PUBLIC SUMMARY DOCUMENT
Product: Buprenorphine hydrochloride with naloxone hydrochloride, sublingual tablets, 2 mg (base) - 500 micrograms and 8 mg (base) – 2 mg, Suboxone®
Sponsor: Reckitt Benckiser Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application
The submission sought a Section 100 listing for the treatment of opiate dependence, within a framework of medical, social and psychological treatment.

2. Background
Buprenorphine hydrochloride with naloxone hydrochloride combination sublingual tablet has not previously been considered by the PBAC.

Currently the Australian Government through the Opiate Dependence Treatment Program funds the cost of buprenorphine hydrochloride supplied as a pharmaceutical benefit through clinics and pharmacies approved by State and Territory Governments.

3. Registration Status
Suboxone was registered by the Therapeutic Goods Administration (TGA) on 27 July 2005 for the treatment of opiate dependence, within a framework of medical, social and psychological treatment.

4. Listing Requested and PBAC's View
Section 100
OPIATE DEPENDENCE TREATMENT PROGRAM
Treatment of opiate dependence, within a framework of medical, social and psychological treatment. Naloxone is included in Suboxone to deter intravenous misuse of the product.

The PBAC noted that the statement "naloxone is included in Suboxone to deter intravenous misuse of the product" was not included in the TGA approved indication.

5. Clinical Place for the Proposed Therapy
Suboxone would provide an alternative to buprenorphine or methadone for the treatment of opiate dependence. There are potential benefits for patients if ongoing daily supervision of administration is not required.

6. Comparator
The submission nominated buprenorphine alone as the comparator. This was considered appropriate by the PBAC.

7. Clinical Trials
The submission presented a single randomised trial in an opiate-dependent population over four weeks comparing: (i) sublingual buprenorphine 16mg with naloxone 4mg; (ii) sublingual buprenorphine 16mg; and (iii) placebo. The trial details are as follows:

Trial/First author	Protocol title	Publication citation
Fudala PJ	Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone.	New England Journal of Medicine 2003;349(10):949-58.

8. Results of Trials

The results of the trial constituting the primary source of evidence are summarised in the following table:

Mean percent urine samples negative for opiates in first phase of the Fudala et al, 2003 trial

Placebo (N=109) Mean (SE)	Buprenorphine with naloxone (N=109), Mean (SE)	Buprenorphine (N=105), Mean (SE)	Difference^ (95% CI)
5.8% (1.7%)	17.8% (2.3%)	20.7% (2.8%)	*-2.75** (-8.9%, 3.4%[#])

^ Buprenorphine with naloxone arm minus buprenorphine alone arm

* Estimated during the evaluation assuming confidence interval is symmetrical around the point estimate of difference

[#] Estimated by nonparametric analysis using the Wilcoxon test

The results presented in the above table show that approximately 18% of patients in the buprenorphine with naloxone arm of the trial recorded opiate-free urine over the 4 weeks of the trial. Therefore, 82% of the trial participants were still using opiates four weeks into a maintenance program. The trial report indicated that a nonparametric analysis using the Wilcoxon test found no statistically significant difference between concomitant buprenorphine with naloxone and buprenorphine but only the confidence intervals are reported and not the point estimate for the difference.

See Recommendations and Reasons for PBAC's view.

9. Clinical Claim

The submission claimed that buprenorphine with naloxone fixed dose combination sublingual tablets were no worse than buprenorphine sublingual tablets.

See Recommendations and Reasons for PBAC's view.

10. Economic Analysis

A preliminary (trial-based) economic evaluation was presented. The choice of the cost-minimisation approach was considered valid. The resources included were drug costs and costs associated with administration and supervision of dosing.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients/year would be between 10,000 to 50,000 in Year 4 of listing, at a cost to the PBS of between $1 million to $5 million.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis compared to buprenorphine, with the equi-effective doses being determined on a milligram for milligram basis.

The PBAC noted that there was no significant difference in the toxicity profile of buprenorphine hydrochloride with naloxone hydrochloride, as compared to buprenorphine alone, due to the low bioavailability of naloxone administered sublingually. The PBAC noted that its Combination Guidelines do not apply to this type of product.

The PBAC recognised the central argument for PBS listing related to the potential for reduced misuse of diverted medication which may reduce the need for supervised administration. It was recognised that this was congruent with the aims of the National

Buprenorphine Policy, which takes a harm minimisation approach to the treatment of opioid dependence. The PBAC noted there was evidence from user surveys that diversion of buprenorphine has been a problem and that diverted doses of methadone and buprenorphine may be administered intravenously.

The PBAC agreed that listing this product would add a useful therapeutic option for the treatment of opioid dependence and one which patients could progress toward, as they become more stabilised on the program, allowing them to return to normal life with a decreased dependency on clinics. The PBAC did however express concern that patients may have access to take away doses for one month and considered this an inappropriately long duration which may be inconsistent with the objectives of concurrent medical, social and psychological treatment. Therefore, the Committee requested that advice be sought from the Intergovernmental Committee on Drugs (IGCD) regarding the proposed take-away dosing arrangements for this product, and more broadly on proposed amendments to the National Buprenorphine Policy to take into account the availability of this product through the PBS. The PBAC also suggested that the IGCD implement arrangements to monitor the uptake and outcomes of use of the product including the extent of diversion and report back to the PBAC 12 months after PBS listing.

Recommendation
BUPRENORPHINE HYDROCHLORIDE with NALOXONE HYDROCHLORIDE, sublingual tablets, 2 mg (base)-500 micrograms and 8 mg (base)-2 mg micrograms

Restriction:	OPIATE DEPENDENCE TREATMENT PROGRAM Treatment of opiate dependence within a framework of medical, social and psychological treatment. NOTE: Treatment must be in accordance with the law of the relevant State or Territory.
Pack Size:	28 (all strengths)

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

In the submission, the sponsor assumed that the majority of Suboxone patients would receive Suboxone as 3-4 take away doses per week or weekly pick-up of Suboxone. Indeed, some States are proposing that Suboxone be available only as take away and weekly dosing, at least initially. The use of monthly take-away dosing is being discussed to be reserved solely for the most stable cohort of patients. Treatment with Suboxone will be in accordance with the law of the relevant State or Territory.

Reckitt Benckiser proposed and is committed to a Risk Management/Market Surveillance of Suboxone. The project is to be conducted by the National Drug and Alcohol Research Centre at UNSW. The post-marketing surveillance of Suboxone will commence in March 2006, and the final report will be submitted December 2008. During this period, the National Drug and Alcohol Research Centre will document the roll-out of Suboxone across Australia in the two years following its release onto the Pharmaceutical Benefits Scheme (April 2006).