Scottish Medicines Consortium

dexrazoxane 20mg/ml, for infusion (Savene®) No. (361/07)

TopoTarget A/S

9 March 2007

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 full submission

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.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication
Treatment of anthracycline extravasation

Dosing information
On three consecutive days, 1000, 1000 and 500 mg/m^2

Product availability date
October 2006

Summary of evidence on comparative efficacy

Extravasation of cytotoxic agents is the unintentional instillation or leakage of these agents into the perivascular or subcutaneous spaces during their administration. Extravasation injury may also occur with administration via central venous catheters. Complications may include necrosis, nerve, vascular, tendon and articular damage, pain and functional defects. Surgical intervention may be required.

Dexrazoxane is a bisdioxopiperazine which is hydrolysed intracellularly to form a chelating agent and is a catalytic inhibitor of topoisomerase, 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. It is not indicated for the treatment of extravasation with cytotoxic agents other than anthracyclines.

The licensed regimen, started within six hours of extravasation, has been investigated in two phase II open uncontrolled studies of almost identical design in which 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 hospitalisation, describe symptoms and clinical progression in the damaged area, and investigate tolerability and/or toxicity of dexrazoxane.

The first study was conducted in 10 sites in Denmark, and was designed such that dexrazoxane would be considered effective if surgery could be prevented in 80% of cases. Of 23 patients who entered this study 18 were evaluable for efficacy and safety and a further five patients were evaluable for toxicity only. None of the evaluable patients required surgical intervention and the effect was significant ($p=0.018$, testing against the null hypothesis that the surgical intervention rate is 20%).

The second study was international (24 sites in Denmark, Germany, the Netherlands and Italy). Of 57 patients entered, 36 were evaluable for efficacy. One of the 36 evaluable patients required surgery and the incidence was estimated at 2.8% (95% CI 0.1-14.5%) meeting pre-defined criteria for a significant reduction compared with a literature-based estimate of the surgery rate. Additionally, one patient in the safety population underwent surgery.

Secondary end-points are summarised in Table 1.

Table 1: Summary of secondary end-points in Phase II 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%)
Disfigurement	0 (0.0%)	1 (2.8%)	1 (1.9%)
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%)

* 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 delay 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

Most patients experienced at least one adverse event described as related to study treatment. When the two studies were combined the most commonly reported adverse events were general and administration site conditions (particularly injection site pain) and gastrointestinal (particularly nausea). Whereas the incidence of gastro-intestinal adverse events was similar between the two studies, injection site events including pain were less common in the second study than the first, possibly reflecting reformulation of the injection.

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%.

Summary of clinical effectiveness issues

Evidence for efficacy of dexrazoxane comes from two non-comparative phase II open trials. 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 extremely rare.

Each trial defined a limit for the rate of surgical intervention below which dexrazoxane would be considered to have achieved a significant reduction compared with an external control. In the first study this was defined as an 80% reduction from a reported Danish frequency of 100% biopsy-positive anthracycline extravasation. In the second, dexrazoxane would be considered effective if it achieved a 70% reduction in a literature estimate that 35% of patients with suspected, not biopsy-verified anthracycline extravasation require surgery.

In those trials, surgery was reserved for patients who developed complications and each patient who required surgery would be classified as a treatment failure. A potential limitation with the external controls is that they may reflect policies and guidelines (e.g. concerning early or late surgical intervention) rather than the rate of development of complications.

Nevertheless, the rates observed in these studies were substantially reduced compared with the historical rates, and the European Public assessment Report (EPAR) for dexrazoxane concludes that the effect demonstrated in these trials can be considered as a clear clinical benefit.

Patients were included in the efficacy analysis only if extravasation was confirmed by fluorescence on biopsy. The EPAR states that, since biopsy is not available at all centres, and none of the biopsy-negative patients required surgical intervention, the indication of dexrazoxane can include patients in whom biopsy is not feasible.

Only one patient with extravasation in a central venous administration site was included in studies, and the Summary of Product Characteristics (SPC) notes that efficacy has not been investigated in a sufficient number of patients with suspicion of anthracycline extravasation from a central venous access device.

The EPAR notes: ‘Safety data from 80 patients treated with dexrazoxane were provided from two non-comparative pivotal trials. No unexpected adverse events were recorded. 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.’

Patients with neutropenia and thrombocytopenia > CTC grade 1 have not been included in the clinical studies. This patient group is expected to be most vulnerable regarding hematological toxicity. Regular haematological monitoring is recommended for all patients receiving dexrazoxane.

Summary of comparative health economic evidence

The manufacturer submitted a cost-effectiveness analysis of dexrazoxane for the treatment of anthracycline extravasation compared to conventional care. Conventional care consisted of symptomatic treatment and the use of surgery if required to cure the extravasation. However, this does not seem to be an appropriate comparator, as in Scottish clinical practice the use of the 'flush' technique is common but this was not reflected as the manufacturer’s comparator.

The economic evaluation was limited by weaknesses in the study design of the dexrazoxane clinical trials. As these trials were non-comparative an indirect comparison had to be conducted to assess the relative effectiveness of dexrazoxane and conventional care. This was measured as the requirement for surgical intervention and patient long-term (3 month) loss of function due to extravasation. Data for these outcomes were derived by combining results from the two dexrazoxane clinical trials and weighted averages from 6 published studies (some over 20 years old) for the comparator. Due to study design limitations the potential for bias is high. A key cost driver in the economic evaluation was surgery, which due to lower estimates of the requirement for surgery for dexrazoxane treated patients (2% compared to 38% for conventional care) reduced the net costs for dexrazoxane. Cost-effectiveness was measured as the incremental cost per patient without functional loss. This was estimated to be £10,500 for dexrazoxane compared to conventional care, but was highly sensitive to varying the rate of surgery estimated for conventional care.

The main weaknesses in the economic analysis were that the choice of comparator appears inappropriate for the Scottish context, and also the lack of an attempt to relate functional loss to quality of life outcomes or utilities for estimating QALYs, as generally required by SMC guidance on economic submissions. It is therefore difficult to assess the value to the NHS in Scotland of dexrazoxane treatment. In addition, the functional loss outcome was a potentially selective proxy measure of quality of life impact – it is unclear what impact other long-term sequelae associated with dexrazoxane such as pain, sensory disturbance and disfigurement would have on patient quality of life outcomes, and how these outcomes compared to conventional care. Other weaknesses included no attempt to estimate the costs or disutility associated with adverse events of dexrazoxane, and resource use estimates for surgery related costs derived from non-UK sources without any attempt to validate these in a UK/Scotland context. In light of these issues, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Since dexrazoxane must be given within 6 hours of extravasation it may have to be held in stock in centres which administer anthracyclines who may therefore incur costs for it even if there are no extravasation incidents at the site.

Dexrazoxane has been granted orphan drug status.

Additional information: comparators

There are no licensed comparators for dexrazoxane and there is a wide range of strategies for management of extravasation including cooling (or warming) the site of extravasation, infiltration of active treatments such as DMSO or corticosteroids and limb elevation. Surgical intervention such as debridement and skin grafting may be used first-line or reserved for patients who develop complications such as ulceration or necrosis. Many Scottish physicians advise that the flush technique is the main treatment of extravasation.

Additional information: costs

A pack of 10 vials with three bags of diluent costs £6750 and will provide a full course of treatment.

Additional information: budget impact

The manufacturer estimated an incidence of between 12 and 118 cases of extravasation in Scotland per annum. Assuming 50% of these cases would be treated with dexrazoxane in the first year, the budget impact (including nurse administration costs) has been estimated at £41k - £400k in year 1 up to £82k - £800k by year 5 with 100% use of dexrazoxane. Savings could be achieved from a reduced requirement for surgery relative to conventional treatment.

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 16 February 2007

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.