**PUBLIC SUMMARY DOCUMENT**
**Product:** Rizatriptan benzoate, tablet, 5 mg and 10 mg (base), wafer, 5 mg and 10 mg (base), Maxalt®
**Sponsor:** Merck Sharp & Dohme (Australia) Pty Ltd
**Date of PBAC Consideration:** November 2009

## 1. Purpose of Application
The submission sought an Authority Required (STREAMLINED) PBS listing for treatment of a patient with a migraine attack.

## 2. Background
This drug had not previously been considered by the PBAC.

## 3. Registration Status
Rizatriptan tablets and wafers were TGA registered on 23 June 1999 for the acute treatment of migraine attacks, with or without aura.

## 4. Listing Requested and PBAC's View
Authority Required (STREAMLINED)
Treatment of a patient with a migraine attack.

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

*For PBAC's view, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy
Migraine attacks will generally be comprised of a combination of symptoms including headache, nausea, photophobia, phonophobia and vomiting. Attacks can be potentially debilitating for the migraineur affecting work and social functioning.

Management of migraine may take a combined approach, including behavioural modification to avoid migraine triggers, the use of pharmaceutical prophylaxis, and acute treatment once an attack commences.

Rizatriptan would provide another treatment option for an acute migraine attack.

## 6. Comparator
The submission nominated sumatriptan as the comparator.

*For PBAC's view, see Recommendation and Reasons.*

## 7. Clinical Trials
The submission included seven controlled trials (studies 008, 029, 030, 046, 052, 060 and 904) comparing rizatriptan with sumatriptan. The submission also conducted a meta-analysis of 5 mg rizatriptan versus 50 mg sumatriptan using studies 029, 046 and 052, and of 10 mg rizatriptan versus 100 mg sumatriptan using studies 008 and 030.

Publication details of the trials presented in the submission are in the following table.

| Trial ID / First author | Protocol title / Publication title | Publication citation |
|---|---|---|
| **Trials comparing 10 mg rizatriptan (tablets/wafers) to 50 mg sumatriptan tablets** | | |
| Study 046[a] Goldstein J et al (1998) | Cross-over comparison of rizatriptan 5 mg and 10 mg vs sumatriptan 25 mg and 50 mg in migraine. | Headache 1998; 38(10): 737-47 |
| Study 052[a] Kolodny A et al (2004) | Comparison of rizatriptan (5 mg and 10 mg tablets) and sumatriptan (25 mg and 50 mg tablets). | Cephalagia 2004; 24(7): 540-46 |
| Study 060 Loder E et al (2001) | Preference comparison of rizatriptan oral disintegrating tablets (ODT) 10 mg and sumatriptan 50 mg tablets in migraine. | Headache 2001; 41(8): 745-53 |
| Study 904 Pascual J et al (2001) | Comparison of preference for rizatriptan 10 mg wafer versus sumatriptan 50 mg tablet in migraine. | European Neurology 2001; 45(4): 275-283 |
| **Trials used in the submission to compare 5 mg rizatriptan tablets to 50 mg sumatriptan tablets (in addition to studies 046 and 052 above)** | | |
| Study 029 Lines C et al (1997) Lines C et al (2001) | Rizatriptan 5 mg versus sumatriptan 50 mg in the acute treatment of migraine. A comparison of visual analog scale and categorical ratings of headache pain in a randomized controlled clinical trial with migraine patients. | Headache 1997; 37(5): 319-20 Pain 2001; 93(2): 185-190 |
| **Trials comparing 10 mg rizatriptan tablets to 100 mg sumatriptan tablets** | | |
| Study 008[b] Visser WH et al (1996) | Rizatriptan vs sumatriptan in the acute treatment of migraine. A placebo-controlled dose-ranging study. | Arch Neurol 1996; 53(11): 1132-37 |
| Study 030 Tfelt Hansen et al (1998) | Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. | Headache 1996; 38(10): 748-755 |

p.o. = *per os* (oral)

[a] Note that these trials were also used in a meta-analysis conducted for the submission to compare the 5 mg rizatriptan and 50 mg sumatriptan arms.

[b] Sumatriptan was only included for those sites in the Netherlands.

The Pre-Sub-Committee Response presented an additional meta-analysis comparing 10 mg rizatriptan with 50 mg sumatriptan, based on data from Studies 046, 052, 060 and 904.

## 8. Results of Trials

**PI recommended doses: rizatriptan 10 mg vs. sumatriptan 50 mg**

The PBAC noted in three of the studies (046, 052 and 060), there were no statistically significant differences in the proportion of patients who experienced pain relief at two hours after treatment. This outcome was statistically significant in Study 904 (0.09 [95%CI: 0.03, 0.15]) favouring rizatriptan 10 mg wafers.

In two of the studies (046 and 052), there were no statistically significant differences in the proportion of patients who experienced freedom from pain at two hours after treatment. This outcome was statistically significant in Studies 060 (0.08 [95%CI: 0.01, 0.15]) and 904 (0.13 [95%CI: 0.06, 0.19]) favouring rizatriptan 10 mg wafers.

There were no statistically significant differences between rizatriptan 10 mg and sumatriptan 50 mg in terms of patients who experienced recurrence of a migraine attack within 24 hours where pain relief was originally achieved.

The PBAC noted that a statistically significant difference of 0.7 [95%CI 0.04, 0.11] was detected for the proportion of patients who experienced freedom from pain at 2 hours after treatment favouring rizatriptan 10 mg in the pooled analysis of four studies (046, 052, 060 and 904). There was evidence of some heterogeneity presented among the trials ($I^2$ = 37.0%). The PBAC considered that this result should be viewed within the context of the open-label design of the studies (060 and 904) in which these differences were observed and the subjective nature of the outcomes.

**High dose: 10 mg rizatriptan vs. 100 mg sumatriptan**
The PBAC noted there were no statistically significant differences between patients treated with rizatriptan 10 mg and patients treated with sumatriptan 100 mg, in terms of the proportion experiencing pain relief or recurrence. There was a statistically significant difference between rizatriptan 10 mg and sumatriptan 100 mg in terms of patients experiencing freedom from pain at two hours after their respective treatments, with more patients being free of pain in the rizatriptan 10 mg group (39%) compared to the sumatriptan 100 mg group (31%).

**Low dose: 5 mg rizatriptan vs. 50 mg sumatriptan**
The results of Study 029 and subsequent meta-analyses indicated that there were no statistically significant differences between the rizatriptan 5 mg and sumatriptan 50 mg treatment groups in terms of pain relief at two hours after treatment, freedom from pain at two hours after treatment, and recurrence within 24 hours where pain relief was achieved at two hours after treatment.

**Dose response: 10 mg rizatriptan vs. 5 mg rizatriptan**
The sponsor presented the results of a meta-analysis of the studies comparing the 5 mg and 10 mg doses of rizatriptan in terms of the proportion of patients who experienced freedom from pain at two hours after treatment. Data were pooled from the relevant arms of five studies (014, 022, 030, 046 and 054). The results suggested that there was a statistically significant difference in the outcome favouring the 10 mg dose over the 5 mg dose (0.08 [95%CI: 0.05, 0.12]).

The PBAC noted that overall, the comparison of the safety data from all the trials indicated few differences between patients receiving rizatriptan and sumatriptan, and considered any differences observed between the 5 mg rizatriptan, 10 mg rizatriptan,
50 mg sumatriptan and 100 mg sumatriptan were unlikely to be clinically important.

*For PBAC's view, see Recommendation and Reasons.*

## 9. Clinical Claim

The submission described rizatriptan 5 mg tablet/wafer as non-inferior in terms of comparative effectiveness and safety over sumatriptan 50 mg tablet, and rizatriptan 10 mg tablet/wafer as non-inferior in terms of comparative effectiveness and safety over sumatriptan 100 mg tablet.

*For PBAC's view, see Recommendations and Reasons.*

**10. Economic Analysis**

The submission presented a cost-minimisation analysis based on the therapeutic claim that rizatriptan 5 mg (tablet/wafer) is non-inferior to sumatriptan 50 mg (tablet) in terms of effectiveness and safety and rizatriptan 10 mg (wafer/tablet) is non-inferior to sumatriptan 100 mg (tablet) in terms of effectiveness and safety.

**11. Estimated PBS Usage and Financial Implications**

The submission estimated the likely number of packs dispensed per year to be less than 10,000 in Year 5, with estimated financial savings per year to the PBS of < $10 million in Year 5.

*For PBAC's view, see Recommendation and Reasons.*

**12. Recommendation and Reasons**

The PBAC recommended the listing of rizatriptan benzoate tablets and wafers on the Pharmaceutical Benefits Scheme as an authority required (streamlined) benefit for the treatment of migraine attack on a cost minimisation basis with sumatriptan succinate tablets. The equi-effective doses are rizatriptan benzoate 10 mg tablets and wafers to sumatriptan succinate 50 mg tablets.

The PBAC considered that rizatriptan 10 mg is of non-inferior efficacy and safety to 50 mg sumatriptan based on the evidence provided. The PBAC did not accept the equi-effective doses proposed in the submission, noting that rizatriptan 5 mg and sumatriptan 100 mg are not the recommended doses in the respective Product Information documents. The PBAC also noted the Product Information for rizatriptan recommends the use of the 5 mg tablet in patients receiving propanolol.

The PBAC considered the meta-analysis approach, or study 029 alone, did not provide sufficient evidence to support the claim of rizatriptan 5 mg being equi-effective to sumatriptan 50 mg. The PBAC noted the meta-analysis combined studies 029, 046 and 052, and that studies 046 and 052 did not have the relevant doses in their randomised cross-over sequences. Further, the PBAC considered the open label design and potentially inadequate randomisation in the wafer cross-over studies, the subjective nature of the pain outcomes measured on a 4-grade scale, and the potential confounders between the treatment groups (including migraine severity and use of prophylaxis) added to the uncertainty of the meta-analysis. The PBAC also did not accept the proposed equi-effective doses of rizatriptan 10 mg and sumatriptan 100 mg, considering sumatriptan 100 mg is not listed on the PBS.

The PBAC did not accept the claim in the submission that patients would use an average of 1.6 sumatriptan 50 mg tablets and only one rizatriptan 10 mg tablet per migraine attack. The PBAC considered it was equally likely that patients may use more than one rizatriptan tablet to treat a migraine attack, as recommended in the Product Information for rizatriptan, and that no basis was provided as to why patients would limit their use to one rizatriptan tablet per attack. Additionally, the PBAC noted that the source indicating an average use of 1.6 sumatriptan 50 mg tablets per attack was observational data collected between 1991 and 1993 from patients entering the Special Access Scheme for sumatriptan, managed by the sponsor

of sumatriptan. The PBAC considered this population may not be representative of the current target PBS population and may now be out of date.

The PBAC considered that a flat pricing structure between the 5 and 10 mg dose forms is not appropriate as the 10 mg dose was generally of superior efficacy in the clinical evidence presented, and noting that the Product Information recommends 10 mg as the optimal dose. The PBAC hence recommended that the 5 mg rizatriptan dose forms should have a lower price than the 10 mg dose forms.

The PBAC considered it was appropriate to not to include in the restriction the requirement to trial ergotamine prior to use of a $5HT_1$ agonist (triptan) to treat an acute migraine attack in line with current migraine treatment guidelines. Similarly, the PBAC recommended that it not be a requirement to fail a reasonable trial of prophylactic medication before use of a triptan. However, the PBAC recommended that the restrictions retain triptans as second line treatment after failure of or contraindication to simple analgesics for the treatment of acute migraine. The PBAC recommended that these recommendations flow on to the other triptans listed on the PBS, naratriptan hydrochloride, sumatriptan, sumatriptan succinate and zolmitriptan.

The PBAC advised that there is uncertainty in the utilisation for rizatriptan and that it is likely that rizatriptan will increase the market for triptans. The PBAC noted that naratriptan and zolmitriptan are both listed on the PBS as authority required benefits with a Special Patient Contribution (SPC), and the listing of rizatriptan as an authority required (streamlined) benefit without an SPC might be a more appealing option to prescribers and patients. Additionally, the PBAC noted that rizatriptan would provide a new dose form of wafers, which may be a treatment option for patients with difficulty taking a tablet dose form due to nausea associated with migraine. The PBAC also considered the changes to the restrictions for triptans will lead to an increase in the utilisation of all triptans, and that there is potential for use of rizatriptan beyond the population specified in the restriction.

The PBAC recommended the Safety Net 20 Day Rule should not apply.

***Recommendation***:
RIZATRIPTAN BENZOATE**,** tablets, 5 mg and 10 mg (base), and wafers, 5 mg and 10 mg (base)

Restriction:

CAUTION:
Rizatriptan 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 (tablets, 5 mg and 10 mg)
4 (wafers, 5 mg and 10 mg)

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 believes that Study 029 and the meta-analysis provide a high level of evidence to support the submission's Clinical Claim. As these analyses demonstrated that there were no statistically significant differences between rizatriptan 5mg and sumatriptan 50mg treatment groups on any migraine treatment endpoint, the sponsor believes it would have been inappropriate to list rizatriptan 5mg at a lower price than that of sumatriptan 50mg and thus has elected not to list this dose form on the PBS.

The sponsor is pleased that the rizatriptan 10mg dose form will be PBS listed and believes that the availability of a triptan without a Special Patient Contribution, in a new wafer form might be a more appealing option to prescribers and patients than alternative treatments.