and demonstrated some positive changes with time but no differential effects associated with treatment.</p> <p>The frequency of infections of the arm was similar during the coumarin and placebo periods.</p> <p>After each six-month period the women were asked whether they thought that the study medication was helping them. Their responses did not suggest that coumarin had benefit during either period</p> <p>The incidence of hepatotoxic effects was substantially higher with coumarin than with placebo. In none of the women did serum aminotransferase concentrations reach 2.5 times the upper limit of normal during the placebo period, whereas in nine women (6%) the concentrations became high during treatment with coumarin (P=0.006), among</p>	<p>Crossover study design without washout period</p> <p>Relatively clear exclusion and inclusion criteria.</p> <p>Relatively large in sample size</p> <p>Randomisation and blind method were not reported</p> <p>Results from the first phrase of 6 months were clearly reported</p> <p>Data for 94% of patients was collected at 6 months</p> <p>Evidence level: 1<sup>+</sup></p>
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		a history of alcohol abuse, or a history of venous thrombosis in the preceding 12 months		them one woman developed jaundice and the serum bilirubin concentration rose to 19.3 mg per decilitre.	
Chang 1996 <sup>31</sup>  Coumarin and placebo were provided by Hamilton laboratories (Adelaide, Australia) and the Lymphoedema Association of Australia	Randomised controlled study Double blinded Two groups matched by Grade, age, sex and duration and cause	Sixty patients with unilateral leg lymphoedema were included, according to the I.S.L. Classification, there were 20 at Grade 1, 32 at Grade 2 and 8 patients with elephantiasis at Grade 3  Thirty seven were women and 23 were men  Five had primary lymphoedema; the rest were caused by: infection (min tinea) filariasis, trauma, surgery for carcinoma, resection of lipoma and pregnancy	<b>Intervention (n=30?):</b> patients received 400mg coumarin (two tablets, each containing 200mg of the medicine) orally a day for six months  <b>Control (n=30?):</b> placebo six months  No compression garments were used at the first six month  For the next six months, each group continued with the coumarin or the placebo, adding two courses of topic leg heating and compression bandaging. The heating was done using a microwave oven for an hour a day for 40 days  <b>Study period:</b> 12 months  <b>Measurement:</b> limb volumes were measured by water-displacement to the hip; leg circumferences were measured at six standard points; every 10 cm above the heel, skin tonometry was performed. Each measurement of the lymphoedematous limb was expressed as a percentage compared with the non-	Over the first six months, there were highly significant improvements in the volume, circumference, and tonometric findings in the intervention group compared with the placebo.  The symptoms also improved significantly during the first six months in the intervention group. Particularly notable were the improvements in the feeling of swelling and of restricted mobility. The feelings of burning pain and/or heaviness also significantly improved.	Methods of randomisation and blind were not reported  Compression bandaging and microwave heating were added during second six months  There is no information about drop-out in the trial  Diverse causes of lymphoedema  Small proportion of patients with lymphoedema following cancer treatment.  Evidence level: 2

			oedematous contralateral leg. Symptoms were recorded.		
Cluzan 1989 <sup>35</sup>	Randomised cross over study (?) The study was reported as a “double blind crossing over study No detailed information on study design was provided.	80 patients with secondary upper limb oedemas  Other information on patients involved was not provided, e.g. primary condition, age and duration of oedema.	<b>Intervention (n=?):</b> Coumarin (Lysedem) 6 tablets a day, the actual dose of the drug was not reported  <b>Control (n=?):</b> placebo  <b>Study period:</b> 9 months  <b>Measurements:</b> clinical score of hardness, heaviness, painfulness and subjective appreciation; circumference and lymphoscintigraphic parameters (speed, clearance and half life)	Limb volume increased by 8.09% in control group, but decreased by 14.49% in the intervention.  Improvements in lymphoscintigraphic parameters were reported in the intervention group  One patient in the control, and two patients in the intervention, developed nausea and digestive disorders.	Lack of information about patients included  Details of study design e.g. number in each group at starting point, randomisation, blind methods were not reported  Crossover point was unclear  Method of limb volume measurement was not reported in detail, the validity of the measurement was not discussed  Dose of coumarin was not reported  Study results were poorly reported.  Evidence level 2-

## Appendix 4. Case histories reported by Cox<sup>19</sup>

Patient General information Diagnosis	Dose (mg/day)	Case history	Comments by authors
P1: Male Age 41 Brucellosis	50	After 6 months on coumarin, his transaminase levels rose to 248 i.u./l (AST) and 500 i.u./l (ALT). These levels returned to normal within 2 months when coumarin was stopped. Two years later he was retreated with coumarin, after 4 months his AST rose to 136 i.u./l, and his ALT rose to 326 i.u./l. These also returned to normal within 1 month after coumarin therapy was stopped.	There were no obvious reasons for the coincidence of coumarin therapy and abnormal LFTs, other than the administration of coumarin
P2: Female Age 38 Chronic infectious mononucleosis	50	After 5 months on coumarin her AST rose to 440 i.u./l, her ALT rose to 696 i.u./l and her AP rose to 253 i.u./l. These levels all returned to normal, within 2 months after coumarin was stopped. The patient was re-treated with coumarin, and after 1 month her AST rose to 125 i.u./l and her ALT to 296 i.u./l. These also returned to normal within 1 month after coumarin was stopped.	There was no clinical reason for the coincidence of abnormal LFTs and coumarin therapy other than the administration of coumarin.
P3: Female Age 64 Carcinoma of	100	Patient was admitted to hospital 5 weeks later with suspected hepatitis. Her serum level of bilirubin was 227 uM/l, her ALT was 467 g/l (normal 37-50 g/l). Coumarin therapy was stopped, and 2 weeks later her LFTs were repeated. Her bilirubin level had risen further to 440uM/l; her ALT had fallen to 410 i.u./l; her AP levels had fallen to 85 i.u./l; her albumin level had fallen further to 32g/l; her globulin level had risen to 35g/l	Her liver biopsy was consistent with viral hepatitis, but her tests were negative for both hepatitis A and B. There was no evidence that her lifestyle was conducive to

the stomach		<p>(normal is 23-32 g/l); and her prothrombin time had risen to 17 s (normal, 14 s). By the following week, all enzyme levels started to return towards normal values. The patient was negative for leptospirosis, cytomeglia virus, hepatitis A and B, and infectious mononucleosis.</p> <p>Her liver ultrasound was normal. A needle biopsy was performed on the liver. This showed ballooning degeneration and liver cell regeneration. Zonal hepatic cell necrosis, hyaline bodies and mild diffuse lymphocytic infiltration were present. There were bile thrombi in the canaliculi. There was no evidence of metastatic cells.</p> <p>Several months later the patient was retreated with coumarin (100 mg/day) and within 6 weeks her ALT level had risen to 944 i.u./l, her AP was 149 i.u./l, and her bilirubin level was 227uM/l. Coumarin treatment was stopped, and her LFTs returned to normal within 5 weeks. An abdominal ultrasound scan showed no abnormalities and clinically the patient is recurrence-free.</p>	<p>developing hepatitis, thus a cause other than viral infection was probably involved. Since the patient was recurrence-free a cause other than liver secondaries was probably indicated. Thus, there was no other apparent reason for the hepatitis other than the administration of coumarin.</p>
<p>P4: Female Age 77 Melanoma</p>	50/500	<p>Patient's serum transaminase levels were raised prior to treatment (her AST was 65 i.u./l and he ALT was 116 i.u./l). After 5 months on coumarin, her AST was 360 i.u./l and her ALT was 625 i.u./l. These returned to normal within 1 month when coumarin was stopped. One month after re-treatment with 100mg/day coumarin her AST was 124 i.u./l and her ALT was 190 i.u./l. These returned to normal within 2 months when coumarin treatment was stopped. She was treated a third time with coumarin of 50mg/day, and after 1 month her AST was 61 i.u./l and her ALT was 96 i.u./l. Again, these returned to normal within 1 month when coumarin treatment ceased. The patient was treated a fourth time with coumarin (500mg/day), and after 1 month her AST was 74 i.u./l and her ALT was 103 i.u./l. These returned to normal within 2 months after</p>	<p>There were no clinical reasons, other than the administration of coumarin, for her elevations in serum transaminase levels.</p>

		cessation of coumarin therapy. The patient's isotope liver scans were normal.	
P5: Male Age 70 Hypernephroma	100/1600	The patient had a nephrectomy prior to treatment with coumarin. After 1 month on 100 mg coumarin and 1000 mg cimetidine per day his LFTs started to rise and within 4 months his ALT level was 273 i.u./l and his AST level was 175 i.u./l. Cimetidine was then replaced by prednisone (60 mg/day) and cyclophosphamide (50 mg/day) 3 days per week, 1 week in 4. Within 1 month his LFTs had returned to near normal. Coumarin was then increased to 1600 mg/day and the patient's treatment on cyclophosphamide and prednisone was continued. His LFTs rose again and reached a peak 3 months later with AST levels of 427 i.u./l and ALT levels of 626 i.u./l. 4 weeks later these had dropped to 238 i.u./l (AST) and 325 i.u./l (ALT), but this AP level had risen to 335 i.u./l. his chest X-ray and isotope liver scan were normal so his coumarin dosage was reduced to 100 mg/day. The patient is still undergoing treatment.	One possibility for his rise in LFTs would be liver secondaries, as the patient had lung secondaries. However, a liver scan showed no abnormalities. This patient probably has an adverse reaction to coumarin. Withdrawal from coumarin could give stronger evidence for this, but the patient's serious condition means that cessation of therapy is a last resort. Immunosuppressive therapy seemed to reduce the LFTs at the lower dose, but not at the higher dose. Possibly continuous immunosuppressive therapy may have a stronger effect in lowering LFTs
P6: Female Age 40 Melanoma	25/300	After 4 months on coumarin (25 mg/day) there was an increase in AST to 512 i.u./l, in ALT to 648 i.u./l and in bilirubin to 20 uM/l. These returned to normal within 1 month when coumarin therapy was stopped. The patient had brain metastases removed, and was re-treated with coumarin (300 mg/day), cimetidine (100mg/day) and dexamethasone (10mg/day). Enzyme levels remained normal (ALT rose very slightly)	This patient had melanoma with brain metastases. There was no evidence of liver secondaries. Her LFTs returned to normal when coumarin therapy was stopped, and

		<p>until the dexamethasone course was completed. Coumarin was lowered to 100 mg/day and cimetidine stopped. The serum transaminase levels started to rise after 1 month, and reached 220 i.u./l (AST) and 260 i.u./l (ALT) by the second month. These returned to normal when coumarin was stopped. Her isotope liver scans were normal. The patient died a short while later.</p>	<p>remained normal until her death, a few months later. This would not be expected in a patient with cancer of the liver. The patient had liver scans, all of which were negative. This would indicate that, if present, any liver tumour would have been very small, and thus, unlikely to cause any major change in LFTS. There was no other obvious reason for abnormal LFTs with this patient. Thus, her hepatitis was probably due to coumarin administration. The return of her LFT levels to normal while on dexamethasone, which is a powerful immunosuppressant/anti-inflammatory drug, would indicate that it may have suppressed an inflammation in the liver, or immune system, induced by coumarin.</p>
<p>P7: Female</p>	<p>25</p>	<p>Her AST and ALT had risen after 3 months on 25 mg coumarin on alternate days, and had reached 340 i.u./l and 380 i.u./l respectively, after 7 months, her dose of coumarin was then increased to 25 mg/day and she was put on prednisone (60mg/day) and</p>	<p>Since the patient had stage IV breast carcinoma a likely cause of the rise in serum transaminases was</p>

<p>Age 60</p> <p>Breast cancer</p>		<p>cyclophosphamide (50 mg/day) on alternate days. Her enzyme levels returned to normal, even though coumarin treatment was continued. Her liver scan was normal.</p>	<p>liver secondaries. The patient's liver scan showed no evidence of metastases. Her LFT results further support this. The small rise in serum transaminases is not consistent with liver secondaries, as it returned to normal so quickly. Since cyclophosphamide and prednisone are potent anti-inflammatory suppressant agents, they may serve to reduce an inflammatory/immune response induced by coumarin.</p>
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