Re-submission

dexrazoxane 500mg vial of powder for intravenous infusion (Savene®) No. (361/07)
TopoTarget A/S

05 September 2008

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

dexrazoxane (Savene®) is not recommended for use within NHS Scotland for the treatment of anthracycline extravasation.

Data from non-comparative, open-label phase II/III studies indicate that administration of dexrazoxane is associated with a relatively low rate of surgery and adverse sequelae following extravasation of anthracyclines.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC and in addition the justification of the treatment's cost in relation to its health benefits was not sufficient.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication
Treatment of anthracyline extravasation

Dosing information
On three consecutive days 1000mg/m^2, 1000mg/m^2 and 500mg/m^2 as a 1- to 2-hour infusion

Product availability date
October 2006. This product has Orphan Drug Status.

Summary of evidence on comparative efficacy

Dexrazoxane is a bisdioxopiperazine which is hydrolysed intracellularly to form a chelating agent and is a catalytic inhibitor of topoisomerase II, a target enzyme for anthracycline antineoplastic agents. Both of these properties may contribute to a protective effect of dexrazoxane on tissue destruction following anthracyline extravasation.

Extravasation of cytotoxic agents is the unintentional instillation or leakage of these agents into the perivascular or subcutaneous spaces during their administration. The degree of injury can range from a very mild skin reaction to severe necrosis necessitating skin grafting, pain and functional defects, hospitalisation and interruption of cancer chemotherapy.

Efficacy was determined from two phase II/III open-label, single-arm, multi-centre studies of almost identical design. The primary objective was to avoid surgical intervention in adult patients with anthracycline extravasation confirmed by fluorescence-positive biopsy. Secondary objectives were to avoid deleterious postponement of further cancer treatment, avoid hospitalization, describe symptoms and clinical progression in the damaged area and investigate tolerability and/or toxicity of dexrazoxane. All patients received dexrazoxane 1000mg/m^2 within six hours of extravasation followed by two further doses; 1000mg/m^2 and 500mg/m^2 repeated after 24 and 48hrs. Acute aspiration was also recommended and local cooling was permitted, but not within 15 minutes of the dexrazoxane infusion. Local treatment with dimethyl sulfoxide (DMSO) or steroids was not allowed. Patients were included in the trial data as evaluable when a diagnosis of extravasation had been confirmed by positive fluorescence microscopy of at least one of the required biopsies. Without fluorescence-positive biopsies, patients were only assessable for safety.

The first study was conducted in 10 Danish sites and was designed such that dexrazoxane would be considered effective if surgery could be prevented in 80% of cases with reference to the Danish Standard where all patients receive surgery. All 23 patients recruited were evaluable for safety and 18 were evaluable for efficacy. None of the evaluable patients required surgical intervention and the effect was significant. Dexrazoxane was demonstrated to be 100% effective (95% confidence interval (CI): 0 to 18.5%), representing a statistically significant effect when testing against the null hypothesis that the failure rate is 20%.

The second study was international (24 sites in Denmark, Germany, the Netherlands and Italy) and was designed such that dexrazoxane would be considered effective if less than 35% of patients required surgery, where the literature-based estimate of the surgery rate was 35-50% in patients with suspected (not biopsy-verified) anthracycline extravasation. All 57 patients recruited were evaluable for safety and 36 were evaluable for efficacy. One of the 36 evaluable patients required surgery and the incidence was estimated at 2.8% (95% CI: 0.1 to 14.5%) and significantly less than the literature reference.

Secondary end-points are summarised in Table 1.

Table 1: Summary of secondary end-points in Phase II/III trials

Trial Evaluable patients	**Danish 18**	**International 36**	**Combined 54**
One or more sequelae	2 (11.1%)	13 (36.1%)	15 (28%)
Sensory disturbances	2 (11.1%)	7 (19.4%)	9 (17%)
Skin atrophy	1 (5.6%)	4 (11.1%)	5 (9.3%)
Pain	1 (5.6%)	9 (25.0%)	10 (18%)
Limitation of movement	0 (0.0%)	3 (8.3%)^	3 (5.6%)
Necrosis (excluding necrosis in biopsy area)	0 (0.0%)	1 (2.8%)	1 (1.9%)
Necrosis (including in biopsy area)	1 (5.6%)	3 (8.3%)	4 (7.4%)
Postponement (or cancellation) of scheduled cancer treatment due to extravasation	6 (33.3%)*	10 (27.8%)*	16 (30%)
Hospitalisation due to extravasation	9 (50.0%)+	13 (36.1%)+	22 (41%)

^ 2 mild Grade 1 cases, and 1 severe case which was a failure patient
* The mean delay was 8.7 days with a range of 2-24 days in the first study and 10 days (7-15) in the second.
+The mean stay was 3.3 days with a range of 1-6 days in the first study and 13 days (1-64) in the second.

Summary of evidence on comparative safety

The adverse event profile for both trials was similar and no unexpected adverse events were recorded. All patients in Danish trial and the majority in the International trial experienced one or more adverse event related or possibly related to dexrazoxane; most were general disorders and administration site conditions (injection site pain) and gastrointestinal (nausea). Most events were graded mild (grade 1) or moderate (grade 2). Patients in the international trial reported less pain and injection site reactions than the Danish trial, which was thought to be due to buffer changes of the solvent. All adverse reactions have been rapidly reversible.

From the combined results, no serious adverse events nor any of the five deaths were considered related to the study medication.

Grade 2-4 laboratory test-based toxicities were very common for white cells, neutrophils, platelets, haemoglobin and hepatic enzymes. Decreased white cell count was reported in 72% of patients and decreased neutrophil count was reported in 60%.

From the latest 6 monthly periodic safety update report, one spontaneous adverse reaction was identified. It was not considered to have any effect on the risk-benefit ratio of dexrazoxane.

Summary of clinical effectiveness issues

Evidence for efficacy of dexrazoxane comes from two non-comparative phase II/III open trials. Therefore it is not possible to identify the extent to which the observed rates of surgery and sequelae represent avoidance of events, which might have occurred without this intervention. The primary endpoint in trials was surgical intervention and, although this was stated to be a surrogate for development of complications of extravasation, it is difficult to transfer this directly from non-UK trials to a Scottish context, as policies towards treatment vary e.g. as to when a surgical or conservative approach is adopted.

There are no data comparing dexrazoxane to the 'flush' technique, which is considered to be the main treatment of extravasation by many Scottish experts. Scottish experts also advised that extravasation is a rare occurrence and requirement for surgery is extremely rare.

The applicant acknowledges that extravasation may present very infrequently and to avoid wastage due to product expiry, advises that product will be replaced free of charge if it has not been used within the first 2 years, effectively extending the shelf-life to 6 years.

There is very limited experience of the use of dexrazoxane in patients with extravasation in a central venous administration device (CVAD) and the Summary of Product Characteristics (SPC) states that study patients with extravasation from a CVAD were not included in the efficacy analysis.

Patients were included in the efficacy analysis only if extravasation was confirmed by fluorescence on biopsy. The European Public Assessment Report (EPAR) states that, since biopsy is not available at all centres or for all patients e.g. central venous access device (CVAD) and none of the biopsy-negative patients required surgical intervention, the indication of dexrazoxane can include patients in whom biopsy is not feasible.

In both trials, following extravasation, acute aspiration was recommended and local cooling was permitted, but not within 15 minutes of the dexrazoxane infusion. Many centres treat mild extravastion with only this type of conservative care unless dimethylsulfoxide (DMSO) or flush-out is required.

The manufacturer's submission is supported by clinical expert input that may not fully reflect current practice in NHS Scotland.

The applicant summarised the available literature on alternative treatments for anthracycline extravasation. Of 19 published papers to support indirect comparison, four were review articles or editorials, two trials involved paediatrics, one was a case report and one concluded that fluorescence was a reliable method for detection of extravasation. Of the remaining trials, six were published in the 1970s and 1980s and three were published in the 1990s. Of the two trials published in 2002, one discussed flush-out (single-arm trial) and one discussed conservative care consisting of a 24hr cool compress and elevation of the affected limb followed by observation and surgery if required.

The EPAR states that most adverse events were attributed to anthracycline-based chemotherapy, with gastrointestinal and haematological toxicity as the most prominent characteristics although due to the absence of a control group difficult to determine.

The EPAR and SPC state that dexrazoxane has not been studied in patients with impaired renal or hepatic function and its use in such patients is not recommended. The treatment is not recommended for paediatric and elderly patients.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis using a decision tree model to compare dexrazoxane with the current mixture of treatments and interventions used in Scotland, being the flush-out surgical procedure, DMSO / topical hydrocortisone and a conservative care / 'wait and see' approach. The time horizon was one year. The main data for dexrazoxane efficacy (surgery requirement and functional loss) were from two open label non-comparative studies, and for the comparators from an indirect comparison with data on surgical need and functional loss from 19 published studies. For the comparator treatments, efficacy parameters from the literature were adjusted using assumptions and expert opinion. Main costs taken into account were the drug costs, administration and monitoring and surgical costs. Utility values were estimated by asking specialist nurses to complete EQ-5D questionnaires for relevant scenarios.

A key result was surgery being required in less than 2% of dexrazoxane patients compared to 20% of flush-out patients, 15% of DMSO patients and 35% of conservative care patients, resulting in a reduction in net costs for dexrazoxane. This, and a lower proportion of patients experiencing functional loss, produced an estimated incremental cost per QALY of £47,536 versus flush-out, £46,552 versus DMSO and £33,088 versus conservative care. The results were very sensitive to the surgery rate for conventional treatment, which had high uncertainty, and also the time horizon and the utility value assumed for patients who did not have functional loss.

The analysis had several limitations in addition to the high base line cost-effectiveness ratios:

- The additional rate of surgery required in the comparator treatments compared to dexrazoxane was much higher than seen in the literature and this was a key influence on the result.
- The results were very sensitive to the assumptions made around patients having functional loss, and the manufacturer assumed that the outcomes on functional loss for flush-out and DMSO (the main comparators) were the same as for conservative care. This will have introduced bias in favour of dexrazoxane.
- Sensitivity to the assumptions regarding duration of functional loss and the utility values used in the analysis.
- Some potential double counting in terms of the costs of comparator treatments e.g. including a standard cost for a surgical procedure for flush-out in addition to individual cost items such as staff time, when the standard cost would include such costs.

Given these issues, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submission: Myeloma UK

Additional information: guidelines and protocols

European Oncology Nursing Society (EONS). Extravasation Guidelines 2007. Guidelines Implementation Toolkit. Provides information on recognising extravasation, treatment options and management.

UK Oncology Nursing Society. Anthracycline Extravasation Management Guidelines. (Adapted from the (EONS) Extravasation Guidelines 2007). Provides information of recognising extravasation, treatment options and management.

The National Extravasation Information Service, 2000-2006. Provides information on recognising extravasation, treatment options and management. Link to West Midlands Regional Chemotherapy Services protocol for Management of Chemotherapy Extravasations, formulated by St Chad's Unit, City Hospital, Birmingham UK.

NHS Hospitals generally have their own guidelines for the treatment of extravasation, which take into account their local setting and whether there is a plastic surgeon on-site.

Additional information: previous SMC advice

Following a full submission, SMC published advice in May 2007: dexrazoxane, 20mg/ml, for infusion (Savene®) is not recommended for use within NHS Scotland for the treatment of anthracycline extravasation**.** There are data indicating that administration of dexrazoxane is associated with a relatively low rate of surgery and adverse sequelae following extravasation of anthracyclines. However these data are from non-comparative, open-label phase II studies, and there are no data comparing dexrazoxane to Scottish Practice. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Additional information: comparators

There are no licensed comparators for dexrazoxane and there is a wide range of strategies for management of anthracycline extravasation including cooling the site of extravasation, infiltration of active treatments such as DMSO or corticosteroids and limb elevation. Surgical intervention such as flush out may be used first-line or used as a second-line treatment. Rescue surgery would include debridement and skin grafting for patients who develop complications such as ulceration or necrosis. Many Scottish physicians advise that the flush technique is the main treatment of extravasation and is usually carried out by plastic surgeons.

Cost of relevant comparators

Drug	Dose regimen	Cost per 3 day course (£)
dexrazoxane	**Day 1, 1800mg; Day 2, 1800mg; Day 3, 900mg, intavenously,**	**6750**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 7/7/08. Costs are calculated for a 1.8m^2 adult.

Additional information: budget impact

The manufacturer estimated that the gross drug budget impact would be £7k in year one rising to £113k in year six. The figures were based on 1 patient being treated with dexrazoxane in year one rising to 17 patients by year six representing market shares of 25% and 80% of eligible patients in years one and six respectively. Comments received from SMC experts suggest that these may be overestimates.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 August 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Mouridsen HT, Langer SW, Buter J, Eidtmann H, Rosti G, de Wit M et al. Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. Ann Oncol 2007; 18(3):546-550.

European Medicines Agency (EMEA). European public assessment report (EPAR) for dexrazoxane. http://www.emea.europa.eu/humandocs/PDFs/EPAR/savene/068206en6.pdf

TopoTarget data on file: Responses from Expert interviews 2008.