Scottish Medicines Consortium

cytarabine 50mg liposomal suspension for injection (Depocyte Ò)
No. (164/05)

Napp Pharmaceuticals

8 April 2005

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

Cytarabine liposomal suspension for injection (Depocyte®) is not recommended for use within NHS Scotland for the intrathecal treatment of lymphomatous meningitis.

Intrathecally administered cytarabine liposomal suspension cleared malignant cells from the cerebrospinal fluid, however effects on symptom improvement were not well defined and the cost-effectiveness compared to cytarabine solution has not been demonstrated.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Cytarabine 50mg liposomal suspension for injection (Depocyte®)

Licensed indication under review intrathecal treatment of lymphomatous meningitis. In the majority of patients such treatment will be part of symptomatic palliation of the disease. It should be administered only under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Dosing information under review 50mg administered intrathecally (via lumbar puncture or intraventricularly via an Ommaya reservoir) every 14 days for two doses (induction therapy), then every 14 days for three doses plus an additional dose 28 days later (consolidation therapy), then every 28 days for four doses (maintenance therapy).

UK launch date: February 2004

Comparator medications

Cytarabine and methotrexate solutions for injection can be administered intrathecally (IT) for the treatment of lymphomatous meningitis..

Cost per treatment period and relevant comparators

Cytarabine liposomal suspension is transported in a box containing a temperature monitoring device to ensure that it is refrigerated, but not exposed to temperatures below 2^0C. The cost of providing one 50mg vial in this way is £1250. The transporting box can accommodate up to five vials and as the number of vials per order increases the cost per vial decreases, with one vial costing £1160, £1075, £985 and £875 when part of an order for 2, 3, 4 and 5 vials, respectively. Stringent storage precautions associated with this drug may result in hospitals procuring only one vial per order and this cost is used below.

Cost per treatment cycle of IT chemotherapy for lymphomatous meningitis.

Regimen	Doses	Cost / cycle (£)	Cycle
Cytarabine liposomal suspension	**Induction: 50mg every 2 weeks (2 doses)** **Consolidation: 50mg every 2 weeks (3 doses),** **then every 4 weeks (for 1 dose)** **Maintenance: 50mg every 4 weeks (4 doses)**	**1250[a]** **1250** **1250** **1250**	**2 weeks** **2 weeks** **4 weeks** **4 weeks**
Cytarabine solution	Induction: 10-30mg / m^2 three times a week	4.00[b]	2-3 days
Methotrexate solution	Induction: 200-500mcg / kg every 2 to 5 days or 12mg / m^2 every week (2 doses) then every four weeks	4.85[c] 4.85[c] 4.85[c]	2-5 days 1 week to 4 weeks

(a) based on cost of one vial per order; (b) based on a body surface area (BSA) of 1.7m^2 and cost of a 100mg/5ml vial (£4.00) in the 48th edition of the British National Formulary (BNF); (c) based on a body weight of 70kg or BSA of 1.7m^2 and cost of a 50mg/2ml vial (£4.85) in the 48th edition of the BNF.

Summary of evidence on comparative efficacy

In an open-label trial, 33 patients with lymphomatous meningitis and Karnofsky performance score (KPS) >50% were randomised, with stratification for acquired-immunodeficiency syndrome (AIDS), into a four-week induction phase and treated with IT cytarabine liposomal suspension 50mg every two weeks or IT cytarabine solution 50mg twice a week. Patients who achieved a complete response could continue their respective drugs, with cytarabine liposomal suspension given every two weeks for six weeks then every four weeks for one dose and cytarabine solution given every week for four weeks then every two weeks for four doses in a consolidation phase. Patients remaining in remission continued their respective drug every four weeks for sixteen weeks in a maintenance phase. A complete response was defined as negative cerebrospinal fluid (CSF) cytology by the end of the induction phase at all sites which were positive at baseline and no neurological progression, with a confirmed complete response requiring these criteria plus confirmation of negative CSF cytology at all previously positive sites within 15 days. Late response was defined by the same criteria as a complete response, but occurred after the induction phase. The efficacy-evaluable population included all patients who received at least one dose of cytarabine liposomal suspension or four doses of cytarabine solution and remained in the study for at least twelve days. In this population, the confirmed complete response rate with cytarabine liposomal suspension was significantly greater than with cytarabine solution, 38% vs. 0%, and the complete response rates was also greater with cytarabine liposomal suspension, 38% vs. 18%. The total number of patients experiencing a response was significantly greater in the cytarabine liposomal suspension group: 81% vs. 27%. These results are detailed below. The European Medicines Agency considers that this study did not provide compelling evidence to support a claim that cytarabine liposomal suspension has superior efficacy. This is further detailed in the clinical effectiveness section.

Number (%) of responders with cytarabine liposomal suspension and cytarabine solution in patients with lymphomatous meningitis .

Number of patients (%) (95% confidence intervals of the percentage)	**Cytarabine liposomal**		**Cytarabine solution**	
	Treated N=17	Evaluable N=16	Treated N=16	Evaluable N=11
Confirmed complete response	6 (35%)* (14 to 62)	6 (38%)* (15 to 65)	0 (0 to 21)	0 (0 to 29)
Complete response	6 (35%) (14 to 62)	6 (38%) (15 to 65)	2 (13%) (2 to 38)	2 (18%) (0 to 52)
Late response	1 (6%) (0 to 29)	1 (6%) (0 to 30)	1 (6%) (0 to 30)	1 (9%) (0 to 41)
Any response	13 (76%)* (50 to 93)	13 (81%)* (54 to 96)	3 (19%) (4 to 46)	3 (27%) (6 to 61)

*p<0.05 cytarabine liposomal suspension vs. cytarabine solution, Fisher's Exact Test

The time to neurological progression was defined as the period between study drug initiation and developing neurological progression, assessed by the physician's global assessment of neurological status, or death. The study was not powered or designed to detect a statistically significant difference between the groups in this endpoint and none was found. Median times to neurological progression with cytarabine liposomal suspension and cytarabine solution in the treated populations were 77 and 48 days, respectively, and in the evaluable populations were 76.5 and 58.5 days, respectively.

KPS data were only available for the induction phase for 16 and 8 patients in the cytarabine liposomal suspension and cytarabine solution groups, respectively, with insufficient data for

the other study periods and the other types of quality of life assessments in the trial. During the induction phase, KPS improved from baseline for 31% (n=5) and 25% (n=2) patients in the cytarabine liposomal suspension and cytarabine solution groups, respectively, with 50% (n=8) and 13% (n=1) in the respective groups having no change and 19% (n=3) and 63% (n=5) in the respective groups experiencing a deterioration in their scores. This study was not powered or designed to detect statistically significant differences between treatment groups in quality of life assessments and none were found.

Summary of evidence on comparative safety

The European Medicines Agency European public assessment report (EPAR) for cytarabine liposomal suspension notes that the safety data for this preparation did not demonstrate any new toxicity compared with cytarabine solution. There appears to be no improved safety profile with cytarabine liposomal suspension. In the trial described previously a treatment cycle was 14 days during the first eight weeks and 28 days thereafter, with each including one dose of cytarabine liposomal suspension or between one and four doses of cytarabine solution. The percentage of cycles in which the most common treatment-related adverse effects occurred were greater in the cytarabine liposomal suspension group compared with the cytarabine solution group: headache 24% vs. 3.6%; nausea 9.0% vs. 3.6% and vomiting 7.9% vs. 3.6%. These are characteristic of arachnoiditis, a common adverse effect with both preparations, with other symptoms including fever, neck rigidity, neck or back pain, meningism, CSF pleocytosis, with or without altered consciousness. Arachnoiditis can be fatal if left untreated. However, in this trial the majority of episodes of arachnoiditis with both drugs were of moderate or lower severity, transient and resolved quickly with treatment.

Summary of clinical effectiveness issues

This trial appears to indicate that liposomal cytarabine has superior efficacy to cytarabine in clearing the CSF of malignant cells. However, the European Medicines Agency considered that it did not provide compelling evidence to support a claim of this nature due to limitations in its methodology and small sample size. The small sample size is, however, inevitable due to the rarity of the disease. The response rate with cytarabine solution in this trial was lower than that observed with this drug in published case studies and the strict criteria for response may have contributed to this. Three patients in the cytarabine solution group had clearing of their CSF cytology at the end of induction, but did not have samples taken from all sites which were positive at baseline and were thus considered to be non-responders due to lack of data. The study report notes that while their response status cannot be established, if these three patients had been considered responders, the response rates for cytarabine solution, 6/14 (43%) in the evaluable population and 6/16 (38%) in the treated population, would be in the range of previously published results for this drug in the treatment of lymphomatous meningitis. Therefore, there may be no significant difference between the drugs in clearing the CSF of malignant cells.

Treatment of lymphomatous meningitis generally aims to relieve symptoms such as cranial nerve palsies, focal sensory and/or motor deficits, headache and encephalopathy. The trial described previously did not provide data on the relative efficacy of cytarabine liposomal suspension and cytarabine solution in relation to symptom improvement and quality of life data were limited. Thus relative benefits in terms of symptom control with these drugs in practice are not known.

In the trial described previously, the majority of lymphomas (>85%) were not AIDS-related. The efficacy and safety of cytarabine liposomal suspension in patients with AIDS-related lymphoma are thus not known.

In practice, the use of cytarabine liposomal suspension would reduce the number of doses administered in the four-week induction phase and ten to twelve-week consolidation phase by 6 and 4, respectively, compared to a cytarabine solution regimen similar to that used in the trial described previously. This would provide a more convenient dosing schedule during the first four months of treatment.

Cytarabine solution is stored at room temperature. Cytarabine liposomal suspension must be stored in refrigerated conditions between 2 and 8 ^{0}C. Exposure to temperatures below this causes the liposomes to rupture, destroying the sustained release mechanism. Therefore the temperature at which it is stored must be continually monitored. During transport this is done via devices attached to the lid of the transporting box and the product. In practice, the storage of cytarabine liposomal suspension may be less convenient than cytarabine solution.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis based on the one clinical trial. Using utility values for the health states "response" and "non-response" of 0.65 and 0.26 respectively, a net cost per QALY gained of £35k was estimated by the manufacturer.

The comparator selected was cytarabine. Methotrexate is also a treatment option but was not included as an additional comparator.

A critical factor was the prediction of progression-free days in the economic evaluation. The manufacturer suggests a mean gain in progression-free days of 54. The trial only demonstrated a median gain of 29 days (ITT population) or 18 days (evaluable population). While the mean and median figures are not necessarily incompatible, the submission did not provide any supporting evidence to help justify why the figures are so different to each other. In addition, it was not clear why the economic model modelled progression-free time when observed survival data are available.

Experts raised concerns that the difference in utility values between progression-free and progressing patients might be overstated and it might more plausibly be half the value used in the submission. Other costs of treating the disease are excluded from the calculation.

Shorter progression-free time and/or a reduction in utility difference would each increase the cost per QALY from the base-case figure above.

In summary, the cost effectiveness in comparison to cytarabine solution has not been demonstrated.

Budget impact

The net cost of using cytarabine liposomal suspension was estimated to be £31k in year 1 rising to £49k in year 5, but this includes day case costs (approximately one-third of the net figure). Excluding the day case costs would suggest a net drug budget impact of £20k rising to £32k. This is based on 32 patients per year with the condition, 24 of whom get active treatment and 5 being treated with cytarabine liposomal suspension in year 1, rising to 8 in year 5.

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 ***11 March 2005.***

Drug prices are those available at the time of SMC assessment.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

SkyePharma. Clinical study report on lymphoma patients in study DTC 92-001. A randomised clinical study to determine the efficacy and safety of DepoFoamÔ encapsulated cytarabine (SKY0101) versus standard therapy for the treatment of neoplastic meningitis in patients with leukaemia, lymphoma or solid tumours (Protocol DTC 92-001): study report on lymphoma patients. 29th August 2002.

Howell SB. Liposomal cytarabine for the treatment of lymphomatous meningitis. Biological Therapy of Lymphoma 2003; 6: 10-14.

European Medicines Agency. European public assessment report for Depocyte. www.emea.eu.int/humandocs/Humans/EPAR/depocyte/depocyte.htm