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# Horizon Scanning Technology Prioritising Summary

# Penumbra system for endovascular thrombus removal for treatment of ischaemic stroke patients

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# PRIORITISING SUMMARY

**REGISTER ID:** **000484**

**NAME OF TECHNOLOGY:** **PENUMBRA SYSTEM FOR ENDOVASCULAR THROMBUS ASPIRATION**

**PURPOSE AND TARGET GROUP:** **THROMBUS REMOVAL FOR TREATMENT OF ISCHAEMIC STROKE PATIENTS**

**STAGE OF DEVELOPMENT (IN AUSTRALIA):**

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

**AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL**

- ☒ Yes — ARTG numbers 157312, 157313
- ☐ No
- ☐ Not applicable

**INTERNATIONAL UTILISATION:**

| COUNTRY | LEVEL OF USE | | |
|---|---|---|---|
| | Trials Underway or Completed | Limited Use | Widely Diffused |
| Canada | ✓ | ✓ | |
| USA | ✓ | ✓ | |
| Germany | ✓ | ✓ | |
| Switzerland | ✓ | | |
| Australia | | ✓ | |

**IMPACT SUMMARY:**

Penumbra Incorporated (Alameda, CA) provides the Penumbra system with the aim of revascularisation (thrombus removal) for patients with acute ischaemic stroke secondary to occlusive disease of the large intracranial vessels. The technology is available through select public hospitals with centres of excellence and specialist services in neurology.

## BACKGROUND

Stroke occurs when a blood vessel supplying part of the brain ruptures (haemorrhagic stroke) or becomes blocked by a clot (ischaemic stroke), and without treatment causes loss of function to that part of the brain. Risk factors for stroke are the same as for any cardiovascular disease: obesity, lack of physical activity, high blood cholesterol levels, high blood pressure and smoking. Stroke mainly affects older people with the rates of stroke increasing markedly with age from about 65 years, with the median age of patients having a stroke in Australia being approximately 79 years (Senes 2006).

Ischaemic strokes are more common (85%) than haemorrhagic strokes, and both may affect functions including movement of body parts, vision, swallowing, communication, and may result in death. Nearly all patients are disabled immediately following a stroke event. Common disabilities include permanent paralysis of one side of the body, speech or swallowing difficulties, problems with memory, personality changes or a range of other difficulties. Depression, anxiety and cognitive impairment are also common after stroke. By the end of the first year, about half of all survivors of stroke remain dependent on others for activities of daily living (Senes 2006).

The Penumbra system has been developed for the early management of ischaemic stroke with the aim of preventing death and the burden of long-term morbidity[1]. The system is designed to restore adequate blood flow via debulking and aspiration of occluding thrombus with the aim of salvaging the ischaemic penumbra – the area surrounding a cerebral infarct that suffers less ischaemia. While considered dysfunctional, the penumbral region is not irreversibly damaged and successful revascularisation is therefore thought to result in improved functional outcomes and quality of life for patients, thus reducing the number of stroke patients requiring intensive rehabilitative regimes. Briefly, the Penumbra system works by advancing a reperfusion catheter over a neurovascular guidewire until it approaches the occluding thrombus.[2] An appropriately sized separator device is then introduced into the proximal part of the thrombus through the reperfusion catheter. After turning on an aspirator pump, the thrombus is effectively 'vacuumed' from the blocked vessel while the separator is alternately advanced and retracted within the reperfusion catheter to aid with the extraction. In the event of residual thrombus after the aspiration, a thrombus removal ring can be used to directly remove the remaining blood clot (Penumbra Pivotal Stroke Trial Investigators 2009). The Penumbra is not designed for use in small branch vessels (personal communication Victorian Department of Health).

[1] The system is contraindicated for treating haemorrhagic stroke, as it is designed specifically for the purpose of clearing an occluded vessel.
[2] The initial access point is the femoral artery via an incision in the groin.

## CLINICAL NEED AND BURDEN OF DISEASE

Stroke poses a significant burden on patients and their families as well as on the health system and aged care services. In 2007, there were 8,623 deaths from stroke in Australia, accounting for approximately 6.3 per cent of all deaths. The mean age at death from stroke was 80.6 years, and the majority of deaths (7,049, 82%) occurred in individuals aged >75 years (AIHW 2010a). In Australia during 2007–08 there were 34,945 public hospital separations with a principal diagnosis of stroke (ICD-10 codes I60-I64), accounting for 352,916 patient days. During this same period there were only 67 public hospital separations for the sequelae of stroke (ICD-10 codes I69.0–I69.4). However, the ICD-10 code I69.4 had 2,033 patient days associated with it, with an average length of stay of 63.5 days (AIHW 2010b).[3]

There is no national information on the incidence of stroke in Australia. It is expected that the ageing of the Australian population will result in an increase in the number of strokes in the future. Of those people who have experienced a stroke in their lifetime, almost half of survivors will experience a disability as a result of that stroke. Of those people who experience a first-ever stroke, one in five people will have died from it within one-month and one in three die within six-months. Within five years, one in six survivors of a first-ever stroke will experience another (Senes 2006).

In New Zealand during the year 2004-05, there were 7,783 public hospital separations for stroke (ICD-10 codes I60-I64) and 121 separations for the sequelae of stroke (ICD-10 codes I69.0–I69.4) (personal communication Analytical Services, New Zealand Ministry of Health).

## DIFFUSION

The Penumbra system has experienced limited diffusion into the Australian health system. Only two major public hospitals, the Queen Elizabeth Hospital in Adelaide and the Royal North Shore Hospital in Sydney, utilise Penumbra's aspiration technique for the physical removal of blood clots in the brain (personal communication Penumbra Neuro Australia Pty Ltd).

## COMPARATORS

Thrombolytic pharmacotherapy is the standard non-mechanical method of revascularisation following acute ischaemic stroke (Novakovic et al 2009). A number of these thrombolytics are available, but most common are the tissue plasminogen activator (tPA) therapies, administered either intravenously or intra-arterially. The

[3] In the 2006 AIHW report by Senes, during 2002-03 there were 68,866 hospital separations with a principal diagnosis of stroke; its sequelae, and rehabilitation for stroke or its sequelae, accounting for 1,073,645 patient days. When accessing the same online data source for these years as those quoted above for public hospital separations, the total number of public hospital separations for stroke and its sequelae was 32,918 (I60-I64) plus 121 (I69), a total of 33,039. It is unclear whether the discrepancies in these numbers is due to private hospital separations.

advantage of the intra-arterial route is local delivery of the drug into the clot with reduced systemic effects. Anticoagulant agents are used as an intervention for acute ischaemic stroke, but remain controversial because they carry a substantial risk of haemorrhage which increases with infarct size, elevated blood pressure and higher dosage.

The most common mechanical methods for removal of clots following acute ischaemic stroke cited in recent literature utilise the MERCI and multi-MERCI endovascular devices which feature helical loops that function to embed the thrombus prior to removal through a micro-catheter. Vacuuming, unique to the Penumbra system, is not involved (Novakovic et al 2009; Abou-Chebl 2009).

### SAFETY AND EFFECTIVENESS ISSUES

A single-arm study of 125 patients (mean age 63.5 years) who presented with acute ischaemic stroke were treated with the Penumbra system in centres across the USA and Europe (Penumbra Pivotal Stroke Trial Investigators 2009)(level IV intervention evidence). Patients presented within eight hours of symptom onset, as per indicated use of the system, and had neurological deficits as defined by a National Institutes of Health Stroke Scale[4] (NIHSS) score ≥8 and an angiograph indicating a thrombolysis in myocardial infarction[5] (TIMI) grade 0 or 1. Patients who presented within three hours of symptom onset had to be refractory to or ineligible for tPA therapy. All had a clinical follow-up of 90 days and CT scans within 24 hours post-treatment were used to detect intracranial haemorrhage (ICH). Symptomatic ICH was defined as CT evidence of a bleed associated with a four-point increase in NIHSS score. If no post-procedure NIHSS score was available for a patient, the ICH was considered symptomatic if death occurred during the 90-day follow-up. Importantly, cases who received additional treatments for the primary occlusion after use of the Penumbra system were considered protocol violations. Adjunctive treatments included other mechanical means of thrombus removal or thrombolytic drugs. Primary outcomes were the proportion of patients with TIMI grade 2 or 3 post-procedure and modified Rankin scale[6] (mRS) score ≤2 at 90 days.

[4] NIHSS is measured across 11 categories with a range of 0 to 30 where 0 indicates normal function and higher scores indicate greater deterioration of function (Stroke Center 2010).

[5] TIMI is graded on a scale of 0-3 where 0 indicates no perfusion, 1 indicates faint flow with incomplete filling of the vascular bed, 2 indicates delayed filling of the vascular bed and 3 indicates normal flow with complete filling of the vascular bed. Similar studies (Kulcsar et al 2010) have used TICI (Thrombolysis in Cerebral Infarction) as the measure for revascularisation, however measures of partial perfusion used for the TICI scale are more subjective and therefore cited less often than the TIMI scale which has been adopted from the cardiology. TIMI is regarded as the standard by most stroke physicians and vascular interventionists (personal communication, senior consultant neurologist).

[6] mRS is a common measure of disability and dependence following stroke. The scale ranges from 0 to 6 with 0 representing no symptoms and 6 representing death.

Results from the procedure are summarised in Table 1. Post-procedure, 102 (81.6%) patients had a TIMI grade of 2 or 3 (54.5 and 27.2% had grades of 2 and 3, respectively). Nineteen procedural complications occurred in 16 (12.8%) patients, including vasospasm, re-occlusion of the target vessel, dissection, perforation, ICH, subarachnoid haemorrhage, anaemia, distal embolisation and secondary stroke. Among these 16 patients, two deaths occurred. Of the 125 enrolled patients, 35 (28%) experienced ICH, of which 14 cases (11.2%) were symptomatic and 21 (16.8%) were asymptomatic. The proportion of patients with 90-day mRS score ≤2 was 25 per cent and all-cause mortality at 90 days was 32.8 per cent.

Analysis of independent predictors of patient outcome showed that lower baseline NIHSS scores and shorter procedure times were associated with good functional outcome as defined by 90-day mRS score ≤2 (p=0.004), and that baseline NIHSS scores exceeding 20 were associated with mortality at 30 and 90 days, p=0.001 and p=0.0005, respectively.

The authors finally compared the revascularisation rates and functional outcomes with several other case series investigating other mechanical and drug based means for clearing occluded cerebral vessels of thrombus. A tabulated comparison (not shown) indicated that revascularisation rates for the Penumbra system compare favourably to other methods but that this did not directly translate to improved clinical function and decreased mortality. Caution is required in the interpretation of such a comparison between case series as the probability of bias and confounding is much greater than in a prospectively designed study, preferably with randomisation, and with clearly described selection of patients for both the intervention and a comparator group (Penumbra Pivotal Stroke Trial Investigators 2009).

Table 1 Neurological and functional outcomes from open versus closed vessels

| | Per cent with Outcome | | | |
|---|---|---|---|---|
| Outcome | All patients (n=125) | Open‡, TIMI 2-3 (n=102) | Closed‡, TIMI 0- (n=23) | p* |
| Discharge NIHSS 0-1 or decreased by ≥10 | 27 | 32 | 5 | 0.01 |
| Good clinical outcome at 30 days† | 30 | 35 | 9 | 0.02 |
| mRS ≤2 at 90 days | 25 | 29 | 9 | 0.06 |
| Death at 90 days | 33 | 29 | 48 | 0.14 |

*Test for difference between outcome proportions; †Composite of discharge NIHSS of 0-1 or decreased by ≥10 points or 30 day mRS ≤2; ‡Outcome of "open" refers to a successfully revascularised vessel whereas "closed" indicates unsuccessful revascularisation

Canadian physicians attempted use of the Penumbra system in 29 consecutive patients with acute ischaemic stroke and arterial occlusion (Menon et al 2010). In two patients, navigation of the catheter to the target vessel was not achieved, and therefore, results for a case series (level IV intervention evidence) of 27 patients (mean age 61 years; 13 male) with arterial occlusions was available. The primary outcome assessed was proportion of patients achieving TIMI grade 2 or 3, while the primary outcome of

clinical relevance was a mRS ≤2 at three months. Adverse events included vessel rupture, dissection and groin complications, ICH as indicated by follow-up CT scan, distal emboli into the occluded vascular bed, and all-cause mortality.

Median NIHSS score on hospital admission was 18 (range 3–32) and all patients had a baseline TIMI grade of 0. A total of 23 (85%) patients achieved a TIMI grade of 2 or 3 post-procedure, but five of these patients required an additional device or technique (e.g. retrievable stent or balloon angioplasty) for thrombus removal. Excluding these patients from analysis the Penumbra system achieved a TIMI grade of 2 or 3 for 67 per cent of the patients. Seventeen patients (63%) also received intra-arterial tPA and four received the platelet aggregation inhibitor, abciximab which may have independent effects on outcome. Thus TIMI scores for the majority of patients are attributable to a combination the Penumbra system and the use of intra-arterial thrombolytics. Similarly, the functional outcomes and all-cause mortality should be interpreted with the use of multiple treatments in mind. Thirteen (48%) patients had a mRS score ≤2 at three months while all-cause mortality at 90 days was 19 per cent (5 patients). Intracerebral haemorrhage was the most common adverse event occurring among nine (33%) patients. Other complications were rare, but this could well be a reflection of the small sample size accrued for this study. Small sample size and lack of direct comparison to alternative treatments also prohibits firm conclusions about clinical outcomes (Menon et al 2010).

A third case series was identified but not further discussed given recruitment of a similar (small) patient number and similar results to Menon et al 2010 (Kulcsar et al 2010) (level IV intervention evidence). The main difference in the study was the use of TICI as a measure of revascularisation rather than TIMI. Kulcsar and colleagues also used concurrent treatments for thrombus removal, therefore the degree of revascularisation and clinical outcomes attributable exclusively to the Penumbra system are not clear despite the claim that there was no significant difference in final revascularisation between groups with and without intra-arterial tPA use.

### COST IMPACT

The cost of treating a stroke patient with the Penumbra system is in the range of $8,000-10,000 based on the cost of required consumables and not including fees for the procedure or anaesthesia. Unit costs for the catheters and separators are $1,560 and $3,275, respectively, and a set-up package may be purchased for $30,000. This package includes two of each of the variously sized consumables, with the sizes being specific to all neurovascular sites from which thrombus may need to be cleared. The cost of the aspirator pump, also included with the set-up package option, is $3,725 (personal communication Penumbra Neuro Australia Pty Ltd). The Penumbra system should provide better clearance of thrombus than a MERCI coil, but at approximately 10 times the cost (personal communication Victorian Department of Health).

## ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

## OTHER ISSUES

The Penumbra system comprises an additional component, the thrombus removal ring, which does not carry FDA approval. However, the rest of the components have received FDA 510(k) clearance for substantial equivalence to the MERCI clot retrievers[7] (Concentric Medical, Mountain View, CA) and the CE mark. It is has been reported by one medical news source (MedGadget 2010) that the results of the trial undertaken by the Penumbra Pivotal Stroke Trial Investigators (2009), which used the clot-grabbing device in only a few cases, led Penumbra to exclude this part of the system from the final submission to the FDA. This appears to be supported by the absence of information for the thrombus removal ring on the Penumbra website (Penumbra Inc 2009). The Penumbra Pivotal Stroke Trial (2009) formed part of the initial submission for 510(k) clearance and the involvement of Penumbra employee's constitutes a conflict of interest issue.

## SUMMARY OF FINDINGS

The included evidence shows that revascularisation rates with the Penumbra system are likely to exceed 80 per cent. Considering the results of case series that examine alternative thrombus clearing methods re-presented by the Penumbra Pivotal Stroke Trial Investigators (2009), the system compares favourably in terms of revascularisation rates. However, evidence from prospective randomised studies is lacking and the firm conclusions about clinical effectiveness of the Penumbra system remain dependent on the emergence of these trials. In particular, trials will require a focus on functional outcomes, as it has not been adequately substantiated that high revascularisation rates translate into long term reduction in patient disability and mortality. Thus any use of this intervention should be considered experimental.

## HEALTHPACT ASSESSMENT:

The low-level of available evidence makes the wider clinical impact of the Penumbra system uncertain at this stage. The technology has already begun to diffuse into the Australian health care system and has potential benefit to those patients who have ready access to the technology in terms of their proximity. The device is substantially more expensive than existing treatments. HealthPACT will seek the opinion of the Neurological Society of Australasia on the current state of the available evidence regarding the Penumbra.

[7]MERCI clot retrievers have a cork-screw conformation to engage and retrieve thrombus and are constructed of nitinol memory wire.

## NUMBER OF INCLUDED STUDIES

| | |
|---|---|
| Total number of studies | 3 |
| Level IV intervention evidence | 3 |

## REFERENCES:


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## SEARCH CRITERIA TO BE USED:

Penumbra, revascularisation*
Stroke/cerebral infarct*/clot/thrombus
Endovascular
Blood