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Molecular adsorbents recirculating system (MARS®): Artificial liver support device for acute liver failure.

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PRIORITISING SUMMARY

REGISTER ID: **000171**

NAME OF TECHNOLOGY: **MOLECULAR ADSORBENTS RECIRCULATING SYSTEM (MARS®)**

PURPOSE AND TARGET GROUP: **ARTIFICIAL LIVER SUPPORT DEVICE FOR ACUTE LIVER FAILURE**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☒	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☒	Yes	ARTG number	81638
☐	No		

The MARS® device is registered with the Australian Therapeutic Goods Administration. The manufacturer has submitted an application for approval to the United States Food and Drug Administration (Teraklin AG 2005). The MARS® device has been granted 510K pre-market approval from the FDA in June 2005 for drug overdose and poisoning treatment.

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Europe			✓
Australia	✓		

IMPACT SUMMARY:

Teraklin AG manufactures the molecular adsorbents re-circulating system (MARS®), a haemodialysis and haemofiltration device, for the treatment of liver failure. The MARS® has been available in Australia since 2002.

BACKGROUND

Liver disorders may be a consequence of any type of liver disease, including viral hepatitis, cirrhosis, and liver damage from alcohol or drugs. Without treatment, a person with liver disease is susceptible to a wide range of complications, including:

- hepatic encephalopathy - scar tissue prevents adequate blood flow through the liver, preventing clearance of toxins. Circulating toxins may affect brain functioning, leading to coma.

- ascites - a build-up of sodium, which leads to fluid retention in the abdominal cavity and in the legs, feet and back (oedema).
- liver failure - liver cells are destroyed faster than replacement rate, until the organ can no longer function.
- cancer - chronic cirrhosis or some forms of hepatitis can make the liver more susceptible to primary cancer (Better Health Victoria, 2005).

A large portion of the liver must be damaged before liver failure occurs (Beers 2005). Liver failure may develop rapidly (days or weeks) or gradually (months or years), possibly progressing to multi-organ failure and death. It is broadly divided into two syndromes: acute liver failure (ALF) and acute-on-chronic liver failure (AoCLF).

The primary role of an artificial liver support device is the removal of toxins from the blood. Early extracorporeal devices for artificial liver support have used procedures such as haemodialysis, haemofiltration, plasma exchange and haemoperfusion using charcoal or polymer-based sorbents (Stange et al 2002). These procedures were not effective in their ability to remove albumin-bound toxic molecules and have demonstrated adverse side effects. There are reported problems with the biocompatibility of using charcoal or ion exchangers in direct contact with blood or plasma resulting in systemic inflammatory responses in early support devices. Attempts to reduce these effects of direct contact between sorbents and plasma proteins have involved the use of membranes that separate blood from the sorbent (Stange et al 2002).

The goal of an effective albumin dialysis system is to remove albumin-bound toxic molecules whilst impeding the loss of other valuable molecules (such as antithrombin III, hormones and clotting factors) that have a molecular weight close to albumin. Albumin dialysis selectively removes protein-bound molecules that use albumin as a specific toxin carrier in blood, such as bile acids and bilirubin, which are not removed by haemofiltration.

The molecular adsorbents recirculating system (MARS®) is a blood detoxification system based on albumin dialysis indicated for patients with ALF and AoCLF. The system removes both protein-bound and water-soluble toxins, which makes it useful for patients with liver failure complicated by renal insufficiency. The aim of MARS® therapy is to provide support of the liver until recovery or as a bridge to transplantation. The principle mechanism of action in MARS® therapy is haemodiadsorption, which combines haemodialysis with adsorption using albumin.

The MARS® system (Figure 1) consists of three compartments – a blood circuit, an albumin circuit and a renal circuit. Blood flows through the dialysis module (step 1), crossing an albumin-impregnated dialysis membrane (step 2). The albumin circuit is filled with 20% human albumin solution, which acts a dialysate. The albumin is pumped through the MARS membrane compartment counter current to the blood flow. Protein-bound toxins and water-soluble substances diffuse into the albumin solution. The albumin dialysate is then passed through an additional dialysis membrane, counter-current to a standard dialysis solution where diffusive clearance or water-soluble substances occurs (steps 3 and 4). The solution is then cleared of its albumin-bound toxins by passage through an activated carbon adsorber and an anion exchanger (steps 5 and 6), (Sen and Jalan 2004). Treatment duration varies between 6-24 hours.

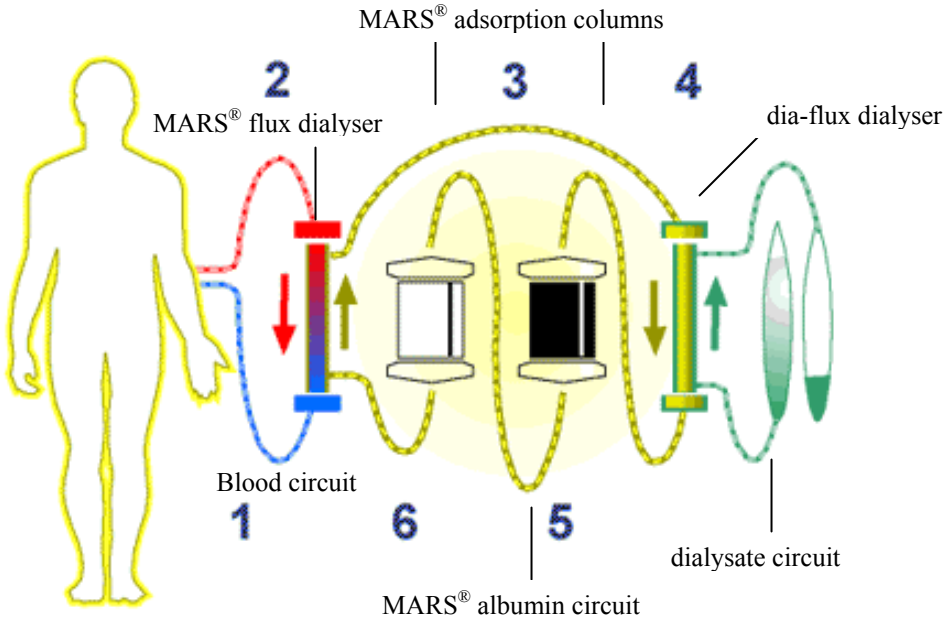

Figure 1. The MARS® albumin treatment method, (Printed with permission, Teraklin AG, 2005)

CLINICAL NEED AND BURDEN OF DISEASE

Cirrhosis is one of the most common causes of liver failure and may be caused by hepatitis infection or excessive alcohol intake. Chronic active hepatitis can progress to both cirrhosis and liver cancer. Cirrhosis contributes significantly to the burden of disease in Australia, both in terms of premature mortality and health system costs (AIHW 2000). The prevalence of hepatitis infections is rising in Australia. In 2001 there was a 45% increase in estimated new Hepatitis C infections, with implications for an increase in chronic liver disease, from previous estimates in 1997 (Australian Hepatitis Council 2002).

In 2002-03 there were 10,730 hospital separations for the principal diagnoses K70 -76 liver diseases (AIHW 2005). The Australia and New Zealand Organ Donation (ANZOD) registry reported that there were 177 liver transplants in 2004 (ANZOD 2005). In January 2005 there were 104 patients awaiting liver transplants (ANZOD 2005) in both countries.

DIFFUSION

The MARS® device became available in Australia in 2002 and to date approximately 20 patients have been treated. More than 4,500 patients had been treated worldwide as of June 2004 (personal communication, Teraklin AG).

COMPARATORS

Once supportive measures to manage liver failure have been unsuccessful, the standard procedure for patients with ALF and AoCLF is liver transplantation. Currently there are insufficient numbers of liver organ donations in Australia to meet the number of patients requiring the procedure.

EFFECTIVENESS AND SAFETY ISSUES

At the time of writing this summary there was a substantial amount of published literature describing the use of MARS®. Much of the data demonstrates beneficial effect of the MARS® therapy on liver failure, although most of the studies are of lower level evidence (level IV Intervention evidence). This summary will report on a recent meta-analysis (level I Intervention evidence) of MARS® treatment compared to standard medical treatment (Khuroo et al 2004).

Outcome measures in the meta-analysis of MARS® therapy in patients with ALF and AoLF were deaths within 30 days of randomisation, bridge to transplantation and effect on hepatic encephalopathy and adverse events (Khuroo et al 2004). This meta-analysis included four randomised trials (level I Intervention evidence) with a total of 67 patients and two non-randomised studies with 61 patients. Of the randomised studies, there were 36 (54%) patients who had received MARS® treatment and 31 (46%) who had received standard medical treatment. Two of the four trials included patients with AoCLF (n=37) and one of these trials also included AoCLF patients with type 1 hepatorenal syndrome. Data on bridge-to-transplantation, effect on hepatic encephalopathy and adverse events were either incomplete or not reported in all four trials, therefore the meta-analysis was performed on all-cause deaths.

Mortality was reported in 68% (21/31) and 33.3% (12/36) of patients in the control and MARS® treatment groups, respectively (Khuroo et al 2004). The primary meta-analysis of the randomised trials with MARS® treatment did not appear to reduce mortality significantly compared with standard medical treatment (RR=0.56, 95%CI [0.28, 1.14], p=0.11). The results of the primary, sensitivity and subgroup analyses are presented in Table 1.

Table 1. Results of Primary Meta-Analysis of MARS® treatment effect on mortality

	No. of events/Patients				
Source	Intervention	Control	RR (95% CI)	p value	p value hetereogeneity
All trials	12/36	21/31	0.56 (0.28, 1.14)	0.11	0.39
Sensitivity analysis#	10/28	13/22	0.72 (0.37, 1.40)	0.33	0.33
AoCLF	7/20	11/17	0.49 (0.012,2.17)	0.35	0.32
ALF	5/16	10/14	0.49 (0.15,1.58)	0.23	0.32

analysis done on 3 trials, trial published as abstract excluded
Source: Khuroo et al 2004

Although three of the four randomised studies (Heeman et al 2002, Mitzner et al, 2000 and El-Banayosy et al 2002) reported a significant benefit of MARS® treatment compared to standard medical treatment this meta-analysis found there was no significant survival benefit with MARS®. It did however report a 44% reduction in mortality with MARS® treatment. Although the results of the meta-analysis and individual studies appear to conflict, it is important to note that the small numbers of patients in each trial included in the analysis may affect the statistical significance in detecting benefit. The review reports that its analysis had less than 40% power to detect a 10% reduction in mortality. It concludes that there is a need for more trials with greater number of patients are required to adequately assess any MARS® treatment effect.

COST IMPACT

The cost of the MARS® device is approximately $AUD 30,000 and a single treatment costs approximately $AUD 5000. Due to the high cost of MARS® treatment in Australia, patients are averaging only three to five treatments and are being treated at a later stage of disease than ideal

(Teraklin AG company representative, 12 May 2005). Using the lowest conservative estimate that all patients on the liver transplant list in Australia would be eligible for and receive 3-5 treatments with MARS® therapy (approximately 100 patients per year) (ANZOD 2005), the estimated cost to the health care system would range from at least $1.6 to $2.6 million per year.

If treatment with the MARS® device was effective in improving morbidity and mortality, it is likely that the high costs of treatment would be offset by a reduction in patients requiring liver transplants and hospital costs of intensive care compared to current supportive therapy and transplantation. At this time of reporting there are no Australian data examining the cost impact of treatment with the MARS®.

A retrospective study (level III-2 intervention evidence) examined 1-year survival, costs and cost-effectiveness of the MARS® in a total of 36 patients with AoCLF (Hessel et al 2003). The outcome measure for cost-effectiveness was the number of survival days in the first year after treatment. The study reported mean 1-year survival in the MARS® treatment group of 261 days and 148 days in the control group. Direct medical costs for the MARS® patients from a societal perspective were approximately four times the amount for the control group. The costs per life year gained were approximately $AUD125,400.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

CONCLUSION:

There is an existing and growing body of higher level evidence of the effectiveness of the MARS® for the treatment of liver failure from Europe and its introduction into the Australian health system. In addition, there is an increasing level of liver failure associated with a rise in Hepatitis C in Australia.

HEALTHPACT ACTION:

Therefore it is recommended that a Horizon Scanning report be conducted.

LIST OF STUDIES INCLUDED	TOTAL
Total number of studies	
Level I intervention evidence	1
Level III-2 intervention evidence	1

SOURCES OF FURTHER INFORMATION:

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SEARCH CRITERIA TO BE USED:

Hepatic Encephalopathy/physiopathology
Liver Failure, Acute/epidemiology/mortality/ therapy
Liver Failure/epidemiology/mortality/ therapy
Liver, Artificial
Serum Albumin/ metabolism