PUBLIC SUMMARY DOCUMENT

Product: ELITRIPTAN HYDROBROMIDE, tablet, 40 mg (base) and 80 mg (base), Relpax®

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: March 2010

1. Purpose of Application

The submission sought an Authority required (Streamlined) listing for the treatment of migraine attacks in patients who meet certain criteria.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Eletriptan hydrobromide 20 mg, 40 mg and 80 mg tablets were registered with the Therapeutic Goods Administration (TGA) on 13 October 2000 for the acute treatment of migraine headache with or without aura.

4. Listing Requested and PBAC's View

Authority Required (Streamlined)

Migraine attacks in patients receiving, or who have failed a reasonable trial of, prophylactic medication and where attacks in the past have usually failed to respond to oral therapy with ergotamine and other appropriate agents, or in whom these agents are contraindicated.

The PBAC recommended the same restriction apply to eletriptan as that recommended for rizatriptan benzoate and the other Pharmaceutical Benefits Scheme (PBS) listed $5HT_1$ agonist (triptans) at the November 2009 PBAC meeting. At the November 2009 PBAC meeting the PBAC considered that it was appropriate not to include the necessity to trial ergotamine prior to the use of a $5HT_1$ agonist, and also that it not be a requirement to fail a trial of prophylactic medication before using a $5HT_1$ agonist. The PBAC however considered that $5HT_1$ agonists should remain second line treatment of migraine attack after failure of, or contraindication to, analgesics.

5. Clinical Place for the Proposed Therapy

Eletriptan would provide an additional triptan for the treatment of migraine attack. The submission claimed that the listing of eletriptan would not change the current treatment algorithm but would provide prescribers with a greater choice of triptans to treat migraine attacks.

6. Comparator

The submission nominated sumatriptan as the comparator, as it is the current market leader in terms of volume of PBS prescriptions for the triptans. This was the appropriate comparator.

7. Clinical Trials

The submission presented 4 head-to-head randomised trials, and meta-analyses of these trials, comparing eletriptan with sumatriptan in patients with acute migraine attacks.

Three of the head-to-head randomised trials had been published at the time of submission as follows:

Trial ID / First author	Protocol title/ Publication title	Publication citation
Study 160-314 Goadsby PJ et al. (2000) Poole PH et al. (1998)	A multicentre, double blind, double dummy, parallel group, placebo controlled, dose response study of oral UK-116,044 (eletriptan) and oral sumatriptan (100 mg) given for the acute treatment of migraine (with and without aura).	 *Neurology* 2000, 54(1):156-63. Abstr P06.002. *Neurology* 1998, 50(4): A375-A6
Study A160-1048 Mathew NT et al. (2003d) Mathew NT et al. (2003c) Mathew NT et al. (2003b)	A multicentre, double-blind, randomised, placebo controlled parallel group comparative study of the efficacy and safety of oral eletriptan (40 mg) and sumatriptan (100 mg) given for the acute treatment of migraine.	 *Headache* 2003,43(3): 214-22. Abstr F30. *Headache* 2003, 43(5):530-1. Abstr. P06.142. *Neurology* 2003, 60(5 Suppl 1): A494-A5.
Study 160-318 Sandrini G et al. (2002) Pryse-Phillips WEM (1999) Funk Orsini PA et al. (2001)	A multicentre, double-blind, double-dummy, parallel group, placebo controlled, study of two dose levels of oral eletriptan and two dose levels of oral sumatriptan given for the acute treatment of migraine (with and without aura).	 *Neurology* 2002, 59(8): 1210-7. *Cephalalgia* 1999, 19:355-6. Abstr P2-K62. *Cephalalgia* 2001, 21(4): 432.

It was noted that sumatriptan tablets were encapsulated to ensure blinding in all the key trials included in the submission. There was evidence of a decreased absorption (27 % lower) in migraine patients over the first two hours for the encapsulated sumatriptan tablets compared with the standard tablets, based on area under curve in the first two hours (AUC_{0-2}), which is the more relevant pharmacokinetic measure of bioequivalence in acute migraine treatment. It was noted that the sumatriptan that is marketed is not encapsulated. However, the PBAC noted that the clinical outcomes did not appear to be affected. The PBAC also noted that the TGA Clinical Evaluator had accepted bioequivalence between the standard and encapsulated sumatriptan tablets.

8. Results of Trials

The main results are summarised below.

Summary of headache response* at 1 and 2 hours across the published key direct randomised trials (risk difference)

Trial ID	E40 vs S50	E80 vs S50	E40 vs E80
Risk difference (95% CI)			
Headache response 1 hour post-dose			
160-314			-0.03 (-0.15, 0.09)

160-318	0.06 (-0.03, 0.15)	0.13 (0.03, 0.22)	-0.07 (-0.17, 0.03)
Pooled analysis	0.00 (-0.11, 0.11) *P=0.98*	0.10 (0.03, 0.17) *P=0.004*	-0.08 (-0.15, -0.02) *P=0.007*
NNT	NA	10 (6, 33)	NNH = 13 (7, 50)
N†	348/354	331/354	472/459
Headache response 2 hour post-dose			
160-314			-0.12 (-0.24, -0.01)
160-318	0.14 (0.04, 0.24)	0.17 (0.06, 0.27)	-0.03 (-0.13, 0.07)
Pooled analysis	0.10 (0.03, 0.18) *P=0.008*	0.15 (0.08, 0.23) *P<0.0001*	-0.07 (-0.13, -0.01) *P=0.02*
NNT	10 (6, 33)	7 (4, 13)	NNH = 14 (8, 100)
N†	344/351	330/351	461/448

CI = confidence internal; E40 = eletriptan 40 mg; S50 = sumatriptan 50 mg; E80 = eletriptan 80 mg.

* Headache response was defined as a reduction of headache severity from moderate/severe (Grade 2/3) pain at baseline to no/mild (Grade 0/1) pain (measured on a 4-grade scale: 0 = no headache, 1 = mild headache, 2 = moderate headache, 3 = severe headache) post dose. This is reported for the first dose of the treatment drugs for all the studies and is for the first attack only in the two multiple attack studies (an unpublished study and 160-318).

† Total number of patients per treatment group

Summary of pain-free response* at 2 hours across the published key direct randomised trials

Trial ID	E40 vs. S50	E80 vs. S50	E40 vs. E80
Risk difference (95% CI)			
160-314			-0.08 (-0.20, 0.04)
160-318	0.12 (0.03, 0.21)	0.18 (0.09, 0.28)	-0.06 (-0.16, 0.04)
Pooled analysis	0.07 (-0.03, 0.17) P=0.19	0.13 (0.04, 0.22) P=0.005	-0.07 (-0.13, -0.01) P=0.02
N†	344/351	330/351	461/448
Relative risk (95% CI)			
160-314			0.78 (0.54, 1.13)
160-318	1.64 (0.12, 2.40)	1.97 (1.36, 2.84)	0.83 (0.62, 1.13)
Pooled analysis	1.36 (0.92, 2.40) P=0.17	1.74 (1.32, 2.28) P<0.0001	0.79 (0.65, 0.97) P=0.02
N†	344/351	330/351	461/448

CI = confidence internal; E40 = eletriptan 40mg; S50 = sumatriptan 50mg; E80 = eletriptan 80mg.

* Pain-free response was defined as grade 0 headache (measured on a 4-grade scale: 0 = no headache, 1 = mild headache, 2 = moderate headache, 3 = severe headache) at two hours post dose. This is reported for the first dose of the treatment drugs for all the studies and is for the first attack only in the two multiple attack studies (an unpublished study and 160-318).

† Total number of patients per treatment group

The PBAC noted that for the primary outcomes of headache response at one hour and the secondary outcome of pain free response at two hours there was no statistically significant difference between eletriptan 40 mg and sumatriptan 50 mg. The PBAC also noted that the results for the primary and secondary outcomes favoured eletriptan 80 mg compared to sumatriptan 50 mg.

The PBAC noted that the safety profile of eletriptan appeared similar to sumatriptan, with no differences in the proportion of patients discontinuing due to adverse events, however that treatment-emergent adverse event rates were, in general, significantly higher for eletriptan. Similarly, the PBAC noted that treatment-emergent adverse event rates were significantly higher for eletriptan 80 mg compared with eletriptan 40 mg.

Overall, there were no differences in the proportion of patients discontinuing due to adverse events for any eletriptan versus sumatriptan comparison, nor for eletriptan 40 mg versus 80 mg.

It was noted that in the comparison of eletriptan 40 mg and sumatriptan 50 mg, the only adverse event for which there was a significantly increased risk was somnolence (RD = 0.04, number needed to harm = 25), and in the comparison of eletriptan 80 mg against sumatriptan 50 mg the only significant differences were for somnolence (RD = 0.053, number needed to harm = 19) and nausea (RD = 0.046, number needed to harm = 22).

Periodic safety data beyond the trials revealed that a series of safety-related revisions were made to the relevant product information documents, but no other action taken by either health authorities or the sponsor.

9. Clinical Claim

The submission described eletriptan 40 mg tablets as non-inferior, and eletriptan 80 mg tablets as superior to 50 mg sumatriptan in terms of comparative effectiveness. The submission also described eletriptan 40 mg and eletriptan 80 mg tablets as similar to sumatriptan 50 mg in terms of comparative safety.

The PBAC considered the results of the four head to head randomised trials comparing eletriptan with sumatriptan and meta-analyses of these trials presented in the submission supported the claim of non-inferior efficacy of eletriptan to sumatriptan.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as eletriptan 40 mg and sumatriptan 50 mg. A flat price was proposed for eletriptan 40 mg and 80 mg.

Based on the evidence overall the PBAC accepted the flat pricing structure proposed in the submission with eletriptan 40 mg and 80 mg to be priced the same as sumatriptan 50 mg.

11. Estimated PBS Usage and Financial Implications

The likely number of packs/year dispensed was estimated to be in the range of 50,000 – 100,000 packs in Year 5.

The financial cost/year to the PBS was estimated to be less than $10 million in Year 5. The submission's estimate of less than $10 million net financial impact for the PBS/RPBS was reliant on the assumptions of a constant ratio of PBS-subsidised to private prescriptions of triptan use and a moderate uptake rate of eletriptan.

The PBAC considered the utilisation of eletriptan is uncertain, noting that two of the PBS listed triptans, naratriptan and zolmitriptan, are listed as Authority required items with a Special Patient Contribution, and that the listing of eletriptan as an Authority required (Streamlined) benefit may be a more appealing option to prescribers and patients.

12. Recommendation and Reasons

The PBAC recommended the listing of eletriptan hydrobromide on the PBS as an Authority required (streamlined) listing for the treatment of migraine attack in patients

where attacks in the past have usually failed to respond to analgesics on a cost minimisation basis with sumatriptan. The equi-effective doses are eletriptan 40 mg and sumatriptan 50 mg.

The PBAC considered the results of the four head to head randomised trials comparing eletriptan with sumatriptan and meta-analyses of these trials presented in the submission supported the claim of non-inferior efficacy of eletriptan to sumatriptan. The PBAC noted that for the primary outcomes of headache response at one hour and the secondary outcome of pain free response at two hours there was no statistically significant difference between eletriptan 40 mg and sumatriptan 50 mg. The PBAC also noted that the results for the primary and secondary outcomes favoured eletriptan 80 mg compared to sumatriptan 50 mg.

The PBAC noted that sumatriptan tablets were encapsulated to ensure blinding in all the key trials included in the submission. The PBAC noted that encapsulation delayed the absorption of sumatriptan however that the clinical outcomes did not appear to be affected. The PBAC also noted that the TGA Clinical Evaluator had accepted bioequivalence between the standard and encapsulated sumatriptan tablets.

The PBAC noted that the safety profile of eletriptan appeared similar to sumatriptan, with no differences in the proportion of patients discontinuing due to adverse events, however that treatment-emergent adverse event rates were, in general, significantly higher for eletriptan. Similarly, the PBAC noted that treatment-emergent adverse event rates were significantly higher for eletriptan 80 mg compared with eletriptan 40 mg.

Based on the evidence overall the PBAC accepted the flat pricing structure proposed in the submission with eletriptan 40 mg and 80 mg to be priced the same as sumatriptan 50 mg.

The PBAC recommended the same restriction apply to eletriptan as that recommended for rizatriptan benzoate and the other PBS listed $5HT_1$ agonist (triptans) at the November 2009 PBAC meeting. At the November 2009 PBAC meeting the PBAC considered that it was appropriate not to include the necessity to trial ergotamine prior to the use of a $5HT_1$ agonist, and also that it not be a requirement to fail a trial of prophylactic medication before using a $5HT_1$ agonist. The PBAC however considered that $5HT_1$ agonists should remain second line treatment of migraine attack after failure of, or contraindication to, analgesics.

The PBAC considered the utilisation of eletriptan is uncertain, noting that two of the PBS listed triptans, naratriptan and zolmitriptan, are listed as authority required items with a Special Patient Contribution, and that the listing of eletriptan as an authority required (streamlined) benefit may be a more appealing option to prescribers and patients. The PBAC also noted however that rizatriptan was also recently listed on the PBS as an Authority required (Streamlined) item.

***Recommendation*:**
ELETRIPTAN HYDROBROMIDE, tablets, 40 mg and 80 mg (base)

Restriction: CAUTION:

Eletriptan is contraindicated in patients with known or suspected coronary artery disease. The drug should not be used within 24 hours of ergotamine or dihydroergotamine use.

Authority Required (STREAMLINED)
Migraine attack in a patient where attacks in the past have usually failed to respond to analgesics.

NOTE:
No applications for increased maximum quantities and/or repeats will be authorised.

Maximum quantity: 4
Repeats: 5

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

The sponsor has no comment.