PUBLIC SUMMARY DOCUMENT
Product: Methoxyflurane, solution, 1 x 3 mL with inhaler, Penthrox®
Sponsor: Medical Developments International Limited
Date of PBAC Consideration: July 2008

1. Purpose of Application

To request an Authority Required PBS listing for the relief of pain in wound dressings or trauma in patients aged 2-18 years or in an Aboriginal or Torres Strait Islander (ATSI) person where alternate treatments are unsuitable; and

To request PBS listing in the Emergency Drug (Doctor's Bag) Supplies.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Penthrox was TGA registered on 23 December 1992 for the following indications:

> Self administration to conscious haemodynamically stable patients with trauma and associated pain, under supervision by personnel trained in its use.
>
> Monitored conscious patients who require analgesia for the relief of pain in short surgical procedures such as change of dressings.

Note: the total maximum dose must not be exceeded

4. Listing Requested and PBAC's View

Authority Required

For the relief of pain in wound dressings or trauma in patients aged 2-18 years where alternate treatments are unsuitable.

For the relief of pain in wound dressings or trauma in an Aboriginal or a Torres Strait Islander person where alternate treatments are unsuitable.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Methoxyflurane is a volatile anaesthetic, which is now only used to provide analgesia.

It will provide clinicians with an additional treatment option for patients requiring rapid non - injectable, non narcotic analgesia**.**

6. Comparator

The submission nominated placebo as the main comparator in paediatric and Aboriginal or Torres Strait Islander patients.

7. Clinical Trials

The submission presented one randomised trial as the pivotal evidence comparing methoxyflurane with placebo in patients aged 1-16 years for pain relief from upper limb

fracture or venepuncture, and 17 supplementary non-randomised studies involving methoxyflurane as an analgesic.

The pivotal trial and the supplementary evidence published at the time of the submission are as follows.

Trial/First author	Protocol title/ Publication title	Publication citation
Direct randomised trial (pivotal evidence)		
Chin R et al (2002)	A randomised control trial of inhaled methoxyflurane pain relief, in children with upper limb fracture (Abstract)	J Paediatric Child Health 2002; 38(5): A13-A14.
Non-randomised studies (supplementary evidence)		
Paediatrics		
Aleksandrin A et al (1976)	Use of subnarcotic concentrations of methoxyflurane in children with burns.	Vestn Khir 1976;116 (5): 99-101
Babl F, et al (2006)	Inhaled methoxyflurane as a prehospital analgesic in children	Emergency Medicine Australasia (2006) 18 , 404–410
Babl F, et al (2007)	A pilot study of inhaled methoxyflurane for procedural analgesia in children.	Paediatric Anesthesia 2007 17: 148–53
Firn S (1972)	Methoxyflurane analgesia for burns dressings and other painful ward procedures in children.	Br J Anaesth 1972; 4(5): 517-22.
Emergency Care Setting		
Buntine P et al (2007)	Pre-hospital analgesia in adults using inhaled methoxyflurane.	Emergency Medicine Australasia (2007) 19, 509–14
Komesaroff D (1979)	Serum fluoride ion levels following the administration of methoxyflurane for analgesia.	Presented at the Australian Society of Anaesthetists Annual General Meeting, Adelaide, South Australia, October 1979
Virenque C et al (1975)	Methoxyflurane analgesia during evacuation of injured persons.	Anesth Analg Reanim 1975; 32(1):149-53.
Burns Dressings		
Laird S et al (1972)	The effect of methoxyflurane analgesia on renal function in burned patients: an investigation.	Postgrad Med J 1972; 48(557): 133-7
Marshall M et al (1972)	Analgesia for burns dressing using methoxyflurane.	Br J Anaesth 1972; 44(1): 80-2.
Packer K et al (1969)	Methoxyflurane analgesia for burns dressings: experience with the Analgizer®.	Br J Anaesth 1969; 41(12): 1080-5.
Packer K (1972)	Methoxyflurane analgesia for burns dressings.	Postgrad Med J 1972; 48(557): 128-32.
Dentistry		
Dragon A et al (1967)	Methoxyflurane preliminary report on analgesic and mood-modifying properties in dentistry.	JADA 1967; 75(5): 1176-81
Edmunds Det al (1975).	Inhalation sedation for conservative dentistry. A comparison between nitrous oxide and methoxyflurane.	BDJ 1975; 139(10): 398-402.
Josephson C et al (1974)	The Cardiff inhaler and penthrane. A method of sedation-analgesia in routine dentistry.	J Dent Ass S.Afr 1974; 29(2): 77-80.
Minor Surgical Procedures		
Reier C (1970)	Methoxyflurane analgesia: a clinical appraisal and detailed description of stage I in man.	Anesth Analg 1970; 49(2): 318-22.
Pain Threshold		
Siker E et	Effect of sub-anaesthetic concentrations of halothane	Anesthesiology 1967;

al (1967)	and methoxyflurane on pain threshold in conscious volunteers.	28(2): 337-42.
Tomi K et al (1993)	Alterations in pain threshold and psychomotor response associated with sub-anaesthetic concentrations of inhalation anaesthetics in humans	Br J Anaesth 1993; 70: 684-6.

8. Results of Trials

The key results from the pivotal randomised trial are summarised in the following tables. Changes of ≥ 4 points on the Faces Pain Scale were considered clinically important.

Median change in Faces Pain Scores in the pivotal trial

McCaskill (manuscript)	Methoxyflurane Median score (range)	Placebo Median score (range)	Reference Median score (range)
Researcher assessed			
Venepuncture Fracture	0 (–10, 10) 4 (2, 8)*	0 (–10, 6) 2 (–2, 8)	–2 (–8, 4)*
Parent assessed			
Venepuncture Fracture	0 (–10, 10) 4 (0, 10)*	0 (–10, 8) 2 (–4, 8)	–2 (–8, 6)*
Child assessed			
Venepuncture Fracture	0 (–10, 10) 4 (0, 10)*	0 (–10, 8) 2 (–4, 6)	–2 (–8, 10)

* Significant difference p<0.05

Proportion of patients with no deterioration in faces pain scores (Venepuncture) and with change of at least 4 in Faces Pain Scores (Fracture) in the pivotal trial

McCaskill (manuscript)	MF n/N (%)	Placebo n/N (%)	Ref n/N (%)	Odds Ratio (95 CI)	Risk Difference (MF vs. P) (95 CI)
Venepuncture group					
Researcher assessed	18/27 (67)	20/28 (71)	7/18 (39)	-	–0.05 (–0.29, 0.20)
Parent assessed	16/26 (62)	21/28 (75)	8/19 (42)	-	–0.13 (–0.38, 0.11)
Child assessed	13/16 (81)	9/17 (53)	5/11 (45)	-	0.28 (–0.02, 0.59)
Fracture group					
Researcher assessed	18/25 (72)	6/21 (29)	-	6.43 (1.78, 23.3)	0.43 (0.17, 0.70)
Parent assessed	18/26 (69)	8/24 (33)	-	4.50 (1.37, 14.78)	0.36 (0.33, 0.69)
Child assessed	13/23 (57)	4/20 (20)	-	5.20 (1.32, 20.49)	0.37 (0.2, 0.57)
All patients responding (Researcher assessed)	36/52 (69)	26/49 (53)			

MF= methoxyflurane, Ref = reference, P = placebo

The supportive non-randomised case series reports showed pain relief after methoxyflurane administration in both adult and paediatric patients, however, the lack of randomisation and control arms in these case reports reduced the rigor of this evidence.

The Therapeutic Goods Administration Therapeutic Goods Administration (TGA) has reviewed the Australian registration status of methoxyflurane, focusing on safety given nephrotoxicity and hepatotoxicity were the reason for the Food and Drug Administration (FDA) withdrawal. It was concluded that the risk of clinically relevant renal impairment and overt hepatic toxicity were very low when methoxyflurane is used as recommended in the product Information (PI).

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that methoxyflurane is superior to placebo in terms of comparative effectiveness in pain relief. The PBAC noted that there was no clinical evidence to support efficacy in children in other clinical settings or in the ATSI population.

For PBAC's views, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a trial-based economic evaluation to estimate the cost per additional responder, defined as a patient who achieves a change of at least four in Faces Pain Scores. The time horizon is limited to a single instance of analgesia.

The results of the univariate sensitivity analyses indicated that the model was most sensitive to the analgesia response rate and duration of consultation time.

The submission estimated the base case incremental cost-effectiveness ratio to be less than $15,000 per responder. Given that only the responders in the upper limb fracture group were included in the calculation of outcome for the base case of the economic evaluation, the estimated ICER should be interpreted as an incremental cost per extra paediatric responder with upper limb fracture.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients/year to be between 10,000 – 50,000 patients in Year 5.

The financial cost/year to the PBS was estimated to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of methoxyflurane in the PBS Doctor's Bag Item List only on the basis of an acceptable incremental cost per extra paediatric responder with upper limb fracture.

In making this recommendation, the PBAC noted that in order to be included in the PBS Doctor's Bag Item List an item must be listed on the PBS, but indicated that it did not consider it appropriate for methoxyflurane to be made available as a general benefit. The PBAC noted that the intent of a Section 85 (s85) PBS listing is community-based access to medicines. Given the reported adverse effects and precautions associated with the use of methoxyflurane, the PBAC considered a s85 listing inappropriate as it would allow for the direct supply of methoxyflurane inhaler to community-based patients and as such has the potential for use not under supervision by personnel trained in its use, which would be contrary to the TGA-approved indication.

However, the PBAC noted that there is a clinical need for a rapid onset, portable and non-narcotic analgesic for use by doctors and nurses in the emergency community-based settings, and that drugs may be made available as pharmaceutical benefits but be distributed under alternative arrangements where these are considered more appropriate. These alternative arrangements are provided for under section 100 of the *National Health Act 1953* and might be considered appropriate for a doctor's bag listing of methoxyflurane.

The PBAC also noted that there are precautions and adverse effects associated with the use of methoxyflurane, however, that when used at analgesic doses and under supervision by personnel trained in its use, these precautions and adverse effects are generally without significant consequence. However, on the basis of the observational studies presented, the PBAC expressed concern that methoxyflurane has the potential for patients to be uncooperative post-therapy and that this may be an issue in a community-based setting. Disquiet was also expressed by the PBAC in response to the report by Babl 2006 of deep sedation in 5 of 15 children under the age of 5 years of age treated with methoxyflurane. Overall, the Committee noted the expert advice at the hearing that methoxyflurane inhaler has been used by Australian emergency services in both adults and children for relief of acute pain for over 30 years without significant concern.

The PBAC noted only one unpublished randomised controlled trial (RCT) was presented in the submission comparing methoxyflurane against placebo for early pain relief in children with upper limb fracture or for venepuncture. The PBAC noted from this single unpublished RCT (McCaskill et al) that methoxyflurane showed statistically significant benefit in early pain relief in children with upper limb fractures (1 to 16 years of age) but no benefit for pain relief for venepuncture or for all trauma.

The PBAC also noted that although the submission provides a number of non-randomised clinical studies dating back to the 1970s supporting the use of methoxyflurane as an analgesic in a variety of settings in both adult and paediatric patient, the lack of randomisation and control arms in these case reports reduces the rigor of this evidence.

Lastly, the PBAC noted that the requested listing for use in the ATSI population had not been reviewed by the Department's ATSI working group, and that consideration by this group should take place before PBAC make a final recommendation in respect of subsidised access. However, the Committee also noted the lack of clinical data to support the requested listing for ATSI patients and expressed concern over the possibility for repeated use in these patients and the associated potential for irreversible renal failure.

Recommendation
METHOXYFLURANE, solution, 1 x 3 mL with inhaler.

Restriction: To be finalised
For Doctor's Bag only

Maximum quantity: 1

13. Context for Decision
The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment
Medical Developments International is delighted with the PBAC's decision to recommend the inclusion of Penthrox in the Emergency Drug (Doctors Bag) Section of the PBS. The

availability of this product provides the community with a safe and effective analgesic agent for the treatment of acute pain.