Submission for Reclassification from

Prescription Medicine

To

Pharmacist Only Medicine

Maxalt® (Rizatriptan)

Merck and Co., Inc.

Table of Contents

Rizatriptan Benzoate
Reclassification from Prescription Medicine to Pharmacist Only Medicine
Comprehensive Table of Contents

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Reclassification from Prescription Medicine to Pharmacist Only Medicine
Comprehensive Table of Contents

Executive Summary

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Migraine is a common neurological disease usually characterized by attacks of unilateral moderate or severe headache, and associated with nausea, vomiting, photophobia and/or phonophobia. A focal neurological disturbance, known as aura, may precede the headache in some cases. The total number of migraine patients is estimated to be 65 million worldwide. The average migraine patient experiences 1 to 3 attacks per month. During migraine attacks at least one third of patients are severely disabled and require bed rest. Therefore, migraine has a direct impact on work loss and social life. Reducing the economic and social burdens of migraine and increasing the treatment opportunities has been recognized as a public health priority.

A variety of treatment options are available for migraine sufferers. Many use nonprescription analgesics, such as non-steroidal anti-inflammatory drugs, due to their convenience and ready availability, although these medications often afford sub-optimal relief, particularly in moderate to severe migraine attacks. Prescription medications such as ergot alkaloids and some anti-emetic drugs have been used with some success, but both classes of drugs have adverse event profiles that make them less than ideal treatment choices.

The triptan medications frequently provide effective relief from migraine attacks, including the associated symptoms. The triptans also have an excellent safety profile. Currently in New Zealand, there are five triptans available by prescription only and two available without a prescription. The availability of MAXALT® Melt 5 mg without a prescription would provide migraine sufferers with a valuable additional option to treat their symptoms and allow them to return to productivity.

The symptoms of migraine are readily distinguishable from those of other types of headaches. Once diagnosed, migraine sufferers are able to recognize their own patterns of symptoms and to determine whether a headache is a migraine or not. It is proposed that rizatriptan be sold without a prescription only to those patients who have been diagnosed with a history of migraine by a physician or by a pharmacist using a Migraine Treatment Questionnaire. This is the same restriction that applies for the sale of sumatriptan OTC. It has been shown that pharmacists are able to effectively diagnose migraine with the aid of a migraine treatment questionnaire, such as the one proposed with this application, and that they can appropriately refer patients to a physician as needed. Pharmacists are accustomed to assisting migraine sufferers, and the training materials that are proposed will further assist them in this task.

The efficacy profile of rizatriptan has been well established. Clinical studies of rizatriptan versus sumatriptan demonstrated comparable efficacy of rizatriptan 5 mg with sumatriptan 50 or 100 mg, with evidence of a superior effect of rizatriptan for relief of nausea. A published meta-analysis found that rizatriptan 5 mg was similar to sumatriptan 100 mg for the measures of headache relief, pain-free at 2 hours, and sustained pain-free (to 24 hours post-dose). Recurrence rates, however, were lower with rizatriptan 5 mg than with sumatriptan 100 mg.

Rizatriptan has an excellent safety profile, which has been well established in clinical trials and post-marketing experience, and was similar to placebo. The incidence of drug-related adverse events in the Phase III trials was 17% for placebo, 24% for rizatriptan 5 mg, 33% for rizatriptan 10 mg, 29% for sumatriptan 50 mg, and 41% for sumatriptan 100 mg. The most common adverse events in a Phase III study of the orally disintegrating tablet were dizziness, nausea, dry mouth, and somnolence. Review of spontaneous adverse event reports from prescription use of rizatriptan confirms that it is generally well tolerated outside of the clinical trial setting, and no new safety concerns have arisen through post-marketing surveillance. Co-administration of rizatriptan with monoamine oxidase inhibitors is contraindicated due to an increase in the systemic exposure of rizatriptan and its metabolite; this contraindication also applies to sumatriptan, which has been approved for non-prescription use at the 50-mg dose. There is no known potential for abuse of rizatriptan, and the migraine-specific pharmacologic action makes misuse for other conditions highly unlikely.

Nonprescription availability of rizatriptan would provide a number of benefits to migraine sufferers and to public health. It would provide an additional option for migraine sufferers to treat their attacks, including those who do not respond well to sumatriptan or other products that are available without a prescription. Additionally, there is evidence that absorption of rizatriptan is not reduced due to the reduced gastric motility that often accompanies migraine attacks, whereas other oral treatments, including sumatriptan, are affected. It would make an additional option available to those who cannot visit a doctor for a prescription. Among those who are able to visit a doctor, it would save a considerable amount of time and resources due to doctor visits that are no longer necessary for the sole purpose of renewing a prescription.

The orally disintegrating tablet (wafer) formulation of MAXALT® Melt also provides benefits to migraine sufferers. Because the wafer dissolves in the mouth, water is not necessary. This provides convenience, because it can be taken even when drinking water is not readily available, but also makes it easier to take for patients who suffer nausea in association with their migraine attacks. Additionally, there is evidence that a large percentage of migraine sufferers prefer the orally disintegrating tablet formulation over conventional tablets.

In conclusion, migraine is a self-limited condition that can be diagnosed by a pharmacist and recognized by the patient. MAXALT® Melt 5 mg has an excellent safety and efficacy profile, with no issues that would prevent its safe use in consultation with a pharmacist. The nonprescription availability of MAXALT® Melt 5 mg would provide migraine sufferers with an additional option for treatment that is effective and generally well tolerated, with some advantages over other currently available nonprescription treatments. The data in this document support the reclassification of MAXALT® Melt 5 mg from Prescription Medicine to Restricted Medicine (Pharmacist Only Medicine) status in New Zealand.

Part A

Rizatriptan Benzoate
Reclassification from Prescription Medicine to Pharmacist Only Medicine
Part A

Part A

1. International Non-proprietary Name of the medicine

Rizatriptan benzoate

2. Proprietary name

MAXALT ® Melt

3. Name of company requesting reclassification

Merck Sharp& Dohme (New Zealand) Ltd

Level 2, Carlton Gore Rd

PO Box 99851 Newmarket

Auckland

4. Dose form(s) and strength(s) for which a change is sought

Dose form: wafer

Strength: 5mg

5. Pack size and other qualifications

Pack size: 2 wafers

Description: MAXALT ® Melt Wafers and individually packed in a foil blister that is enclosed in a paper sachet, two sachets are then enclosed in a plastic container which is in an outer cardboard carton

6. Indications for which change is sought

MAXALT ® Melt is indicated for acute treatment of Migraine with or without aura.

MAXALT ® Melt should only be used when there is a clear diagnosis of migraine

7. Present classification of medicine

Prescription Only Medicine

8. Classification sought

Pharmacist Only Medicine (Restricted Medicine)

9. Classification status in other countries (especially Australia, UK, USA, Canada)

Sumatriptan 50mg tablets: United Kingdom OTC approval 2006

New Zealand OTC approval 14 February 2008

Naratriptan 2.5mg tablets: Germany OTC approval 2006

Zolmatriptan 5mg nasal spray: Sweden OTC approval December 2007

New Zealand OTC application July 2009

10. Extent of usage in NZ (New Zealand) and elsewhere (e.g. sales volumes) and dates of original consent to distribute

MAXALT™ wafers were granted consent for distribution in NZ in February 1999 however due to a lack of government funding MAXALT™ wafers were not actively promoted in NZ. In June 2008, MAXALT™ wafers were granted a full fund listing by PHARMAC and the product has been actively promoted since then. The market share of the triptan market

for MAXALT™ has increased from 0.5% to 6% between June 2008 and December 2008 and is on target to reach 25% by December 2009.

Forecasted triptan market growth in 2009 is 16% and 8% for 2010, due to MAXALT™'s entry into the market.

Forecasted unit sales of MAXALT™ in New Zealand by end of 2009 is 114,769.

MAXALT™ sales for 2008 (US $ millions) for the top ten countries plus New Zealand is shown in Table 1, along with the dates of regulatory approval for both the wafer and tablet formulations. As of 20 July 2009 a total of 25,18,815 five mg tablets/ wafers and 376,451,400 ten mg tablets wafers have been sold world wide.

Table 1
MAXALT™ Sales in 2008 and Formulation Approval Dates

	10mg		5mg		Formulation Approval Dates			
	Tablet	Wafer	Tablet	Wafer	10 mg Wafer	10 mg Tablet	5 mg Wafer	5 mg Tablet
USA	$ 201.9	$ 170.1	$ 14.0	$ 13.9	29-Jun-98	29-Jun-98	29-Jun-98	29-Jun-98
Germany	$ 7.2	$ 15.0	$ 0.3	$ 0.7	25-Sep-98	25-Sep-98	25-Sep-98	25-Sep-98
Canada	$ 4.4	$ 16.7	$ 0.6	$ 1.5	16-Jul-99	16-Jul-99	16-Jul-99	16-Jul-99
Japan	$ 2.7	$ 16.7			17-Jul-03	17-Jul-03		
Spain	$ 2.5	$ 13.9			27-May-99	27-May-99	10-Jun-98	10-Jun-98
UK	$ 2.5	$ 11.7	$ 0.9		24-Jun-98	24-Jun-98	23-Jun-98	24-Jun-98
Netherlands	$ 1.8	$ 11.5		$ 0.3	12-Feb-98	12-Feb-98	12-Feb-98	12-Feb-98
Italy	$ 1.4	$ 11.9	$ 0.2		25-May-99	25-May-99	25-May-99	25-May-99
Norway	$ 1.5	$ 4.2	$ 0.1		19-Feb-99	19-Feb-99	19-Feb-99	19-Feb-99
Greece		$ 3.0			12-Aug-98	12-Aug-98	12-Aug-98	12-Aug-98
New Zealand		$ 0.3	$ 0.001		25-Feb-99	25-Feb-99	25-Feb-99	25-Feb-99
Source: IMS MTA								

11. Labelling or draft labelling for the proposed new presentation(s)

Refer to Appendix 1 for draft packaging and CMI (package insert)

12. Proposed warning statements if applicable

The following warning statements are proposed for the carton, they are included in more detail in the package insert (CMI) (Appendix1) and in the Datasheet (Appendix 2)

This product contains aspartame

Caution: Do not take MAXALT® Melt if you have any of the following; heart problems; vascular problems; uncontrolled high blood pressure; an allergy to rizatriptan or any of the ingredients listed in the enclosed leaflet. Do not take MAXALT® Melt if you are taking other medicines for the treatment of migraine or the treatment of depression (MAOI) see enclosed leaflet for further information.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change

None

Part B

Rizatriptan Benzoate
Reclassification from Prescription Medicine to Pharmacist Only Medicine
Part B

1.1 Background

1.1.1 Overview of this segment of submission

This portion of the document provides a consumer-based rationale for offering an additional ingredient and formulation into the OTC marketplace for treatment of migraine.

1.1.2 Current Marketplace

In 2006, sumatriptan 50 mg tablets were reclassified from Prescription Medicine to Restricted Medicine (Pharmacist Only Medicine) in New Zealand. This product is available in packages of 2 tablets. Prior to this time, consumers with migraine needed to talk to a doctor in order to obtain prescription medications for migraine relief.

While migraine sufferers currently have a non-prescription triptan option to relieve their migraines, many of them have not tried this option up until now, for reasons which will be discussed later. Instead, about half of all migraine sufferers rely on over-the-counter analgesics for relief [1]. In many cases, this relief is sub-optimal [2]. Also, because there is little guidance available regarding the use of these OTC analgesics for migraine, there is the potential that self-medication with analgesics could lead to medication-overuse headaches [3], which have been described as persistent and oppressive [4].

In 2009, zolmitriptan 5 mg nasal spray was reclassified as a Restricted Medicine.

1.1.3 Differences between MAXALT® Melt and Sumatriptan

MAXALT® Melt offers several advantages in the current marketplace for migraine treatment:

- The availability of rizatriptan offers another option for sufferers, some of whom might not get optimal relief from sumatriptan due to individual differences in responses to medications.
- The Melt formulation is quick and easy to take and there is no need to have water available.
- After trying the Melt formulation, many sufferers prefer it to conventional oral tablets [5; 6].
- There is evidence that rizatriptan does not have decreased absorption due to reduced gastric motility during migraine, like sumatriptan does [7]

1.2 Consumer Benefits

1.2.1 Description of Migraine and Barriers to Treatment

Migraine is a problem that has afflicted human beings throughout history [8]. It is a primary episodic headache disorder which likely has a genetic component [9; 10]; many sufferers

report a family history of migraine. Once diagnosed, symptoms are easily recognizable and the illness is self-limiting.

Key symptoms are moderate or severe in intensity. The sufferer experiences pain which can be one-sided and/or pulsating and is aggravated by routine physical activity. An attack which is untreated or unsuccessfully treated can last anywhere from 2 hours to 2-3 days. Accompanying symptoms can be nausea, vomiting, and intolerance of normal levels of light and sound [4].

The World Health Organization (WHO) ranks migraine among the world's most disabling medical illnesses [11]. In addition to the physical pain it causes, it can also have a significant impact on quality of life: "Repeated headache attacks, and often the constant fear of the next one, damage family life, social life and employment. For example, social activity and work capacity are reduced in almost all migraine sufferers..." [4] In addition, WHO asserts that the long-term effort of dealing with chronic headaches such as migraines might also predispose individuals to other illnesses such as depression. In fact, depression is three times more common in people with migraine or severe headaches than in healthy individuals [4; 12]. It is not at all surprising that a large study found that the three most important attributes for a migraine treatment are complete pain relief (87%), lack of recurrence (86%), and rapid onset of pain relief (83%) [13].

Triptans, first introduced in the early 1990s, revolutionized the treatment of migraine and are first-line drugs for severe attacks and for less severe attacks that do not adequately respond to analgesics [9; 8]. Early intervention, right when the headache begins, can prevent escalation, thereby increasing the effectiveness of the treatment [2; 14].

However, the evidence shows that many sufferers do not receive effective care. For example, studies have shown that among representative populations in both the US and the UK, only about half of migraine sufferers had seen a physician for a headache-related reason in the previous year, and only two-thirds had been diagnosed correctly. Most were using over-the-counter analgesics only [4]. A 1999 article reported that in New Zealand, only about 30% of migraine sufferers consulted a doctor [15]. Thus, there is a clear, unmet consumer need for better treatment and management of migraine.

There are several important barriers to treatment for these sufferers [4; 1]:

- Misunderstanding of their condition by the sufferers themselves, who feel that they should not go to a doctor for "just a headache". Only about half of migraineurs have been diagnosed to have migraine.
- Lack of comprehensive knowledge among many health care practitioners about this illness. As a result of not having effective (or any) interaction with health care professionals, many sufferers are not aware of prescription triptan treatment or the availability of a nonprescription alternative.
- Lack of understanding of the illness among the general public and the consequent trivialization of the condition.

- Political and economic barriers by governments which do not understand the burden that headache ailments place on society.

1.2.2 Benefits of MAXALT® Melt

General benefits of an additional OTC triptan:

Individuals vary dramatically in their response to specific medications; these responses can be idiosyncratic and unpredictable. In the US, the FDA has approved seven oral triptans in the last 10 years, and none has emerged as unquestionably the best option for all sufferers [2]. New Zealand has five different triptans registered as prescription medications, and two are available OTC. Because not all individuals react to specific triptans in the same way [16], an additional alternative oral formulation OTC triptan could provide relief for those who do not respond to sumatriptan or zolmatriptan.

The availability of another OTC triptan will help to build awareness in the general population of sufferers about the condition and the possible treatments, leading to better management in the population as a whole.

Having another triptan available from a pharmacist will increase the potential for those who do not wish to visit a doctor or cannot do so conveniently, to obtain effective treatment quickly, thereby blunting the intensity and longevity of the migraine experience.

An analysis by Tfelt-Hansen [17] indicates that if 50% of those with migraine were to consult a health care practitioner three times a year on average, this would bring about over 80 million consultations in the EU each year. Thus, the analysis concludes that the availability of triptans OTC makes a lot of sense for the management of this self-limiting but burdensome and grossly undertreated disorder.

Specific benefits from MAXALT® Melt:

The most important treatment attributes desired by migraine sufferers are understandably focused on speed and completeness of relief. However, 56% of sufferers also say that the route of administration is important to them [13].

The quickly-dissolving wafer form is more palatable to some people than conventional oral tablets. In one large study where patients used the rizatriptan wafer formulation and were asked preference versus conventional tablets, the majority of those with a preference chose the wafer [5]. Another study directly compared rizatriptan 10-mg wafers to sumatriptan 50-mg tablets in a randomized, open-label, crossover outpatient study [6]. Almost twice as many patients preferred the rizatriptan formulation to the sumatriptan tablet. Reasons for preference included both faster relief of headache pain and being easier to take.

In addition, there is no need to have water available with the Melt. Therefore, they can be taken at any time, providing quick relief when a migraine attack begins, to sufferers who do

not have liquids handy. This can be particularly relevant if the sufferer typically has nausea associated with the migraine [8; 10]. In a review of all current triptan formulations, Gladstone & Gawel report that quickly-dissolving wafers have rapidly grown as an alternative to conventional oral tablets, injections, and nasal sprays due to their tolerability and convenience [8].

Also, there is evidence that rizatriptan does not have decreased absorption due to reduced gastric motility during migraine, like sumatriptan does [7].

1.3 Public Benefits

1.3.1 Underestimation of Impact of Migraine

According to the World Health Organization, "Headache has been and continues to be underestimated in scope and scale, and headache disorders remain under-recognized and under-treated throughout the world" [4]. There are significant economic and social burdens from migraine which could be alleviated with broader access to effective treatments.

1.3.2 Economic Impact of Enhanced Migraine Treatment

Because headache disorders such as migraine are most common and most disabling in the most productive years (mid-20s to mid-50s), estimates of the financial cost to society are enormous. This is primarily due to lost working hours and reduced productivity. In the UK, about 25 million working- or school-days are lost to migraine alone every year [4].

According to a research report by Colmar Brunton published in 1999, the economic cost of migraine to the New Zealand economy is about NZ$80 million, based purely on working days lost (about 700,000). This figure did not take into account the additional costs of seeking medical treatment [15].

A 1997 study by Legg et al. measured the economic impact of prescription sumatriptan use on lost labor costs to an employer. The study found that patients self-reported a significant decrease in lost labor costs as the result of the availability of effective treatment, and the authors concluded that the benefit-to-cost ratio for the employer was 10:1 [18]. Increasing the availability of effective migraine treatment would thus have a positive impact on these economic burdens, as sufferers would be able to return to work more quickly and with less reliance on the medical system.

1.3.3 Social Impact of Enhanced Migraine Treatment

The social impact of increasing the availability of effective migraine treatment is an indirect benefit that can be felt most by two groups: the individual sufferers along with their household members, and pharmacists:

<u>Individual sufferers and household members</u>

Studies have shown that migraine has a profound impact on quality-of-life assessments by sufferers [19] as well as household partners and other family members of sufferers [20; 8]. Because sufferers would have access to more effective treatment and could obtain it more quickly and conveniently than they could by visiting a doctor, they could experience a quicker return to a normal life, enhancing family responsibilities and interactions.

Pharmacists

- Pharmacists, who frequently counsel customers about their migraines [21] and who have had limited treatment options to offer, will have an additional alternative for their migraine sufferers, thus enabling them to achieve a higher probability of success with their customers. Pharmacists will have educational materials to give to their customers that will further assist these sufferers in learning about this illness and thus better managing it over the long term.
- Pharmacists will receive training and materials that help them to better assist their customers who are in need of treatment for migraine. The materials will include a questionnaire (Appendix 3) that pharmacists will administer to potential users of MAXALT® Melt. The three screening questions which are included in the questionnaire have been validated to identify migraine sufferers in a very high proportion of cases [22]. Additional questions will confirm that potential users do not have contraindications that would preclude use of the product. This questionnaire will serve a valuable awareness function for both pharmacists and their customers by improving their diagnostic skills for this ailment. The knowledge from the training materials will also teach pharmacists to recognize when a customer should instead be referred to a doctor, thereby having an even greater positive impact on the public health.

In all of these ways, pharmacists can play a greater education and guidance role with their customers, benefiting both parties.

In addition to the two key groups above, the reduced need among migraine sufferers to seek medical assistance could enable doctors and other health care practitioners to better focus on those ailments that are more difficult for patients to self-recognize and self-treat.

1.4. Evidence and Rationale for Reclassification

1.4.1 Treatment of Migraine

A variety of treatment options are available for migraine sufferers. Some of the more commonly used medications are analgesics, such as non-steroidal anti-inflammatory drugs, which are available without a prescription. However, these medications have limited efficacy in moderate to severe migraine episodes [23].

Ergot alkaloids have been used extensively to treat moderate to severe migraine episodes. Anti-emetic drugs with antidopaminergic activity, such as metoclopramide, domperidone, and phenothiazine, have some efficacy against migraine headaches as well as some of the

associated symptoms. However, both of these classes of medications have adverse event profiles that make them less than ideal treatment choices.

The triptan class of medications, or 5-HT1B/5-HT1D agonists, provide effective relief from symptoms of migraine, including headache, nausea, photophobia, phonophobia, and aura. Working through the calcitonin gene-related peptide (CGRP) pathway, the relief they provide is specific to migraines; they are not effective against other types of headaches. The triptans also have an excellent safety profile.

Despite the availability of more effective treatments, many migraine sufferers continue to treat their attacks with non-prescription analgesics [24], due partly to their convenience and ready availability. As such, they frequently receive non-optimal relief. Until recently, all triptans were available only by prescription. One triptan (sumatriptan) has now been available without a prescription in New Zealand for approximately 3 years and a second (zolmatriptan) has recently been reclassified as a Restricted Medicine. The non-prescription availability of MAXALT would increase patients' access to effective migraine treatment.

1.4.2 Rationale for Restricted Medicine Status

The rationale for switching MAXALT® Melt 5 mg from Prescription Medicine to Restricted Medicine status can be summarized as follows:

- Migraine is a self-limited condition that can be recognized by the patient and diagnosed by a pharmacist with the assistance of a Migraine Treatment Questionnaire.
- Another triptan (sumatriptan) has been available with Restricted Medicine status in New Zealand for approximately 3 years. No significant problems have occurred during that time that would indicate that such a medication is not suitable for Restricted Medicine status. In addition, zolmitriptan nasal spray has recently been reclassified as a Restricted Medicine.
- There is a clear advantage to having another triptan available without a prescription to ensure that patients have ready access to the most available treatments. This switch would provide more choices to patients, particularly those who may not receive effective relief from other available treatments.
- The new dosage form in MAXALT® Melt would give migraine sufferers another option in how they feel they can best treat a migraine attack.
- Non-prescription access would make it easier for migraine sufferers to use MAXALT® early in the course of a migraine attack, when treatment is most effective.
- MAXALT® has well-established safety and efficacy profiles. The 5-mg dose is the lowest approved for use in New Zealand and has proven efficacy while maintaining a wide margin of safety. This is also the preferred dose for several groups of sufferers, including those taking propranolol and those with hepatic or renal insufficiency, so a warning for these groups of sufferers is not necessary.

2. Ease of Diagnosis

2.1 Self-Diagnosis

The symptoms of migraine are readily distinguishable from those of other types of headaches. Once diagnosed, migraine sufferers are able to recognize their own patterns of symptoms and to determine whether an attack is a migraine or not. Furthermore, the minutes of the 35th Medicines Classification Committee meeting note that when reviewing the proposed reclassification of sumatriptan OTC, the committee agreed that migraines, once correctly diagnosed, are easily recognized by the consumer.

It is proposed that rizatriptan be sold without a prescription only to those patients who have been diagnosed with a history of migraine by a physician or by a pharmacist using the Migraine Treatment Questionnaire. This is the same restriction agreed to by the Medicines Classification Committee for the sale of sumatriptan OTC.

2.2 Diagnosis by a Pharmacist

It has been shown that pharmacists are able to diagnose migraine and guide migraine sufferers in the treatment of the condition. For many years, pharmacists have assisted consumers in the appropriate selection and use of over-the-counter products to treat headaches, including migraines. A survey of pharmacists in the US indicated that they are experienced and comfortable with assisting patients with migraine, but concluded that the use of standardized treatment guidelines would be helpful [21].

As was done when sumatriptan was reclassified, it is proposed that rizatriptan be dispensed by pharmacists using a migraine treatment questionnaire. Pharmacists are accustomed to following treatment protocols for various treatments, including the use of triptans to treat migraine, and therefore would only dispense the medication to consumers for whom it is appropriate. A study conducted in the UK, Australia, and Germany showed that pharmacists were able to use a migraine questionnaire to effectively diagnose migraine and determine which sufferers were appropriate for treatment with a triptan, while referring others to a physician [25]. Additionally, the minutes of the 35th Medicines Classification Committee meeting regarding the proposed reclassification of sumatriptan OTC indicate that the committee felt that pharmacists would be able to effectively diagnose migraine with the aid of a migraine questionnaire. Since the reclassification of sumatriptan in 2006, there have been no significant problems that would contradict the committee's judgment.

The experience of pharmacists in helping patients with their migraines will be extremely valuable if rizatriptan is reclassified. The availability of this medication without a prescription, in a dosage form not currently available, would give pharmacists another option in assisting migraine sufferers, particularly those who have not achieved acceptable efficacy from other medications they have used or who have trouble using the currently available dosage forms.

Pharmacist training and support materials will include the following:

Migraine Questionnaire

A questionnaire to assist pharmacists in diagnosing migraine and determining which sufferers are suitable for treatment with rizatriptan will be developed. This questionnaire will be based upon those currently in use by pharmacists for the nonprescription use of sumatriptan in New Zealand and the UK and the use of naratriptan in Germany.

Pharmacist Training

In collaboration with the relevant professional bodies, MSD will develop educational materials to help pharmacists understand which headache sufferers should be dispensed this medication. This will include a simple algorithm to determine which sufferers have migraine, which of those may safely use rizatriptan, and which sufferers should be referred to a physician for further evaluation.

Patient Education

A clearly written CMI will be provided to patients who purchase rizatriptan. This CMI will describe who should and should not use the product, directions for use, and what potential adverse effects the user should be aware of. It will also indicate when the migraine sufferer should seek further consultation with a physician or pharmacist.

3. Relevant Comparative Data for Like Compounds

3.1 Pharmacology compared to Sumatriptan and Zolmitriptan

The pharmacological mechanisms of action of rizatriptan, sumatriptan, and zolmitriptan are similar. Sumatriptan has a lower bioavailability than rizatriptan and zolmatriptan (14% versus 40% and 39% respectively). Rizatriptan seems to reach C_{max} more quickly than sumatriptan. The faster oral absorption of rizatriptan than sumatriptan is supported by a comparative study where the median t_{max} was 1.3 (range of 1 to 3) hours for rizatriptan tablets and 2.5 (range 1 to 4) hours ($P< 0.001$) for sumatriptan [26]. Rizatriptan tablets were used for the comparative study and the rate of absorption is somewhat slower for the orally disintegrating tablet (wafer) formulation, MAXALT® Melt, with T_{max} averaging 1.6 to 2.5 hours [27]. The pharmacokinetic profile of sumatritpan and zolmitriptan were not influenced by concomitant administration of propranolol [26].

3.2 Efficacy Compared to Sumatriptan and Zolmitriptan

Clinical studies of rizatriptan versus sumatriptan demonstrated comparable efficacy of rizatriptan 5 mg with sumatriptan 50 or 100 mg with evidence of a superior effect of rizatriptan 5 mg for relief of nausea. Long-term efficacy of rizatriptan was compared to that of usual standard care (most commonly sumatriptan [84%]). The median percentage of attacks in which patients had pain relief at 2 hours postdose was 90%, 80% and 70% for

rizatriptan 10 mg, 5 mg, and standard care respectively [NZ MAXALT New Medicine Application approved 25 Feb 1999].

A published meta-analysis of 53 randomized, controlled, double-blinded clinical trials of triptans compared the efficacy of the seven commercially available triptans [28]. The 100 mg dose of sumatriptan was used as the reference compound. Rizatriptan 5 mg was similar to sumatriptan 100 mg for the measures of headache relief, pain-free at 2 hours, and sustained pain-free (to 24 hours post-dose). Recurrence rates, however, were lower with rizatriptan 5 mg than with sumatriptan 100 mg. The efficacy of sumatriptan 50 mg and zolmatriptan 2.5 mg was also similar to that of sumatriptan 100 mg.

3.3 Safety Compared to Sumatriptan and Zolmitritptan

The safety profiles of sumatriptan and zolmatriptan are similar to that of rizatriptan. In the above-mentioned published meta-analysis of 53 randomized, controlled, double-blinded clinical trials of triptans, most triptans were not statistically different with regard to the rates of adverse events, and the safety profile of rizatriptan 5 mg, zolmatriptan 2.5 mg, and sumatriptan 50 mg was similar to that of sumatriptan 100 mg [28; 29]. Differences in total AE rates must be interpreted carefully as they could indicate different methods of collecting and defining AEs, a study population with a higher threshold for reporting AEs, or both.

Sumatriptan 50 mg and 100 mg were compared to rizatriptan 5 mg and 10 mg in Phase III trials. The incidence of drug-related adverse events in the Phase III trials was 17% for placebo, 24% for rizatriptan 5 mg, 33% for rizatriptan 10 mg, 29% for sumatriptan 50 mg, and 41% for sumatriptan 100 mg.

The primary safety concern for all triptans is cardiovascular. Although the pharmacokinetic properties of each triptan differ, there is no evidence that any one triptan presents less of a vascular risk than another. When used in the appropriate patient population, triptans are safer than older non-migraine-specific drugs [30].

4. Local Data or Special Considerations Relating to New Zealand

4.1 Local Data Regarding the Burden of Migraine

The New Zealand Migraine Sufferers Support Group conducted a survey regarding migraine treatments and symptoms. The vast majority of respondents experienced severe symptoms during a typical attack including nausea and vomiting (80%). Forty-five percent of the respondents said they were unable to function. In this survey, it was reported that the majority of migraine sufferers preferred tablets (65%) compared with injection (27%) or nasal spray (33%). Preferences between traditional tablets and oral disintegrating tablets were not studied.

The World Headache Alliance estimates that the economic cost of migraine to New Zealand's economy to be approximately $80 million. This only includes the loss of working days and does not consider the additional cost to the health system when migraine sufferers seek medical attention [15].

4.2 Formulation Options

Currently sumatriptan 50 mg tablets and zolmatriptan 5 mg nasal spray are approved for non-prescription use in New Zealand. The approval of rizatriptan would provide migraine sufferers in New Zealand with an increase in formulation options for their migraine treatment.

There are many advantages to the oral disintegrating tablet. It will dissolve within seconds on the tongue without the need for liquids or chewing, allowing for the consumption anywhere at any time at the onset of a migraine attack, offering greater patient tolerability and convenience. Since as many as 20% of the general population has difficulty swallowing pills or prefer not to do so, the oral disintegrating tablet is an important alternative to conventional oral tablets. Rapid dissolving tablets are particularly useful for migraine patients whose nausea and/or vomiting precludes swallowing tablets and patients whose nausea and/or vomiting makes the likelihood of complete absorption unpredictable [8].

Further, there are various disadvantages to using the intranasal spray. These include nasal irritation, bitter after-taste, less discreet administration, inconsistent absorption, and variable efficacy secondary to incorrect self-administration technique [8].

5. Interactions with Other Medicines

The known drug interactions for rizatriptan can be categorized by their effect and are summarized as follows:

Increased systemic exposure of rizatriptan

Co-administration of rizatriptan with propranolol has been shown to increase plasma concentrations of rizatriptan by 70%. This increase is probably due to first-pass metabolic interaction between the two drugs, since MAO-A plays a role in the metabolism of both rizatriptan and propranolol. Concurrent administration of rizatriptan 10 mg and propranolol was permitted in the short-term parts of two of the Phase III studies. There did not appear to be an increase in adverse events, but the number of patients exposed was small. As a safety precaution, all patients taking propranolol in the extension were assigned to rizatriptan 5 mg. No concerning effects were observed in the 96 patients who received rizatriptan 5 mg concomitantly with propranolol in the extensions. Consequently, only the 5 mg dosage of rizatriptan should be used by patients taking propranolol. However, patients are permitted to take two 5 mg doses in a 24-hour period. In a drug interaction study, nadolol and metoprolol

did not alter plasma concentrations of rizatriptan [NZ MAXALT New Medicine Application approved 25 Feb 1999].

Monoamine oxidase (MAO) inhibitors have also been shown to increase the systemic exposure of rizatriptan and its metabolite. Concomitant use of rizatriptan with non-selective MAO inhibitors and MAO-A inhibitors is contraindicated [27]. This contraindication also applies to sumatriptan, which has been approved as a non-prescription drug. The NZ Data Sheet warns that concurrent administration MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated.

Potential for vasospastic reactions

Since ergot-containing drugs can cause prolonged vasospastic reactions, there is a theoretical basis suggesting that use of rizatriptan with these drugs could lead to additive vasospastic reactions. Similarly, use of rizatriptan with other 5-HT_1 agonists could theoretically lead to additive vasospastic reactions. Therefore, rizatriptan should not be taken concomitantly with other 5-HT_1 agonists or within 6 hours of ergotamine-type medications [27]. The Overdosage sections of the U.S. product circulars for the seven triptans currently marketed in the United States were reviewed for the signs and symptoms associated with overdoses, which could give an indication of potential outcome if these medications were combined. There were 2 reports of increased blood pressure with naratriptan at doses 4 to 10 times the maximum prescribed dose. Otherwise, there were no reports of adverse events consistent with vasospastic reactions for any of the other triptans even at doses that were generally several folds above the approved dosages.

Serotonin Syndrome

Serotonin syndrome is characterized by the triad of altered mental status (e.g., agitation, confusion, hallucinations), autonomic dysfunction (e.g., labile blood pressure, hyperthermia, mydriasis), and neuromuscular abnormalities (e.g., hyperreflexia, incoordination, akathisia). Its pathophysiology is not completely understood and has been believed to be caused by excess stimulation of 5-HT_{1A} receptors [31]. However, current animal models indicate that it is mediated by $5HT_{2A}$ receptors, although there may be a contribution from $5HT_{1A}$ receptors [32]. Rizatriptan is a selective 5-HT_{1B} and 5-HT_{1D} agonist with weak affinity for 5-HT_{1A} receptors and no significant activity at 5-HT_2 receptors. There have been reports of serotonin syndrome occurring during combined use of selective serotonin reuptake inhibitors (SSRIs)/ serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans although the reporting rate is very low. Shapiro and Tepper estimated the annual incidence of SSRI/triptan combination serotonin syndrome to be <0.03% which was lower than the estimated incidence due to SSRIs alone [32]. Furthermore, a sufficiently powered prospective safety study which evaluated polypharmacy and subcutaneous sumatriptan tolerability was conducted in 12,339 migraineurs [33]. SSRIs were used by 14.5% of patients and the frequency of central nervous system adverse events within 24 hours of sumatriptan administration was not increased in those who used SSRIs when compared to those who did not (~0.25%). These

data, in addition to the pharmacology of rizatriptan, demonstrate that the risk of serotonin syndrome with SSRI/triptan use is very low, if present at all.

The proposed data sheet and CMI contain adequate warnings of these interactions.

6. Contraindications

MAXALT Melt is contraindicated in patients with:

- hypersensitivity to rizatriptan or any of the ingredients
- concurrent administration of monoamine oxidase (MAO) inhibitors, or use within 2 weeks of discontinuation of MAO inhibitor therapy

Based on the mechanism of action of this class of compounds, MAXALT Melt is also contraindicated in patients with:

- uncontrolled hypertension
- established coronary artery disease, including ischaemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischaemia), signs and symptoms of ischaemic heart disease, or Prinzmetal's angina.

7. Possible Resistance

Not applicable

8. Safety Summary

This Safety Summary briefly summarizes the extensive data with prescription rizatriptan. Rizatriptan was first approved on 21-January-1998 in Mexico as a prescription drug for the acute treatment of the headache phase of migraine attacks and has been registered and approved in 72 countries, including New Zealand. There is a wealth of safety information available from clinical trials and spontaneous reports received during prescribed use of rizatriptan 5 and 10 mg doses. These data clearly establish the safety of rizatriptan. Of note, the safety profile of rizatriptan 5 mg is comparable to placebo.

8.1 Postmarketing Data

8.1.1 Market Experience

MAXALT® was first approved (in Mexico) on 21-Jan-1998 and was approved in New Zealand on 20-Feb-1999; it is currently registered and approved in 72 countries. MAXALT® is available in two dosage strengths, 5 mg and 10 mg, and each dosage is available in two formulations: tablet and orally disintegrating tablet (wafer). As of 20-Jul-2009, a total of 25,189,815 five mg tablets / orally disintegrating tablets (wafers) and 376,451,400 ten mg tablets / orally disintegrating tablets (wafers) have been distributed. If one assumes that a

'typical' patient with migraine will have three attacks per month and will require 1.5 doses per attack (for a total of 54 doses per year), then the worldwide patient exposure is estimated to be 466,478 patient-years for 5 mg rizatriptan and 6,971,322 patient-years for 10 mg rizatriptan (for a total of over 7.4 million patient-years) [34; 35; 36; 37; 38; 39].

8.1.2 Summary of Postmarketing Safety Data

Merck & Co., Inc. maintains a database of all adverse experiences spontaneously reported to the company during marketed use of its products. This Worldwide Adverse Experience System (WAES) offers the opportunity to monitor adverse experiences that have occurred during the extensive marketed use of prescription rizatriptan since 1998. This is a voluntary reporting system and therefore data are often incomplete. However, the ability to monitor, even in a limited way, the large population that has been exposed to rizatriptan is a valuable tool to detect infrequent and previously unrecognized adverse experiences associated with the drug. Review of these data confirms that rizatriptan is generally well tolerated outside of the clinical trial setting.

The information presented in Table 1 shows the AE profile of rizatriptan by System Organ Class (SOC). In many of the SOCs presented there are a very small number of reports. The information presented does not raise any new safety concerns.

Table 1
Summary Tabulation of Spontaneous Reports Received from Health Care Providers for Rizatriptan Benzoate

System Organ Class	Reports Received from Market Introduction to 20-Jul-2009 (% of total reports)[±]
Blood and lymphatic system disorders	8 (<1)
Cardiac disorders	192 (8)
Congenital, familial and genetic disorders	9 (<1)
Ear and labyrinth disorders	36 (1)
Endocrine disorders	4 (<1)
Eye disorders	73 (3)
Gastrointestinal disorders	412 (17)
General disorders and administration site conditions	762 (32)
Hepatobiliary disorders	5 (<1)
Immune system disorders	26 (1)
Infections and infestations	20 (1)
Injury, poisoning and procedural complications	347 (15)
Investigations	101 (4)
Metabolism and nutrition disorders	19 (1)
Musculoskeletal and connective tissue disorders	174 (7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6 (<1)
Nervous system disorders	786 (33)
Pregnancy, puerperium and perinatal conditions	26 (1)
Psychiatric disorders	168 (7)

Renal and urinary disorders	26 (1)
Reproductive system and breast disorders	30 (1)
Respiratory, thoracic and mediastinal disorders	159 (7)
Skin and subcutaneous tissue disorders	196 (8)
Social circumstances	27 (1)
Surgical and medical procedures	11 (<1)
Vascular disorders	111 (5)
DISTINCT NUMBER OF REPORTS	2372

* Note numbers of reports do not add up to totals because the same report can include more than one Adverse Drug Reaction.

[34; 35; 36; 37; 38; 39]

8.2 Clinical Adverse Events During Short-Term Treatment in Phase III – Oral Disintegrating Tablet

The most common types of clinical adverse events following treatment in the Phase III study of the oral disintegrating tablet were dizziness, nausea, dry mouth, and somnolence. The incidence of drug-related clinical adverse events for rizatriptan 5-mg oral disintegrating tablet were 35%, which was equal to placebo (35%), while the rizatriptan 10-mg oral disintegrating tablet was 45% Clinical adverse events were typically mild or of moderate severity and short-lasting.

9. Potential for Abuse or Misuse

Triptans have no known abuse potential. No abuse, tolerance, withdrawal, or drug-seeking behavior has been observed in patients treated with rizatriptan in clinical studies. No association between these behaviors and use of rizatriptan has been established by post-marketing adverse experience reporting. Also, since triptans have no other pharmacologic action other than to relieve migraine headaches, misuse for other conditions, including non-migraine headache, is extremely unlikely.

10. Conclusion

Migraine is a common neurological disease usually characterized by attacks of unilateral moderate or severe headache, and associated with nausea, vomiting, photophobia and/or phonophobia. A focal neurological disturbance, known as aura, may precede the headache in about 20% of the migraine attacks [40]. The total number of migraine patients is estimated to be 65 million worldwide. The average migraine patient experiences 1 to 3 attacks per month. During migraine attacks at least one third of patients are severely disabled and require bed rest. Therefore, migraine has a direct impact on work loss and social life [25]. Reducing the burden of migraine and increasing the treatment opportunities has been recognized as a public health priority [25].

The information summarized in this document demonstrates that the 5-mg dose of rizatriptan is safe and efficacious. If the label is followed, there are no risks that would require a physician to monitor use of rizatriptan in patients previously diagnosed to suffer from migraine. The 5-mg dose of rizatriptan has an adverse-effect profile that is similar to

placebo. Triptans are not effective against tension headache, so there is minimal risk of patients treating non-migraine headaches with an OTC triptan such as rizatriptan.

According to the data, the current benefit/risk of rizatriptan 5 mg supports the change in prescription status of MAXALT® (rizatriptan benzoate 5 mg) from prescription only to non-prescription.

11. Literature References

Literature References

Literature References

1. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention Study. Headache 2007;47:355-63.

2. Wenzel R, Dortch M, Cady R, Lofland JH, Diamond S. Migraine headache misconceptions: barriers to effective care. Pharmacotherapy 2004;24(5):638-48.

3. Zed PJ, Loewen PS, Robinson G. Medication-induced headache: overview and systematic review of therapeutic approaches. Ann Pharmacother 1999;33:61-72.

4. World Health Organization. Fact Sheet No 277: Headache Disorders, World Health Organization, March 2004. http://www.who.int/mediacentre/factsheets/fs277/en/ [accessed 16-Nov-2009],

5. Ahrens SP, Farmer MV, Williams DL, Willoughby E, Jiang K, Block GA, et al. Efficacy and safety of rizatriptan wafer for the acute treatment of migraine. Rizatriptan Wafer Protocol 049 Study Group. Cephalalgia 1999;19(5):525-30.

6. Pascual J, Bussone G, Hernandez JF, Allen C, Vrijens F, Patel K. Comparison of preference for rizatriptan 10-mg wafer versus sumatriptan 50-mg tablet in migraine. Eur Neurol 2001;45(4):275-83.

7. Cutler NR, Jhee SS, Majumdar AK, McLoughlin D, Brucker MJ, Carides AD, et al. Pharmacokinetics of rizatriptan tablets during and between migraine attacks. Headache 1999;39(4):264-9.

8. Gladstone JP, Gawel M. Newer formulations of the triptans: advances in migraine management. Drugs 2003;63(21):2285-305.

9. Silberstein SD. Migraine. Lancet 2004;363:381-91.

10. Bigal ME, Lipton RB, Krymchantowski AV. The medical management of migraine. Am J Ther 2004;11(2):130-40.

11. World Health Organization. World health report 2001: Mental health: new understanding, new hope. Geneva, 2001.

12. Breslau N, Schultz LR, Stewart WF, Lipton RB, Lucia VC, Welch KMA. Headache and major depression: is the association specific to migraine? Neurology 2000;54:308-13.

13. Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy. Headache 1999;39(Suppl 2):S20-S26.

14. Cady RK, Sheftell F, Lipton RB, O'Quinn S, Jones M, Putnam DG, et al. Effect of early intervention with sumatriptan on migraine pain: Retrospective analyses of data from three clinical trials. Clin Ther 2000;22(9):1035-48.

15. World Headache Alliance. Migraine in New Zealand 1999, World Headache Alliance, 1999. http://www.w-h-a.org/index.cfm?spKey=archive&spId=C1F6FBA0-FC10-59AD-EC042A315A6FED94&highlight=new%20zealand [Accessed 16-Nov-2009],

16. Saper JR. What matters is not the differences between triptans, but the differences between patients. Arch Neurol 2001;58(9):1481-2.

Literature References

17. Tfelt-Hansen P, Steiner TJ. Over-the-counter triptans for migraine: what are the implications? CNS Drugs 2007;21(11):877-83.

18. Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak JI. Cost benefit of sumatriptan to an employer. J Occup Environ Med 1997;39(7):652-7.

19. Lipton RB, Liberman JN, Kolodner KB, Bigal ME, Dowson A, Stewart WF. Migraine headache disability and health-related quality-of-life: a population-based case-control study from England. Cephalalgia 2003;23(6):441-50.

20. Lipton RB, Bigal ME, Kolodner K, Stewart WF, Liberman JN, Steiner TJ. The family impact of migraine: population-based studies in the USA and UK. Cephalalgia 2003;23(6):429-40.

21. Wenzel RG, Lipton RB, Diamond ML, Cady R. Migraine therapy: a survey of pharmacists' knowledge, attitudes, and practice patterns. Headache 2005;45(1):47-52.

22. Rapoport AM, Bigal ME. ID-migraine. Neurol Sci 2004;24(Suppl 3):S258-S260.

23. Diener HC, Kaube H, Limmroth V. A practical guide to the management and prevention of migraine. Drugs 1998;56(5):811-24.

24. Lipton RB, Scher AI, Steiner TJ, Bigal ME, Kolodner K, Liberman JN, et al. Patterns of health care utilization for migraine in England and in the United States. Neurology 2003;60(3):441-8.

25. Diener H-C, Dowson A, Whicker S, Bacon T. Development and validation of a pharmacy migraine questionnaire to assess suitability for treatment with a triptan. J Headache Pain 2008;9:359-65.

26. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. Drugs 2000;60(6):1259-87.

27. New Zealand Package Insert: MAXALT® (rizatriptan benzoate 5 mg and 10 mg tablets) and MAXALT® Melt (rizatriptan benzoate 5 mg and 10 mg wafers): March 2008.

28. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358:1668-75.

29. Dahlöf CGH, Dodick D, Dowson AJ, Pascual J. How does almotriptan compare with other triptans? a review of data from placebo-controlled clinical trials. Headache 2002;42:99-113.

30. Jamieson DG. The safety of triptans in the treatment of patients with migraine. Am J Med 2002;112:135-40.

31. Martin TG. Serotonin syndrome. Ann Emerg Med 1996;28(5):520-6. http://www.sciencedirect.com/science/article/B6WB0-4HGF712-B/2/05835509d5c102b9f600501fc7a983f1

32. Shapiro RE, Tepper SJ. The serotonin syndrome, triptans, and the potential for drug-drug interactions. Headache 2007;47:266-9.

Literature References

33. Putnam GP, O'Quinn S, Bolden-Watson CP, Davis RL, Gutterman DL, Fox AW. Migraine polypharmacy and the tolerability of sumatriptan: a large-scale, prospective study. Cephalalgia 1999;19:668-75.

34. Memo to file from Replogle A: WAES data: comparison of AE reports received during prior renewal period with the current renewal period, 2009.

35. MRL Periodic Safety Update Report: Rizatriptan Benzoate, MSD: 21-Jan-2007 to 20-Jul-2007, 03-Aug-2007.

36. MRL Periodic Safety Update Report: Rizatriptan Benzoate, MSD: 21-Jul-2007 to 20-Jan-2008, 04-Feb-2008.

37. MRL Periodic Safety Update Report: Rizatriptan Benzoate, MSD: 21-Jan-2008 to 20-Jul-2008, 04-Aug-2008.

38. MRL Worldwide Product Safety Report: Rizatriptan Benzoate, MSD (Periodic Safety Update Report 22) 21-Jul-2008 to 20-Jan-2009, 03-Feb-2009.

39. MRL Worldwide Product Safety Report: Rizatriptan Benzoate, MSD (Periodic Safety Update Report 23): 21-Jan-2009 to 20-Jul-2009, 03-Aug-2009.

40. Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. Headache 2005;45(Suppl 1):S3-S13.