RAPID REVIEW

Defibrotide

for treatment or prophylaxis of veno-occlusive disease

South Australian Medicines Evaluation Panel

Government of South Australia
SA Health

Summary of SAMEP review

Date of SAMEP meeting:	14th November 2012

Name of medicine	**Defibrotide**
Dosage form	Solution for infusion
Indication(s)	Prophylaxis of veno-occlusive disease for patients undergoing chemotherapeutic myeloablation prior to hematopoietic stem cell transplantation (HSCT). Treatment of veno-occlusive disease post-HSCT.
TGA registration status	Defibrotide is not registered by the Therapeutic Goods Administration for use within Australia.
Cost	Defibrotide costs $266 per 200mg vial. At a treatment dose of 25mg/kg/day (in 4 divided doses), a 3-week course costs between $44,688 and $67,032

Note: No formulary application was received for this medicine. This is a SAMEP-initiated rapid review due to the number of Individual Patient Use (IPU) requests for this medicine exceeding the threshold for review as directed under SA Health policy.

SAMEP recommendations

Based on the lack of evidence (appendix 1), the low sensitivity and specificity with regards to the diagnosis, the very high cost and the uncertainty with regards to outcomes, SAMEP recommend rejecting further IPU requests for either treatment or prophylaxis of veno-occlusive disease (VOD). The recommendation is based on the following issues highlighted in the review:

- Whilst defibrotide appears to be a relatively safe drug for the management of a serious condition with limited alternative treatment options, there is a paucity of evidence published regarding the potential benefits of this medicine, with no placebo-controlled trials having been conducted in adults. In children one phase III RCT has been published for prophylaxis of VOD, but not for treatment.
- No attempts have been made by the manufacturer to register the drug in any country and no regulatory authority has previously reviewed this medicine.

- Much of the available evidence is available as abstracts only, which raised suspicions of publication bias.

- VOD is very difficult to diagnose and the incidence is dependent upon the clinical criteria used. There are differing methods of symptomatic diagnosis with associated differences in sensitivity and specificity. Using the Baltimore criteria (or 3 of the Seattle criteria) the estimated specificity is 92% and sensitivity 56%. If only two of the Seattle criteria are used the specificity is approximately halved (Richardson, Linden et al, 2009).

- The prognosis is based upon the severity of VOD. Mild to moderate disease usually resolves completely however severe disease is often fatal, associated with multi-organ failure. The *Bearman model* may assist in predicting the severity of VOD which could be potentially useful to define inclusion criteria if required, but subject to caveats as the model does not include all underlying risks (Bearman, 1995).

- Once treatment is initiated, the criteria for ceasing treatment with defibrotide appears to be undefined, creating uncertainty with regards to cost per treatment course.

- Cost of defibrotide – SAMEP agreed that the price of a drug should reflect the research and development costs and the measure of the health value it delivers. The survival benefits are not proven with defibrotide and therefore provide no justification for the price. There is also no incentive for the company to apply for registration in a country where sales are driven by physician demand and costs covered by state funding.

- "Standard of care" may have been established through provision of the medicine via access programs overseas and physicians may see it as ethically the correct thing to do now. In addition, SAMEP felt that clinicians may feel an obligation to treat due to having already invested so much into the care of the transplant patient.

- There is some evidence for the use of ursodeoxycholic acid (UDCA) for prophylaxis of VOD (but not for treatment). Transplant patients have a high incidence of mucositis and UDCA is often not very palatable and difficult to tolerate in these patients, however UDCA may be administered nasogastrically if required.

- From the consumer perspective, assurance that the medicine is actually effective is important. If false hope is being given to patients by administering the drug, it is unethical.

- The cost-effectiveness is unclear due to the lack of efficacy data. Even if the assumption is made that 100% of patients will survive if given defibrotide, it is still not cost-effective at the current cost. The greatest evidence to support its use is in children, and in this population the doses are smaller and therefore the cost per QALY likely to be more favourable.

Appendix 1 Review of the evidence

Evaluation by other jurisdictions:

Defibrotide for the treatment or prophylaxis of hepatic veno-occlusive disease ***has not*** been evaluated by any of the following organisations:

- Pharmaceutical Benefits Advisory Committee (PBAC)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Scottish Medicines Consortium (SMC)
- All Wales Medicines Strategy Group
- National Institute for Health and Clinical Excellence (NICE)

Defibrotide has been designated orphan drug status by the FDA in the United States in 2003 and by the European Medicines Agency in 2005.

A search of Cochrane Systematic Reviews database found two protocols for reviews to be conducted for defibrotide in hepatic veno-occlusive disease (one for ***treatment***, one for ***prophylaxis***), but currently no Cochrane Systematic Reviews have been completed with regard to this drug/indication.

Search strategy for additional evidence

Refer to appendix 2 for search strategy for additional published evidence.

Brief Overview of Evidence

Randomised controlled trials

Prophylaxis of veno-occlusive disease: A Medline search (search strategy in appendix 1) identified one phase III open-label randomised clinical trial investigating the use of defibrotide for the prophylaxis of veno-occlusive disease (VOD) in children post HSCT (Corbacioglu, Cesaro et al. 2012). The trial was industry-sponsored. No randomised trials were identified for the prophylaxis of veno-occlusive disease in adults. A non-randomised historical controlled study of prophylaxis of veno-occlusive disease in 52 adults was published in 2004 (Chalandon, Roosnek et al. 2004). Because the control group were selected historically from patients who had undergone HSCT the study is likely to be subject to selection bias.

Treatment of veno-occlusive disease: No placebo-controlled randomised controlled trials were identified investigating the use of defibrotide for treatment of VOD in adults or children. A case-series of 88 patients administered defibrotide for the treatment of veno-occlusive disease in adults and children was published in 2002 (Richardson, Murakami et al. 2002). The treatment was industry-funded and there was no control arm therefore no conclusion can be made from this publication regarding the effect of defibrotide, given that many cases of veno-occlusive disease are known to resolve with supportive therapy alone (Plessier, Rautou et al. 2012).

Appropriate comparator

Heparin, low-molecular weight heparin, ursodeoxycholic acid and prostaglandin E1 have all been studied in the prevention of VOD with mixed results (Plessier, Rautou et al. 2012). Once VOD is established, apart from supportive management of fluid retention, sepsis, renal, respiratory and circulatory failure, no specific therapy has been shown definitively to be beneficial (Plessier, Rautou et al. 2012). To date, there is no FDA-approved therapy for hepatic VOD in the United States.

Efficacy

The phase III open-label RCT reported 18 cases of VOD out of 159 (11.3%) in HSCT patients treated prophylactically with defibrotide, compared to 34 cases out of 166 (20.4%) in the control arm of the study (per protocol analysis) (Corbacioglu, Cesaro et al. 2012). This represents a risk difference of -9.3%. The study did not measure the outcome of VOD with an intention-to-treat analysis. Of the patients randomised to the defibrotide group, 21 were not included in the final analysis (11.7%) and in the control group 10 were not included in the analysis of outcomes (5.7%). Selection bias can therefore have contributed to the results favouring defibrotide.

The diagnosis of VOD in this study was defined as the presence of 2 or more of:

- ↑ bilirubin concentration (>34µmol/L)
- Hepatomegaly
- Ascites
- Unexplained weight gain of more than 5% from baseline

An increased bilirubin concentration was not a clinical requirement for diagnosis in this study. Of the patients diagnosed with VOD, 13 in the defibrotide had an increased bilirubin concentration, and 22 in the control group. More recent studies include the presence of hyperbilirubinaemia as an essential requirement for the diagnosis of VOD. The risk difference in this study is reduced to -7% if only the patients diagnosed with VOD with hyperbilirubinaemia are considered true cases. The low sensitivity of the diagnostic criteria is a limitation of this study, as well as the open-label design which can lead to measurement bias, which is important in the measurement of VOD where measurement is more subjective.

There are no randomised controlled trials for the prophylaxis of VOD with defibrotide in adults. There are also no published randomised trials of the treatment of clinically diagnosed VOD with defibrotide.

In summary, more data are required to make a definitive opinion on the efficacy and utility of defibrotide for the treatment and/or prophylaxis of veno-occlusive disease.

Safety

Results of the phase III RCT in children showed the incidence of adverse events were similar between the defibrotide and the no-treatment group (Corbacioglu, Cesaro et al. 2012). In a case-series study in adults, reported adverse effects include nausea, transient mild hypotension, fever, abdominal cramping and vasomotor symptoms such as hot flushes (Richardson, Murakami et al. 2002). One published report of anaphylaxtic shock due to defibrotide has been published (Artesani 2006). A subsequent skin-prick test in this patient confirmed a type-1 hypersensitivity reaction. Other pseudo-allergic reactions reported with defibrotide use include sweating, tachycardia, erythema, pruritus and local cutaneous reactions (Morabito, Gentile et al. 2009).

Areas of uncertainty

- The diagnostic accuracy of VOD, based on clinical criteria and the classic triad of tender hepatomegaly, hyperbilirubinaemia and fluid retention varies widely. The sensitivity of the diagnosis based upon clinical criteria is low, especially as other hepatic complications are common after HSCT such as graft-versus-host disease or infection (Sartori, Cesaro et al. 2012). The gold standard for diagnosis of VOD is transvenous liver biopsy however the procedure is dangerous in these HSCT patients due to the high risk of bleeding and other complications.

- Due to the absence of randomised controlled trials in adults, the efficacy in the treatment or prophylaxis of VOD in adults is unknown. The best available evidence for prophylaxis in adults is the historically-controlled case study published in 2004 which was not adequately controlled for selection bias (Chalandon, Roosnek et al. 2004). Only uncontrolled observational studies or case-series data is available for the treatment with defibrotide of adults with diagnosed with veno-occlusive disease.

- The clinical severity of VOD ranges from mild to severe. Patients with mild to moderate VOD frequently have complete recovery with supportive measures only. In contrast patients with severe VOD appear to have a poor prognosis. It is unclear what prognostic indicator would determine which patients have ‘severe’ disease. Because of the lack of randomised controlled trials, it is difficult to determine any benefit from baseline that can be attributed to defibrotide as many patients with mild to moderate VOD recover fully with supportive therapy.

- There may be a degree of ethical obligation felt by the treating clinician to provide all possible rescue therapy, even with limited evidence of effect, to treat severe VOD that is caused as a result of treatment prescribed.

Appendix 2 Search strategy

Cochrane Database of Systematic Reviews

Search strategy:

1. defibrotide.mp. [mp=title, short title, abstract, full text, keywords, caption text]
2. prociclide.mp. [mp=title, short title, abstract, full text, keywords, caption text]
3. 1 or 2
4. veno occlusive disease.mp. [mp=title, short title, abstract, full text, keywords, caption text]
5. 3 and 4

Returned 2 citations on 24th Sept 2012, of which both were protocols for reviews in progress

Medline

Search strategy:

1. clinical trial.mp.
2. clinical trial.pt.
3. random$.mp.
4. tu.xs.
5. 1 or 2 or 3 or 4
6. randomised clinical trial.mp.
7. randomized.ab.
8. placebo.ab.
9. 5 or 6 or 7 or 8
10. defibrotide.mp.
11. prociclide.mp.
12. 10 or 11
13. 9 and 12
14. exp Hepatic Veno-Occlusive Disease/
15. 13 and 14

Returned 66 citations on 24th Sept 2012, including 1 phase III randomised clinical trial

Cochrane Central Register of Controlled trials

Search strategy:

1. clinical trial.mp.
2. clinical trial.pt.
3. random$.mp.
4. tu.xs.
5. 1 or 2 or 3 or 4
6. randomised clinical trial.mp.
7. randomized.ab.
8. placebo.ab.
9. 5 or 6 or 7 or 8
10. defibrotide.mp.
11. 9 and 10
12. exp Hepatic Veno-Occlusive Disease/
13. 11 and 12

Returned 2 citations on 24 Sept 2012

REFERENCES

Artesani, M. C. (2006). "Anaphylactic shock to defibrotide." Allergy 61(8): 1022-1022.

Bearman SI. (1995). "The syndrome of hepatic veno-occlusive disease after marrow transplantation". Blood 85(11):3005-20.

Chalandon, Y., E. Roosnek, et al. (2004). "Prevention of veno-occlusive disease with defibrotide after allogeneic stem cell transplantation." Biology of Blood & Marrow Transplantation 10(5): 347-354.

Corbacioglu, S., S. Cesaro, et al. (2012). "Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial." Lancet 379(9823): 1301-1309.

Gentium (2012). "[homepage on the Internet]." Villa Guardia, Italy [cited 2012 Oct 10]. Available from: http://www.gentium.it/manufacturing/defibrotide

Morabito, F., M. Gentile, et al. (2009). "Insights into defibrotide: an updated review." Expert Opinion on Biological Therapy 9(6): 763-772.

Plessier, A., P.-E. Rautou, et al. (2012). "Management of hepatic vascular diseases." Journal of Hepatology 56, Supplement 1(0): S25-S38.

Richardson, P. G., C. Murakami, et al. (2002). "Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome." Blood 100(13): 4337-4343.

Richardson, P., E. Linden, et al. (2009). "Use of defibrotide in the treatment and prevention of veno-occlusive disease." Expert Review of Hematology **2**(4): 365-376.

Sartori, M. T., S. Cesaro, et al. (2012). "Contribution of fibrinolytic tests to the differential diagnosis of veno-occlusive disease complicating pediatric hematopoietic stem cell transplantation." Pediatric Blood & Cancer 58(5): 791-797.

Sweetman, S. E. (2012). Martindale: The complete drug reference. . London, Pharmaceutical Press. Electronic version [cited 2012 Oct 10]. Available at: http://www.medicinescomplete.com/mc/martindale/current/18626-y.htm?q=defibrotide&t=search&ss=text&p=1#_hit.