All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Dexrazoxane (Savene®)
TopoTarget

Advice No: 0207 – June 2007

Recommendation of AWMSG:

Dexrazoxane (Savene®) is not recommended for use within NHS Wales for the treatment of anthracycline extravasation due to lack of robust evidence of clinical and cost effectiveness.

This report should be cited as:

All Wales Medicines Strategy Group. Final Appraisal Report – Dexrazoxane (Savene®) June 2007

1.0 RECOMMENDATION OF AWMSG:

The advice represents the view of the All Wales Medicines Strategy Group and was arrived at after evaluation of the evidence submitted by the manufacturers up to and including 15th January 2007. Local Health Boards and Trusts are expected to follow recommendations from AWMSG within 3 months of Ministerial endorsement. AWMSG advice is interim to NICE guidance should this be subsequently published. Individual clinicians should take account of guidance issued by NICE or AWMSG when exercising their clinical judgement, unless there is evidence to justify not doing so in the light of the particular circumstances of an individual patient.

Date: 12th June 2007

Dexrazoxane (Savene®) is not recommended for use within NHS Wales for the treatment of anthracycline extravasation due to lack of robust evidence of clinical and cost effectiveness.

Key factors influencing the recommendation:

- AWMSG considered that insufficient evidence for clinical effectiveness was provided. There was a lack of data comparing dexrazoxane to current standard approaches used to treat suspected anthracycline extravasation. There are no controlled comparative trials so that the data provided is in effect a series of case reports.

- As the studies were uncontrolled, the safety profile of dexrazoxane relative to other treatment approaches remains unclear. AWMSG acknowledges that many of the observed adverse events in patients receiving dexrazoxane could be anticipated from other studies, or are those known to be associated with administration of chemotherapy agents. Nevertheless, significant treatment related adverse events were reported. Since dexrazoxane would need to be considered as the first treatment option due to the timing of administration (within six hours), AWMSG considered that there was insufficient comparative safety evidence to advocate the use of dexrazoxane as a first-line therapy.

- The economic model used in the cost-effectiveness analysis of dexrazoxane does not consider all relevant comparators. It was thought by AWMSG to favour dexrazoxane by comparing it with a ‘wait-and-see’ approach before proceeding to surgery, rather than standard active treatments.

- The model assumes that dexrazoxane would be used after biopsy proven anthracycline extravasation; such biopsies, within six hours, are not standard practice in NHS Wales (or the rest of the UK) when extravasation is suspected.

- The model submitted assumed that over a third of affected patients, if not treated with dexrazoxane, would otherwise proceed to surgical intervention, which AWMSG did not consider to represent practice within NHS Wales. This assumption further influenced the cost effectiveness estimate submitted.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Dexrazoxane (Savene®) is indicated for the treatment of anthracycline extravasation[1].

2.2 Dosing:
Dexrazoxane (Savene®) should be given as an intravenous infusion over one to two hours, once daily for three consecutive days at a recommended dose of 1000mg/m^2 for the first two days, and then 500mg/m^2 on the third day. The first infusion should be initiated as soon as possible and within the first six hours after the accident. Administration must be under the supervision of a physician experienced in the use of cancer chemotherapeutic agents[1]. Further details can be found in the Summary of Product Characteristics[1].

2.3 Market authorisation date: 28 July 2006 [2]

2.4 UK Launch date: October 2006 [2]

3.0 DECISION CONTEXT

The anthracyclines doxorubicin, epirubicin, daunorubicin and idarubicin are widely used intravenous, cytotoxic drugs in oncology. However, due to awareness among medical professionals and careful administration practices (including the use of central venous catheters), anthracycline extravasation may occur in as few as 0.1% to 1% of all administrations[3-5]. The vast majority of extravasation injuries are non-complicated, but they can often result in pain, erythema, inflammation and discomfort. Symptoms can be immediate in onset, but there may also be a chronic progression of tissue damage over weeks and months, which, if left undiagnosed or inappropriately treated, can lead to tissue necrosis and functional loss of the limb concerned[5]. Furthermore, extravasation injury may lead to prolonged hospitalisation stays for observation or surgery, or delay in the administration of further chemotherapy, thereby diminishing the cancer patient's quality of life [3,6].

At present, there is no clear consensus on how such extravasation should be clinically managed. The application of dimethylsulphoxide (DMSO) topically to the extravasated site, followed by hydrocortisone cream and cold compression is a commonly recommended conservative approach[3,5]. Antidotes lack rigorous scientific support, although there is some evidence to support the use of DMSO [7,8]. In patients with ulcerations, one option is early surgical intervention with extensive debridement of the involved area followed by skin grafting. However, only one-third of vesicants are thought to give rise to ulceration and, unless there is persistent swelling, erythema, pain or the presence of large areas of tissue necrosis or skin ulcerations, most surgeons are thought to opt for the more conservative approach before surgery [8].

Dexrazoxane is a topoisomerase II inhibitor and iron chelator, and is thought to protect against normal-tissue cytotoxicity of topoisomerase poisons such as doxorubicin, epirubicin and daunorubicin. The company submission states that dexrazoxane (Savene®) is the first and, currently, the only licensed antidote with efficacy in cases with biopsy proven anthracycline extravasation [3]. This antidote has to be given as soon as possible and within the first six hours of extravasation. Consequently, if considered for use within NHS Wales, it would be viewed as a first-line therapy.

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Due to the accidental nature and low incidence of extravasation, dexrazoxane has only been studied in a small number of patients. Due to ethical concerns, clinical trials were uncontrolled so there was no direct comparison of dexrazoxane with other standard conservative treatment options such as DMSO and/or steroids. However, this makes it difficult to assess the efficacy of dexrazoxane with regards to postponement of cancer treatment, hospitalisation and sequelae. No indirect comparisons of efficacy were made clear in the company submission. Furthermore, many of the adverse events observed in patients receiving dexrazoxane are known to be associated with administration of chemotherapy agents, and as the studies were uncontrolled, the safety profile of dexrazoxane remains unclear. Consequently, the Committee is of the opinion that further trials are needed to assess the clinical efficacy and safety of dexrazoxane in anthracycline extravasation.

4.2 Review of the evidence on cost-effectiveness

Although dexrazoxane is the only agent licensed specifically for the management of anthracycline extravasation, there are other recognised and established treatments for this condition. The economic model used in the cost-effectiveness analysis of dexrazoxane does not consider all relevant comparators; it is populated with outcomes data that would appear to bias the cost-effectiveness analysis in favour of dexrazoxane; it does not employ a measure of effectiveness that can be considered meaningful when making decisions on the cost-effective use of resources; and it does not consider all relevant costs. Given these issues, and the absence of any other compelling evidence of cost-effectiveness, the the Committee is of the opinion that (regardless of dexrazoxane's possible ultra-orphan drug status; refer to Section 8), the economic case for the use of dexrazoxane has not been adequately proven.

5.0 LIMITATIONS OF DECISION CONTEXT:

- Further, controlled trials are needed to assess the efficacy of dexrazoxane in anthracycline extravasation.
- Efficacy has also not been demonstrated adequately with extravasation relating to a central venous access device.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY:

6.1 Clinical efficacy:

The company submission included the results of two Phase II trials (TT01 and TT02) that formed the basis of registration applications in the EU and the US. A small number of clinical case reports have also been published, however, due to the level of evidence that such clinical case reports provide, they are not discussed below [4, 9-12].

6.1.1 Clinical trials — TT01 and TT02 [3, 13-14]

The purpose of both studies was to assess the efficacy and tolerability of intravenous dexrazoxane as an antidote in biopsy-verified anthracycline extravasation. The trials were multi-centre, prospective, open-label, and single-arm. The first study enrolled 23 patients (TT01) and 57 patients were involved in the second study (TT02); all were adults and had an extravasation diagnosis (that excluded other vesicant involvement) confirmed by positive fluorescence microscopy.

Local treatment with DMSO or steroids, were not allowed. However, acute aspiration was recommended and local cooling was permitted to within 15 minutes of the dexrazoxane infusion. Patients were treated with a three-day schedule of consecutive doses of intravenous dexrazoxane (1000mg/m^2 body surface area (BSA), 1000mg/m^2 BSA and 500mg/m^2 BSA) and were assessed at 24 hours, 48 hours, weekly for the following month and then on Day 90 (final day of follow-up). An independent review committee evaluated the efficacy and safety data.

The primary endpoint in these studies was the rate of surgical intervention. Secondary endpoints in both studies included: the occurrence of necrosis, postponement of scheduled cancer treatment, hospitalisation due to extravasation, and sequelae (sensory disturbances, skin atrophy, pain, disfigurement, and limitation of movement).

Results:
The anthracycline extravasated in all of the participants in TT01 and most (96.5%) in TT02 was either epirubicin or doxorubicin, with slightly more patients receiving epirubicin than doxorubicin in both studies. Overall, 80 patients participated in both trials; however, nearly one third (32.5%; 26 out of 80) were not evaluable for efficacy, mainly due to negative biopsies.

In the studies combined, one out of the 54 patients who were evaluable for efficacy required surgical intervention. Necrosis, which did not require surgery, occurred in four patients all together. This included two cases of necrosis in the biopsy area. In study TT01, planned cancer treatment was delayed for a mean of 8.7 days (range: two to 24) in six patients (33%). In TT02, a similar percentage of patients (27.8%) and mean duration of delay (ten days; range: seven to 15) was observed. Of the evaluable patients from study TT01 (n=18), nine were hospitalised due to extravasation for a mean of 3.3 days (range: one to six days) and in study TT02, 13/36 patients (36.1%) were hospitalised for a mean of 13 days (range: one to 64). Overall, 16.7%, 9.3%, 18.5%, 2.8%, and 5.6% of patients experienced sensory disturbances, skin atrophy, pain, disfigurement, and limitation of movement, respectively.

6.1.2 Points to note from both studies:

- Due to the accidental nature and rare occurrence of extravasation, dexrazoxane has only been studied in a small number of patients. Furthermore, nearly one third (26 out of 80) of those enrolled were not evaluable for efficacy, mainly due to a lack of confirmation of anthracycline extravasation by biopsy
- As the trials were both single-arm, uncontrolled trials, there was no direct comparison of dexrazoxane with other standard conservative treatment options such as DMSO and/or steroids.
- The lack of a control group in the design of the study was due to ethical concerns. However, this makes it difficult to assess the efficacy of dexrazoxane with regards to postponement of cancer treatment, hospitalisation and sequelae; all of which are as relevant as the need for surgical intervention. No indirect comparisons were made clear in the company submission.
- Only one patient with extravasation relating to a central venous access device was included in the trial data (TT01 and TT02); this patient was not included in the efficacy evaluation.
- The company submission concludes that, in studies TT01 and TT02, treatment with dexrazoxane prevented the progression of extravasation and, therefore, prevented the need for surgical intervention in 53 of 54 patients with biopsy proven anthracycline extravasations. However, it is not clear how many of those patients would have actually required surgical intervention.

- Mouridsen and colleagues report that, in the first study (TT01), dexrazoxane was regarded as effective if surgery could be avoided in 80% of cases. This was based on the fact that they reported the pre-study operative frequency in biopsy-positive anthracycline extravasation in Denmark as 100%. Although the actual incidence of surgical intervention for anthracycline extravasation is not clear from the literature, this figure appears high[3,6,8], and the Committee are uncertain therefore if this is reflective of practice in Wales.
- In the second study (TT02), the company estimated the incidence of surgery after treatment with dexrazoxane at 2.8% (95%CI: 0.1-14.5%). Furthermore, the company submission compares this to an incidence of surgery of 35–50% in the literature. The source of this figure is not clear from the references used in the company submission and since these references were published (mainly in the 1980s), the identification and management of extravasation has improved.
- The mean area of extravasation (defined by the area of swelling and redness) was noted in both studies, but not the volume of extravasation involved. The severity of an extravasation injury depends (in part) on the amount and concentration of the extravasated drug[3]. The absence of this information makes determining the place of dexrazoxane in the treatment of extravasation injuries more difficult (See paragraph 9.2).
- Further, controlled trials are needed to assess the efficacy of dexrazoxane in anthracycline extravasation.

6.2 Safety:

- Many of the adverse events observed in patients receiving dexrazoxane are known to be associated with administration of chemotherapy agents. As the studies were uncontrolled, the safety profile of dexrazoxane relative to other treatment approaches remains unclear.
- The most frequent adverse events were wound infections (10%), nausea (18.8%) and vomiting (7.5%). Injection site reactions were frequent in study TT01 (60.8%; 14 out of 23 patients) but were reduced in study TT02 after buffer changes to the solvent.
- In TT01, 12 serious adverse events (SAEs) were reported for seven different patients (four patients had more than one SAE reported). Eight events in four patients were assessed as being related to dexrazoxane. Two events were related to local injection site reactions and two were related to neutropenia/neutropenic fever/infection. In TT02, 20 patients experienced SAEs, with nine patients experiencing SAEs that were described as having a suspected/probable relationship to treatment. The relationship was given as suspected for all treatment-related SAEs except two: an infection at the biopsy site and pneumonia, which were both described as probably related to treatment. No further details of the SAEs were available from the company submission.
- All deaths occurring during the TT01 (two deaths) and TT02 (three deaths) studies were reported as unrelated to the study medication.
- Patients with neutropenia and thrombocytopenia greater than CTC Grade I (Common Toxicity Criteria) were not included in the clinical studies[1].
- Efficacy and safety have not been evaluated in children, the elderly, and patients with hepatic or renal impairment.
- Further, controlled trials with longer-term follow-up are needed to assess the safety of dexrazoxane in anthracycline extravasation.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:
There is no clear consensus on the treatment of anthracycline extravasation, but a commonly recommended conservative approach included a combination of:

- Dimethylsulphoxide (DMSO)
- Hydrocortisone cream
- Cold Compression
- IV corticosteroids

In some cases, extravasation injury can require surgical debridement.

7.2 Comparative effectiveness:
- TT01 involved 23 patients from centres in Denmark. TT02 involved 57 patients from Denmark, The Netherlands and other EU centres. Therefore, an assumption has been made by the submitting company that the patient population and treatment administration would be applicable in Wales.
- Evidence for dexrazoxane efficacy is limited by the lack of a head-to-head comparator in the trials submitted by the company, and currently there are no known ongoing or planned comparative studies.
- Only patients with anthracycline extravasation confirmed by fluorescence-positive biopsy were enrolled in the trials. Such confirmation is not stated as a requirement of the licensed indication and, as such, the efficacy of dexrazoxane may be different in clinical practice.
- The advantages and disadvantages of treatment with dexrazoxane over current therapies have not yet been proven.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for NMG to consider
The key economic issue for the AWMSG to consider is:

1. Whether the additional benefits offered by dexrazoxane over relevant comparators justify the additional costs, and if so,
2. Whether the total budgetary impact of supporting the use of dexrazoxane is acceptable.

8.2 Review of published evidence on cost-effectiveness
Standard literature searches conducted have not identified any published economic studies of the use of dexrazoxane in the management of anthracycline extravasation.

8.3 Review of company submission on cost-effectiveness

8.3.1 Summary of the evidence:
The manufacturer submitted a cost-effectiveness analysis of dexrazoxane versus “conventional care” (defined by the company as a wait-and-see approach in which only symptomatic, non-curative treatment is provided until surgery is deemed necessary). This conventional care did not include the use of DMSO, which is recommended in many extravasation guidelines for the management of anthracycline extravasation. The lack of a comparison against DMSO, which appears to have a body of evidence supporting its use, may therefore be argued to limit the usefulness of the cost effectiveness analysis.

The effectiveness measure used in the analysis was loss of limb functionality, which was chosen on the basis of it being a proxy for health-related quality of life in these patients. Whilst loss of limb functionality undoubtedly has a significant impact on patient quality of life, it is unlikely in itself to adequately reflect the full impact of extravasation on patients, or fully demonstrate the effectiveness of treatments for extravasation. In addition, no consideration is given to the degree of functional loss experienced, or the duration or reversibility of that functional loss, as a result of extravasation.

As clinical studies of dexrazoxane were uncontrolled, outcomes data to populate the decision model to reflect the conventional care comparator had to be obtained from six studies identified in a literature search [18-23]. These studies are best described as case series, the patients within which are used as historical controls for the patients in the dexrazoxane studies. To be used in this way, the patients who are included in these case series must be similar to the patients in the dexrazoxane studies. In addition, the treatment received by the patients in these case series must be similar to the conventional care defined in the company submission, and the data available from these case series should be sufficiently complete to provide the efficacy and outcomes data required for the decision model. This was not the case with these studies.

It is important to note that the outcomes data used to populate the model for dexrazoxane is based on data obtained from a population in which anthracycline extravasation was confirmed by biopsy. The SPC does not specify that confirmation of anthracycline extravasation is required before the use of dexrazoxane, and in clinical practice it is possible that anthracycline extravasation will not always be confirmed. Therefore, there is a possibility that dexrazoxane will be used erroneously in the clinical setting (studies TT01 and TT02 indicate that 16% of suspected anthracycline extravasation cases were subsequently proven negative upon biopsy). This would be associated with increased direct costs without a corresponding decrease in costs and resource use associated with surgery.

A sensitivity analysis was conducted to test the effect of varying the probability of surgery in conventional care between 0 and 1 (the probability of surgery in the six studies used ranged from 0.075 to 0.91). The range of probabilities used in this sensitivity analysis are not plausible and do not reflect the likely range of probabilities of surgery in patients receiving conventional care in practice today (unless conventional care is defined as including immediate surgical intervention, which is unlikely given the documented success of more conservative approaches). This sensitivity analysis served only to highlight the uncertainties and unreliability of the data used in this model.

8.3.2 Summary of key findings from the company submission in cost-effectiveness:

Bearing in mind the issues outlined above and in Appendix 2, the base case analysis suggests the incremental cost per additional patient without loss of function (dexrazoxane versus conventional care) is £10,517. However, great uncertainty surrounds this estimate, as it ranged from dexrazoxane being dominant (less expensive and more effective) to £573,642 per additional patient without loss of function, depending on the probability of requiring surgery with conventional care. It is difficult to put these figures into context as an analysis based on QALYs as the denominator was not performed.

8.4 Review of evidence on budget impact

8.4.1 Summary of the evidence:

The budget impact model contains an unknown degree of uncertainty in a number of its components.

In estimating the incidence of anthracycline extravasation in Wales, a number of assumptions have been made. These include assumptions around the estimated incidence of extravasation and the number of anthracycline infusions administered each year in Wales. Data derived for the UK have been translated into data for Wales on the basis of population estimates.

The manufacturer estimates that between six and 59 patients may suffer anthracycline extravasation in Wales in each of the next five years. This technically qualifies dexrazoxane as an ultra-orphan drug. However, there is insufficient information available on the prevalence of anthracycline extravasation in Wales for dexrazoxane to be considered an ultra-orphan drug. The incidence of extravasation is variously reported as being between 0.1% and 6%. The choice of the manufacturer's range of 0.1% to 1% in the budget impact analysis is not transparent, and conveniently achieves an upper limit that is within the ultra-orphan drug definition. The Committee consider that this may not necessarily be the case.

A significant source of uncertainty in the budget impact analysis, as in the cost effectiveness analysis, is the assumed probability of surgery in patients receiving conventional care (assumed to be 0.38). This assumption may significantly overestimate the direct savings that are claimed to arise from a reduction in surgery with the use of dexrazoxane. No attempt has been made in the company's budget impact analysis to test the effect of different probabilities of surgery on net resources and costs.

The budget impact model does not consider the impact of confirmation of anthracycline extravasation in clinical practice.

8.4.2 Summary of key findings from the company submission on budget impact:

The manufacturer's budget impact analysis suggests that the total direct cost of dexrazoxane (drug and administration costs only) would be £6,795 per extravasation event. Between six and 59 patients may be eligible for treatment with dexrazoxane in Wales each year, which would cost between £40,770 and £400,905 annually. Based on a probability of surgery with conventional care of 0.38, the costs avoided due to a reduction in surgery has been estimated as £3,489 per patient treated with dexrazoxane instead of conventional care. The uptake of dexrazoxane has been estimated as 50% in the first year, rising to 100% in years four and five.

Based on these uptake figures, and taking an incidence rate of anthracycline extravasations as 6 per year in Wales, the net resource implications have been estimated as £9,918 in the first year, rising to £19,836 in years four and five. Based on these uptake figures and taking an incidence rate of 59 per year, the net resource implications have been estimated as £97,527 in the first year, rising to £159,054 in years four and five.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- At present, there is no clear consensus on how anthracycline extravasation should be clinically managed.
- There is a National Extravasation Reporting Scheme, also known as the 'Green Card Scheme,' which is co-ordinated by the National Extravasation Information Service (Refer to Section 9.2) [5,15].
- Details of the special warnings and precautions for treatment with dexrazoxane, as well as interaction with other medicinal products, can be found in the Summary of Product Characteristics[1].
- It is the view of the Committee that dexrazoxane is not suitable for shared care.

9.2 Related advice:

National Extravasation Information Service (NEXIS) (Refer to Appendix 1) published a position statement on the use of dexrazoxane in the treatment of anthracycline extravasation. It states the three-day course should be administered in anthracycline extravasation injuries to: all large volume peripheral extravasation with an unequivocal diagnosis (volumes greater than 5mls), those of uncertain diagnosis, but where an anthracycline is the suspected drug (greater than 10mls in volume), or extravasations from a central or peripherally inserted long line. Anthracycline extravasations between 1.5 and 5ml or those in whom the diagnosis may not be certain (up to volumes of 10mls) need to be treated promptly, but the role of dexrazoxane is still unclear, and in these situations DMSO is the antidote of choice. NEXIS further recommends that the introduction of this new antidote needs to be audited for its efficacy in actual practice, and further research work performed to better refine and develop its use [5,15].

9.3 Previous AWMSG/NICE advice

None.

9.4 Medical Expert

Medical expert opinion was sought and provided prior to the meeting.

9.5 Patient Interest Group

A patient interest group submission was sought but not received.

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APPENDIX 1 Additional clinical information

The National Extravasation Information Service (NEXIS) is a non-profit making organisation based at City Hospital, Birmingham, UK. The service was made possible by a number of unrestricted educational grants from UK pharmaceutical industry and 'Pulse Trust' [15].Available at:http://www.extravasation.org.uk/Dexrazoxane.htm

APPENDIX 2 Health economic review

Company submission — cost-effectiveness

1. Description of company submission

The company submission included a cost-effectiveness analysis (i.e. not a cost-utility analysis)[3]. A decision model compared the effect on the requirement for surgery and loss of function in the extravasation-affected limb for dexrazoxane versus "conventional care" (defined by the company as a wait-and-see approach in which only symptomatic, non-curative treatment is provided until surgery is deemed necessary). Data to populate the model were taken from the two pivotal, single arm studies of dexrazoxane (TT01 and TT02) and from the published literature available on other treatments/ management options.

It should be noted that the evidence base for all of the various management options is generally poor, due in part to the relatively rare occurrence of extravasation and certain ethical and operational barriers to the conduct of large, robust clinical trails in this area. There are a number of questionable assumptions used in the decision model and cost-effectiveness analysis, which are to a degree a reflection of this limited evidence base.

The actual model has not been provided, but the structure is described, the sources of data inputs are largely explained, and justifications have been presented for the approach taken. However, there are some fundamental issues with the effectiveness measure used in the cost-effectiveness analysis and the evidence used to generate the outcomes data for the comparator chosen. These issues would be expected to impact on the reliability of the results of cost-effectiveness analysis significantly.

2. Population

The company submission[3] states that the population represented in the cost-effectiveness analysis is defined as all patients suffering from one or more anthracycline extravasations, which it takes to mean that the analysed patient population is not defined by age, gender, ethnic background or underlying disease. It goes on to state that "…all patients diagnosed with anthracycline extravasation are candidates for treatment with Savene". However, the Summary of Product Characteristics (SPC) notes that dexrazoxane has not been evaluated in, and so is not recommended in, children, the elderly, and patients with hepatic or renal impairment[1]. Efficacy has also not been demonstrated adequately in extravasation from a central venous access device. In addition, studies TT01 and TT02 excluded patients with an ECOG performance status of less than two.

It is important to note that the dexrazoxane data is taken from studies TT01 and TT02, which were conducted between 2001 and 2005 and involved all extravasations being confirmed by biopsies. In contrast, the "conventional care" data is taken from six studies that were published between 1982 and 1994, and which did not all involve confirmation of extravasation[18-23].

The company submission notes that, based on the published literature, the incidence of anthracycline extravasation could be 0.1% to 6%, but most of the published literature dates some years back[3]. The company submission rightly suggests that, due to increased awareness, more careful administration of anthracyclines and the use of central venous catheters [and developments in catheter technology generally], the incidence of anthracycline extravasation today is likely to be at the lower end of this estimate (a range of 0.1% to 1% is suggested, although no justification is provided for this specific range). It is, therefore, likely that the conventional care population

simulated in the decision model differ in a number of respects (such as baseline risk of extravasation and the management of suspected extravasation) from the dexrazoxane population in the studies, and from the patient population seen today. This would have the effect of biasing the outcomes of treatment used in the decision model, and any subsequent cost-effectiveness analysis, in favour of the dexrazoxane population.

3. Perspective and time horizon

The cost-effectiveness analysis has been conducted from the perspective of the NHS. Only direct health effects of extravasations have been incorporated (i.e. other health effects arising as a consequence of extravasation, such as delay in chemotherapy, have not been incorporated in the model and are not explored elsewhere) and only direct medical costs have been included. No costs that may relate to Personal and Social Services have been incorporated.

The company submission acknowledges that costs associated with loss of function of a limb are likely to form a substantial component of the total potential costs of management of anthracycline extravasation[3]. The effects of this omission are difficult to predict. If dexrazoxane was found to be unequivocally superior to the current approaches to the management of anthracycline extravasation in terms of preventing loss of function, then the omission of such costs would potentially bias the analysis against dexrazoxane. However, the discussion that follows on the comparator used in the decision model, the clinical inputs, healthcare resource utilisation and costs, explain why this situation does not exist.

The time horizon for the decision model and analysis has been limited to the treatment duration. The company submission suggests that duration of hospitalisation following surgery has been reported to vary between 0 and 80 days. Therefore, on the basis of this relatively short time horizon, no discounting was applied to the model in the company submission. There are reports in the literature of sequelae persisting much longer than this time frame (for example, Reilly and colleagues[17]). However, the lack of detail surrounding the clinical inputs of the model does not permit this type of analysis.

4. Comparator

As studies TT01 and TT02 were single-armed, uncontrolled studies, there are no direct comparisons of dexrazoxane against other treatment approaches. The company submission contains a brief overview of treatment approaches, based on a search of extravasation guidelines from across several European countries. The company submission notes that there are several approaches described[3]. The variation that exists amongst the recommendations of the different guidelines is likely a reflection of the poor evidence base that exists across all approaches to the treatment of anthracycline extravasation.

Some, but not all, of the identified guidelines recommend the use of dimethylsulphoxide (DMSO) in addition to ice packs. The company submission highlights this, and claims that, as the clinical efficacy of DMSO has never been proven in biopsy-verified cases, its use remains controversial[3]. In addition, the duration of treatment, frequency of application and concentration of DMSO recommended in guidelines varies, and agents such as DMSO are not licensed for the treatment of anthracycline extravasation.

A full literature search for studies of the efficacy of DMSO has not been conducted but, given the fact that DMSO is commonly included in extravasation guidelines across Europe, it is likely that the evidence base for DMSO is no less robust than that for any other approach to the management of extravasation of anthracyclines. There is a body of evidence in the literature that supports the use of DMSO (supportive studies are

included in the company's bibliography), and indicates similar efficacy to that observed for dexrazoxane in studies TT01 and TT02, albeit, not in patients with biopsy confirmed extravasations.

Given the above, and despite it not having a marketing authorisation, the fact remains that DMSO is a recognised and commonly used approach to the management of extravasation. The exclusion of DMSO as a comparator limits the usefulness of the cost-effectiveness analysis, and may bias the analysis in favour of dexrazoxane.

5. Clinical inputs

5.1 Efficacy and Health Outcomes

5.1.1 Choice of outcome measure

The company submission explains the difficulties of linking utility values to the treatment outcomes of anthracycline extravasation assessed in the available clinical trials[3]. However, they failed to explore other available options for estimating utilities, e.g. through the use of public or patient surveys. Therefore, instead of using QALYs and conducting a cost-utility analysis, the decision model uses loss of functionality of the extravasation-affected limb as the outcome measure and the basis of the cost-effectiveness analysis.

According to the company submission[3], loss of limb functionality was chosen as a proxy for health related quality in these patients as it has a direct and lasting impact on health related quality of life. Other endpoints of the dexrazoxane study are considered in the company submission and are ruled out as possible outcome measures for the model on the basis of their being more appropriate as inputs (e.g. hospitalisation and surgery), considered only indirectly or temporarily relevant to the patients quality of life (e.g. necrosis or pain) or not suitable due to uncertainty regarding their impact on quality of life (e.g. delay in chemotherapy).

Whilst it is agreed that loss of limb function would be expected to have a negative impact on patient quality of life, this is by no means the only or necessarily the greatest component of health related quality of life for patients suffering from anthracycline extravasation. Pain, sensory disturbance and disfigurement from necrosis may also have a long lasting impact. In itself, functional loss, therefore, could be viewed as an inadequate outcome measure for demonstrating the effectiveness of treatment. There are also other issues with this proxy measure of effectiveness. No consideration is given to the degree of functional loss (e.g. extravasation that led to mild impairment of movement in the non-dominant arm of a patient would have a lesser impact than severe impairment of movement in the patient's dominant arm), or to the duration or reversibility of that functional loss. Therefore, although loss of function was chosen to avoid some of the uncertainties associated with using other measures, the lack of use of an appropriate outcome (e.g. QALY) limits the usefulness of the analysis.

The decision model assumes that no loss of function is observed if surgery is not required. It is not known how reliable this assumption is. Given that the data used to derive the probability of surgery with conventional care are flawed (they have the effect of increasing the probability of surgery in this treatment group), the assumption that no loss of function is observed if surgery is not required would potentially bias the model and cost effectiveness analysis in favour of dexrazoxane (which has a much lower probability of surgery).

5.1.2 Dexrazoxane efficacy and outcomes data

The probability data for outcomes associated with dexrazoxane are taken from studies TT01 and TT02. The primary endpoint of these studies was the rate of surgical intervention. Loss of functionality (called limitation of movement in the studies) was among one of the secondary endpoints in these studies. The company submission states that, before the efficacy data were transformed into probabilities, adjustments were made to better fit the intended probabilities[3]. It is unclear what this means, as no further details are provided.

It is worth reflecting on the potential use of dexrazoxane in "real clinical practice". The SPC does not specify that confirmation of anthracycline extravasation by biopsy is a requirement for the use of dexrazoxane[1], and it is possible that dexrazoxane would be used in real clinical practice in non-proven cases. By considering the data from studies TT01 and TT02 it can be seen that, of 80 patients suspected of suffering from anthracycline extravasation (23 in TT01 and 57 in TT02), 13 had negative biopsies (4 in TT01 and 9 in TT02) [16]. This may crudely suggest that, if anthracycline extravasation is not confirmed, dexrazoxane may erroneously be used in16% of all suspected anthracycline extravasations. The cost-effectiveness analysis takes no account of this potential "real clinical practice" use of dexrazoxane, which would have the effect of inflating the costs of use of dexrazoxane, without a corresponding increase in efficacy. If confirmation of anthracycline extravasation is undertaken in real clinical practice, then the outcomes and healthcare resource use associated with that confirmation would also need to be taken into account.

The company submission claims that the use of dexrazoxane may reduce the psychological distress of patients and hospital staff and could prevent further reduction in quality of life of cancer patients by avoiding necrosis and the need for surgical intervention. These claims are not incorporated in the economic model and are not supported by any evidence in the company submission[3].

5.1.3 Conventional care efficacy and health outcomes data

The data used to generate probabilities of the outcomes for the conventional care group have a number of flaws and introduce a significant amount of uncertainty that would impact upon the reliability of the cost-effectiveness analysis. The "conventional care" data used to populate the decision model are taken from six carefully selected studies that were published between 1982 and 1994[18-23]. The company submission notes that data are lacking describing the severity of extravasation (and this is the case with the dexrazoxane studies described in the company submission). However, there are a number of other issues with some of these studies, which question their suitability for providing information on the treatment involved in conventional care and the outcomes of that approach to treatment.

The studies are best described as case series and the company submission is in effect using the patients in these case series as historical controls for the patients in the dexrazoxane studies. To be used in this way, the patients who make up these case series must be similar to the patients in the dexrazoxane studies. In addition, the treatment received by the patients in these case series must be similar to the conventional care defined in the company submission, and the data available from these case series should be sufficiently complete to provide the efficacy and outcomes data required for the model.

Two of these studies (Andersson et al 1993 and Linder et al 1983) [18,19] do not provide any useful information in relation to conventional care as defined by the company submission as they discuss only patients who have already been referred for surgery. In addition, the two largest studies (Larson 1985 and Larson 1982) [20,21] do not provide sufficient details to determine the probabilities of outcomes that are required to populate the conventional care side of the model.

The probability of surgical intervention in these six studies varies widely (between 0.075 and 0.91). The effect of this variation was explored in the decision model using a one-way sensitivity analysis. For those studies that are able to provide data on loss of function in patients undergoing surgery, the probability ranged between 0 and 1. The overall probability of cure without loss of function in patients requiring surgery has been calculated as 0.17 but the way this probability was arrived at involves a great degree of uncertainty, given that the two largest studies (accounting for around 50% of the total number of patients in the six studies) did not provide this data.

According to the company submission, the six studies included 263 patients, of which 100 required surgery, which generates a probability of requiring surgery with conventional care of 0.38. Exclusion of the irrelevant studies [18,19], which would be justified, would reduce this probability to 0.23 (45/195).

5.2 Adverse events

The economic model does not consider the impact of any adverse events associated with dexrazoxane or conventional care. Safety and adverse event data are provided in the company submission, but no consideration is given to them in the economic or budget impact sections.

Many of the observed adverse events in patients receiving dexrazoxane are known to be associated with administration of chemotherapy agents (e.g. nausea, neutropenia). As the studies of dexrazoxane were uncontrolled, it is difficult to establish which, if any, adverse events should be considered for incorporation in the decision model and cost-effectiveness analysis.

6. Healthcare resource utilisation and cost

The decision model considered a range of healthcare resource, collated from a number of different sources and based on a number of assumptions.

The total number of days' general ward admission (irrespective of surgery) was taken from studies TT01 and TT02, and reported as 6.4 days. This does not seem to tally, however, with the company submission, which states the median duration of hospitalisation was 3 days in both trials, and the draft manuscript for submission to The Annals of Oncology, which provides a mean of 3.3 days and 13 days for studies TT01 and TT02, respectively.

In the case of resources used during surgical procedures, the data are based on the "average" for procedures carried out in the six studies of conventional care. However, these studies are dated, and may not appropriately reflect the resource use associated with surgery for extravasation across the wider patient population today. The number of operations required for completion of treatment is taken from the study by Linder and colleagues[19], which was a review of patients with severe extravasation injuries (300cm^2 of tissue loss). As discussed earlier, the data used to derive the probability of surgery with conventional care are flawed. The use of these data to assign healthcare resource use is also possibly flawed and potentially biases the cost-effectiveness analysis in favour of dexrazoxane (which has lower rates of surgery, and hence the use of surgery-related healthcare resources).

Costs applied to the healthcare resources outlined above have been collated from a number of sources and a number of assumptions have been made regarding their application. This is not unusual and is necessary when no economic analyses have been conducted alongside clinical trials.

7. Results

7.1 Base-case

The base case analysis suggests the incremental cost per additional patient without loss of function (dexrazoxane versus conventional care) is £10,517. However, this result needs to be interpreted in the context of the many limitations, assumptions and uncertainties of the data used to populate the decision model. These data are unreliable and are likely to have significantly biased the results of the cost-effectiveness analysis in favour of dexrazoxane. In addition, the comparator chosen for the decision model does not consider the use of DMSO, which is commonly recommended in several national and international extravasation guidelines. Another major limitation is the fact that the decision model employs an outcome measure that is uninformative for the purposes of calculating an economic outcome. The usefulness of the cost-effectiveness estimates generated using this model is therefore significantly limited for informing decisions on the cost-effective use of healthcare resources.

This result also needs to be interpreted in the context of confirmed anthracycline extravasation for the use dexrazoxane treatment. In real clinical practice, anthracycline extravasation may not be confirmed, and the impact of potential erroneous use of dexrazoxane in these circumstances has not been considered in any part of the company submission.

7.2 Sub-group analysis

No sub-group analyses have been considered in the economic model.

8. Sensitivity analysis

To test the impact on the cost-effectiveness estimates of some of the assumptions used in populating the decision model, three one-way sensitivity analyses have been conducted. The aim of sensitivity analyses should be to explore the robustness of the cost-effectiveness estimates observed in the base-case, by applying a plausible range of probabilities to the parameters of interest. Unfortunately, the sensitivity analyses conducted do not adequately achieve this.

8.1 Loss of function following surgery (dexrazoxane group)

The base case analysis assumes that the one patient who required surgery in the dexrazoxane studies suffers loss of function. As the model does not take account of any varying degree of loss of function, this one patient has the effect of creating 100% loss of function for patients receiving dexrazoxane who require surgery. In contrast, as the data used to populate the model for conventional care generates a probability of 0.83 for loss of function in those requiring surgery, the model was run with the probability of functional loss in those requiring surgery set the same for dexrazoxane and conventional care.

As would be expected, this had little effect on the estimates of cost-effectiveness. This sensitivity analysis is not very informative, as there is significant uncertainty in the estimated probability of loss of function with conventional care.

8.2 Probability of requiring surgery with conventional care

The probability of requiring surgery with conventional care is a major influence in this decision model and the cost-effectiveness estimates it generates. The probability of surgery amongst the six studies ranges from 0.075 to 0.91. To explore the effect of this wide range of probabilities on the estimates of cost-effectiveness, the model was run with probabilities of requiring surgery with conventional care ranging from 0 to 1.

As would be expected, this has a major impact on the resulting cost-effectiveness estimates. At a probability of 0, the cost per additional patient without loss of function treated with dexrazoxane compared with conventional care would be £573,642. At a probability of 1, dexrazoxane dominates conventional care. The actual threshold at which dexrazoxane dominates conventional care is not presented.

The use of this wide range of probabilities, and the results generated by the model as a result, serve only to reinforce the concerns around the uncertainties and unreliability of the data used in the model (for conventional care). The range of probabilities used in this sensitivity analysis are not plausible and do not reflect the likely range of probabilities in practice today (unless conventional care is defined as including immediate surgical intervention, which is unlikely given the documented success of more conservative approaches).

No sensitivity analysis using the probability of surgery with dexrazoxane has been conducted, which would have been useful.

8.3 Loss of function without surgery for dexrazoxane

The base case analysis assumes that patients not requiring surgery have no loss of function. The model was run to test the impact of including two patients who received dexrazoxane and did not require surgery, but who suffered loss of function. As would be expected, this resulted in a small increase in the cost per additional patient without loss of function. This sensitivity analysis adds little to the overall assessment of this model and the cost-effectiveness estimates it generates.

Company submission — budget impact analysis

Specific data on the incidence of anthracycline extravasation is not readily available. The budget impact analysis provided in the company submission has relied upon an assumed incidence range of 0.1% to 1.0%. It is not specifically stated how this estimate has been arrived at. There is no indication that this incidence has been tested against clinical opinion in Wales (or any other country).

Data on the number of anthracycline infusions given each year in Wales are also not readily available. To arrive at the total number of infusions given per year in Wales, the company submission describes how IMS sales data from 1997 have been converted into mg volumes, volume sales of drug compounds have been set equal to consumption of drugs, and the total number of infusions per country (presumably countries in the UK) has been calculated as the sum of anthracycline infusions. Population figures have then been used to estimate the number of infusions in the UK and translate this into estimates for the population of Wales. There are clearly many uncertainties in this estimation, including the reliability of IMS data on sales volumes from 10 years ago being applicable to volumes used today, and the degree to which volumes of sales of drug actually correspond to volumes used. The translation of UK volumes of use to Wales would seem reasonable.

On the basis of these assumptions and calculations, and applying the (uncertain) incidence of extravasation of 0.1% to 1.0%, the manufacturer's analysis suggests that there would be approximately 6 to 59 cases of anthracycline extravasations in Wales each year. As it is assumed that each extravasation event is an acute event and the time horizon is the period of acute treatment, prevalence is set to equal the incidence, and this remains unchanged for each of the 5 years of analysis.

The direct costs associated specifically with dexrazoxane treatment have been confined to the drug cost (£6,750 for a complete three-day course) and the additional nurse time required administering the daily infusion (assumed to be 3 x 30 minutes at £15 per 30 minutes). This totals £6,795 per course of treatment.

Based on the above range of anthracycline extravasations each year (6 to 59), the annual direct costs to NHS Wales would be £40,770 to £400,905.

It is worth noting that no consideration has been given to the effect on direct costs of confirming anthracycline extravasations before the use of dexrazoxane. The company submission claims that direct savings from the use of dexrazoxane would be achieved due to a reduction in the rates of surgery required for extravasation management. The probability of surgery with conventional care has been considered as 0.38 in the budget impact analysis, in line with the base case cost-effectiveness analysis, and the probability with dexrazoxane has been taken as 0.019. On this basis, the company claims that the net reduction in surgery is 36%. Surgery has been costed as £9,645, although no description of how this figure has been arrived at is presented. This 36% reduction has then been translated into a cost saving of 0.36 x £9,645, which amounts to around £3,500 per patient treated. Based on the rate of anthracycline extravasation of 6 to 59 per year in Wales, (and assuming all received dexrazoxane) the direct cost savings would range from around £21,000 to £206,000 per year. This estimate of cost savings is uncertain due to the uncertainty around the assumed rate of surgery with conventional care.

This potential over-estimation in direct cost savings has been carried through all other calculations of net resource use. No sensitivity analyses have been presented.

The budget impact analysis considers that uptake in years 1,2,3,4, and 5 would be 50%, 75%, 90%, 100% and 100%, respectively. As the comparator throughout the company submission has been conventional care, and has excluded DMSO, no information has been provided on displaced medicines.