AstraZeneca

Submission for

Reclassification from

Prescription Medicine

to

Pharmacist Only Medicine

Zomig® (Zolmitriptan)

AstraZeneca Limited

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Auckland

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Executive Summary

Migraine is a common condition, approximately 3 times more common in women than in men and is estimated to affect 10% to 15% of the worldwide population. Migraines are characterised by neurological, gastrointestinal (nausea and or vomiting) and autonomic symptoms such as photophobia and phonophobia. Attacks usually last between 4 and 72 hours.

The chronic and debilitating nature of migraine, with attacks that occur unpredictably and unexpectedly, can impede patients' ability to carry on with normal activities of daily living, thereby reducing their quality of life. Emotional distress, depression, reduced vitality, disturbed sleep and anxiety at the prospect of future attacks are all common. Such effects can be minimised through adequate provision of an effective, acute migraine medication.

Migraine is also debilitating from an economic perspective as it imposes an enormous health burden on society. Lost work and productivity account for 80-89% of the economic burden of migraine[i].

Conventional oral tablets are effective and convenient for many migraine patients; however, following oral administration, drug absorption during migraine attack may be impaired by gastric stasis. In addition, nausea and vomiting associated with migraine may preclude oral administration. Non-oral formulations overcome these limitations, and offer patients additional benefits in terms of speed of onset of action. Subcutaneous administration is an alternative option, providing fast onset of efficacy and intra-patient consistency, but many patients are reluctant to self-inject.

Zomig Nasal Spray overcomes some of the limitations of oral administration, providing rapid absorption directly across the nasal mucosa resulting in a fast onset of action with out the associated side effects of injection.

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Zomig Nasal Spray offers patients a fast, highly effective and non-invasive alternative to the conventional oral tablet. Data presented in this submission indicates that zolmitriptan nasal spray has significant nasopharyngeal absorption and is rapidly detectable in plasma following dosing. Clinical trials demonstrate a fast onset of action, high and sustained efficacy, and a good tolerability profile.

The potential of zolmitriptan as a Restricted Medicine has been established with the recent approval of sumatriptan as a Restricted Medicine (Gazette Notice dated 14 September 2006).

Zolmitriptan and sumatriptan both belong to the same class of compounds known as serotonin (5-hydroxytryptamine [5-HT]) receptor agonists otherwise know as “triptans”. The pharmacological mechanisms of action of zolmitriptan and sumatriptan are similar[i].

On evaluation of the OTC sumatriptan application the Medicines Classification Committee agreed that sumatriptan would be suitable for OTC sale as migraines are a self-limiting condition and once the condition had been correctly diagnosed it was easily recognised by the consumer.

Due to the extensive safety evaluation undertaken by the UK MHRA for sumatriptan, the committee was satisfied that the safety profile for sumatriptan was acceptable for OTC sale.

In a published review of zolmitriptan[ii], the authors concluded that the adverse event profile of oral zolmitriptan 5 mg versus sumatriptan 100 mg were very similar. The two drugs didn’t differ with respect to the incidence of potential CNS related adverse events. In a separate review of OTC Triptans[iii], Tfelt-Hansen reported that the safety of triptans are equally similar when used in the recommended dose range.

The Medicines Classification Committee did request that the OTC sale sumatriptan product contain the following specific warnings:

- Use of product with irregular heartbeat
- Use with allergy to sulfonamides
- Use with other migraine medicines

These statements are included in the proposed datasheet and CMI for Zomig Nasal Spray.

The recommendations made by the MCC regarding the sumatriptan application have been applied to this application in respect to the proposed indication, contraindications and possible cross allergy to sulfonamides and the use of the Migraine Treatment Questionnaire.

As oral administration can be associated with limited efficacy and issues in administration in some patients, a nasal spray formulation available OTC offers a novel, convenient, and reliable method of dosing.

Zolmitriptan is a suitable candidate for reclassification as a restricted medicine based on the similarities to sumatriptan.

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PART A

1. International Non-proprietary Name of the Medicine

Zolmitriptan

2. Proprietary Name(s)

Zomig Nasal Spray

3. Company Requesting Reclassification

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4. Dose Form(s) and Strength(s)

Dose form: Nasal Spray Solution Strength: 5 mg

5. Pack Size and Other Qualifications

Nasal Spray: One pre-filled nasal spray device in a cardboard carton.

6. Indications for Which Change is Sought

Zomig Nasal is indicated for the acute treatment of migraine with or without aura. Zomig Nasal should only be used where there is a clear diagnosis of migraine.

7. Present Classification of Medicine

Prescription Only Medicine

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8. Classification Sought

Pharmacist Only Medicine

9. Classification Status in Other Countries

Zolmitriptan 5 mg Nasal Spray:

Sweden:
OTC Date of approval: December 2007
(Classification equivalent to Pharmacy Only Medicine)

Sumatriptan 50 mg Tablets:

United Kingdom
OTC Date of approval: 2006

New Zealand
OTC Date of approval: 14 February 2008

Naratriptan 2.5 mg Tablets

Germany
OTC Date of approval: 2006

10. Extent of Usage in NZ and Elsewhere

Due to the lack of government funding despite a positive recommendation from PTAC, Zomig has not been marketed in New Zealand. Zomig was first approved in Sweden in March 1997. As of March 2008, zolmitriptan has been approved in 93 countries for the treatment of migraine with or without aura. Zomig Nasal Spary is approved in more than 20 countries and is marketed in various European countries (including Austria, Germany, and the UK) and the USA.

It is estimated that a total of 16 million patients have been exposed to zolmitriptan[iv].

Since launch of Zomig Nasal in 2002, more than 8 million doses have been sold world wide and 97% of these have been Zomig Nasal 5 mg.

Table 1: YTD Sales Data: September 2008 ($US millions)

Country	Tablet Formulation	Nasal Formulation
USA	$102.1	$12.3
France	$18.6	-
Germany	$5.6	$2.6
Spain	$3.4	$0.7
United Kingdom	$2.7	$1.8
Sweden	$3.0	$2.6
Italy	$2.2	-
Switzerland	$1.7	$0.6
Japan	$9.6	-
South Africa	$0.3	-

11. Proposed Labelling and Patient Information Leaflet

Refer Appendix 1 for draft carton labelling and CMI (pack insert). Please note that the actual design of the label is to be determined, the draft carton is provided to indicate text.

12. Proposed Warning Statements (to be included in pack insert)

Warning statements advising patients when not to take Zomig Nasal Spray are listed in on the proposed CMI (refer Appendix 1) and proposed datasheet (refer Appendix 2). Conditions and concomitant medication which the pharmacist needs to be aware of are listed the proposed CMI. Significant warning statements will also be included on the proposed carton (Refer Appendix 1)

13. Other Products Containing the Same Active Ingredient(s) and which would be affected by the Proposed Change

None.

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PART B

1. Expected Benefits to Consumer and public

Sumatriptan 50 mg tablets in packets of 2 are currently available as a Pharmacist Only Medicine for oral use for the relief of migraine attacks with or without aura in patients who have a stable, well established pattern of symptoms.

Up until the recent reclassification of sumatriptan 50 mg tablets to Pharmacist Only Medicine migraine sufferers have had to present to the GP for a prescription to receive treatment with a triptan. However those that require non-oral formulations due to gastrointestinal disturbances associated with migraines are still required to consult a GP. It is certainly the case that the perceived inconvenience of a visit to the physician for "just a headache" often drives patients to sub-optimal, 'over the counter' preparations and away from the most appropriate treatment for their disease. Such under-utilization of migraine-specific treatment not only leads to unnecessary disability and dissatisfaction.

Benefits to Consumer

Reclassifying Zomig Nasal to Restricted medicine in addition to sumatriptan tablets benefits the consumer by:

- providing a wider choice of triptan formulations available OTC.
- providing an alternate treatment to those who do not respond to sumatriptan[v] or other OTC migraine medication
- providing an OTC treatment which is rapidly absorbed
- providing an alternate OTC triptan to those who experience GI disturbances which limits the effectiveness of a tablet formulation.

Providing a wider choice of OTC triptans.

Increasing the triptan options available without prescription potentially encourages more patients to use a more effective treatment, which in turn may potentially improve migraine management.

Patients who are less seriously afflicted by migraine are less likely to visit their GP for prescription treatments. The addition of Zomig Nasal Spray as a restricted medicine in addition to sumatriptan tablets provides this groups of patients with easier access to an effective treatment.

Providing an alternate triptan treatment.

Not all patients respond to sumatriptan treatment. Inclusion of Zomig Nasal without prescription, provides pharmacists with alternatives to those who do not respond to sumatriptan.

Providing a non-oral formulation without prescription for those who suffer from GI disturbances

Gastrointestinal disturbances such as gastric stasis during a migraine attack affect the absorption of oral dosage forms leading to erratic or non-existent absorption of medication. Nausea and vomiting can lead to patient inability to ingest oral medication.

In a survey of 500 migraine patients, it was found that nausea occurred in 90% of all migraine patients, whilst vomiting occurred in 70% of patients. Nearly one third of patients experienced nausea over the majority of migraine attacks. Nearly one third of patients experienced vomiting over the majority of migraine attacks[vi]. Of the patients who experienced nausea, 30.5 % indicated that it interfered with their ability to take oral medication and of those who experience vomiting 42.2% indicated that it interfered with their ability to take orally administered medication.

Absortpion of Zomig Nasal Spray bypasses the gastric system which is characteristically affected by migraine.

Providing an alternate non-oral triptan formulation.

The only non-oral triptan available in New Zealand is sumatriptan injection which is only available via prescription. Despite the rapid onset of action, injections are seen to be difficult and more painful and people would obviously prefer an alternative method of drug delivery than injection. Sumatriptan injection is also associated with dose form adverse reactions such as injection site reactions.

Administration of Zomig Nasal Spray is much less painful than injection and can be used discretely.

Benefits of Zomig Nasal Spray.

Rapid Absorption

Zomig Nasal Spray is more rapidly absorbed than oral tablets. Detectable levels of zolmitriptan are present within plasma between 2 and 5 minutes after nasal administration compared with 10 minutes after oral administration. A PET study revealed zolmitriptan was present in the central nervous system after 5 minutes following intranasal administration[vii]. Ten minutes after administration, Zomig Nasal Spray has achieved 38% of maximum plasma concentration (C_{max})[vii]. Although the absorption is more rapid, comparative AUC values show that total patient exposure is similar for the nasal spray and oral tablet formulation[vii].

Rapid Onset of Action

Significant pain-free rates were observed in patients as early as 15 minutes post dosing with Zomig Nasal Spray compared with placebo ($p<0.001$)[viii].

Gawel et al[ix] demonstrated significant headache response at 10 minutes post dose compared with placebo ($p=0.0079$), and significantly higher pain free rates from 30 minutes post dosing ($p=0.0039$)[ix]

Charlesworth et al[x] confirmed these findings in a with significant headache response at 15 minutes post dose compared with placebo ($p=0.00115$) and significant pain-free outcomes at 30 minutes post dose ($p<0.005$)[x].

Zomig Nasal Spray is a convenient, easy to use medication that patients can self administer with ease and has no impact on GI disturbances with a fast onset of action.

Benefits to Public

A research report by Colmar Brunton published in 1999[xi], estimated the economic cost of migraine to New Zealand economy at $80 million based on an estimated 700,000 lost working days. This figure does not account for the additional cost to the health system when migraine sufferers seek medical help.

Migraine sufferers are typically absent from work, or have reduced effectiveness while at work. Migraines also impact on home and social activities.

The availability of a fast acting non-oral treatment which doesn't require presentation to a GP increases treatment options available to the consumer and permits fast access to an effective treatment via a pharmacy. This in turn potentially allows the migraine sufferer to return to normal activity more rapidly. Reclassification of Zomig Nasal Spray increases the opportunity for potential cost savings associated with resuming productivity faster. In addition, quick access to an effective treatment such as Zomig Nasal Spray may encourage patients to medicate early on the initial onset of symptoms potentially improving efficacy and reducing severity of an attack.

Easy access to Zomig Nasal Spray via a pharmacist in addition to sumatriptan tablets may encourage more patients to use triptans and thereby, improve migraine management in general. In addition, the ability to educate consumers at a Pharmacy level by way of counselling and the Migraine Treatment Questionnaire ensures that migraine sufferers become more aware of their condition and are able to self-diagnose more rapidly and receive appropriate treatment which in turn would benefit their overall quality of life.

Results of a small observational study[ii] in 32 patients who treated at least 10 migraine attacks with zolmitriptan showed that it greatly reduced disruption to normal activities caused by migraine. Prior to zolmitriptan therapy the total number of days absent from work was 85 due to migraine. After zolmitriptan treatment was started this was reduced to only 13.5 days (3.86 vs 0.61 days per patient). Patients also predicted that they would visit their doctor less frequently than in the past if using zolmitriptan.

The availablility of Zomig Nasal Spray via a Pharmacist potentially reduces the economic burden of migraine by providing quick access to an effective treatment which isn't affected by GI disturbances and reduces the need for sufferers to seek medical assistance.

2. What Migraine Sufferers want from a treatment

Results from a large survey[xii] show that the three most important attributes for a migraine treatment are:

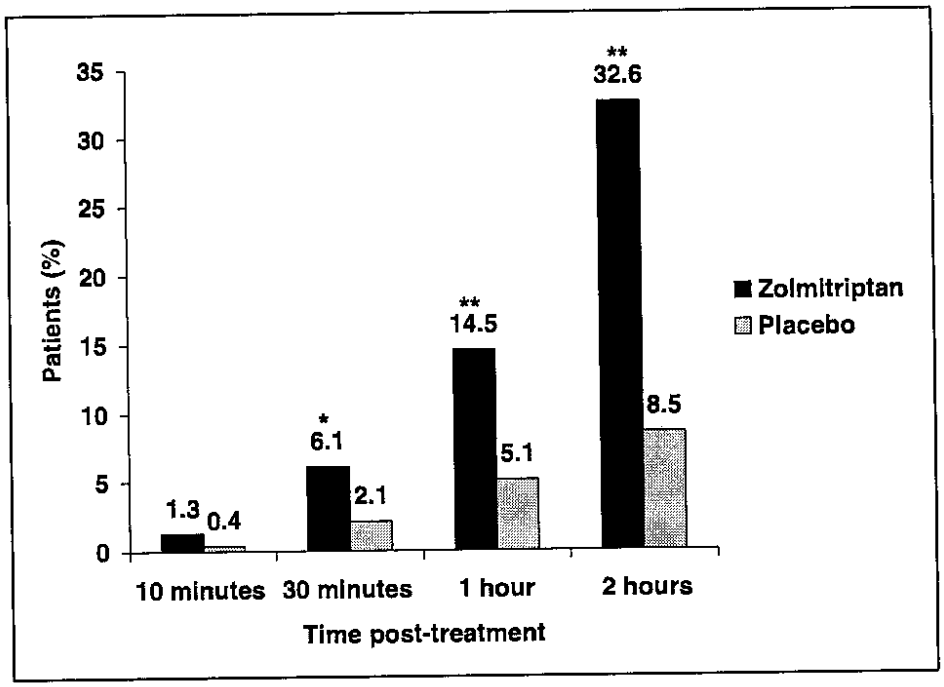
- complete pain relief (87%)
- lack of recurrence (86%)
- rapid onset of pain relief (83%)

Complete Pain Relief

Zomig Nasal Spray is superior in achieving pain-free outcomes compared to placebo and zolmitriptan 2.5 mg tablets. Charlesworth et al[x] reported significant differences of patients pain-free at 30 and 45 minutes and at 1, 2 and 4 hours post dose with Zomig Nasal Spray compared to placebo and at the 30 and 45 minute time points zolmitriptan 2.5 mg tablets. In addition, pain reduction (at least a 1-point decrease in headache intensity) was significantly improved with Zomig Nasal Spray 5 mg when compared to zolmitriptan 2.5 mg tablets at all time points between 15 minutes and 2 hours post dose.

Gawel et al[ix] confirmed Charlesworth's results with significant total symptom relief at 1 hour post dose of Zomig Nasal Spray 5 mg (see Figure 1) compared to placebo. The difference between Zomig Nasal Spray 5 mg and placebo was significant from 30 minutes post dose, with approximately one-third of patients experiencing total symptom relief by 2 hours post dose. Two-hour symptom relief was also superior with Zomig Nasal Spray in patients with differing baseline headache intensities such as mild (61.3% vs 15.8%) moderate (33.2% vs 9.0%), or severe (23.9 vs 4.8%).

Figure 1 – Total Symptom Relief Rates up to 2 hours post-dose
***p<0.01; p<0.0001.**



Lack of Recurrence

Charlesworth et al[x] also reported that a complete headache response (defined as a 2-hour headache response, no recurrence and no use of escape medication with 24 hours) was reported for 49.2% of attacks in patients receiving Zomig Nasal Spray 5 mg. In addition, Zomig Nasal Spray 5 mg enabled resumption of normal activities in a greater percentage of attacks at all time points compared with the zolmitriptan 2.5 mg tablets in patients who experienced limitations of normal activity at baseline.

In a separate study, Charlesworth et al[xiii] reported that 70% of patients were treated successfully with a single dose of Zomig Nasal Spray 5 mg. Seventy one percent of these patients were pain free by 2 hours.

Rapid Onset of Pain Relief

The speed of onset with respect to headache relief is very fast with Zomig Nasal Spray. Charlesworth et al[x] reported significant differences in headache response rates observed from as early as 15 minutes compared to placebo (10.6% vs 5.1%). Subsequent time points up to 4 hours were also significantly higher than for placebo. When compared to

zolmitriptan 2.5 mg oral tablets, Zomig Nasal Spray 5 mg was significantly more effective at 15, 30 and 45 mintues and at 1 and 2 hours[x].

Tolerability

Efficacy of zolmitriptan appears to be maintained following repeated administration for multiple attacks of migraine over a prolonged period of time (≤1 year), with high headache response rates reported over all attacks[ii]. A long term study evaluating efficacy and tolerability by Adelman et al[xiv] demonstrated that 67% of patients who treated five or more attacks with zolmitriptan 5 mg orally reported it to be effective in 80% to 100 % of attacks. Therefore, zolmitriptan 5 mg is effective in 4 out of 5 attacks in the majority of patients.

Patient Treatment Preference

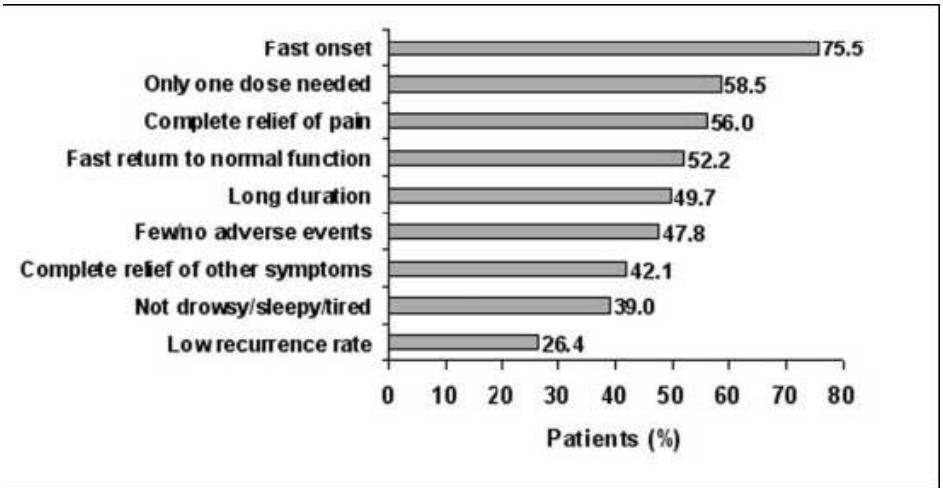
In a Swedish study of treatment preference in clinical practice, patients were invited to treat up to 6 migraine attacks with 5 mg of Zomig Nasal Spray. Data from 232 patients were analysed. Most patients (89%) were already using a triptan as migraine treatment. The majority of patients (68.5%) wished to continue using Zomig Nasal spray; the most common reason being its fast onset of action. Almost half of the patients (47.8%) wishing to continue with Zomig Nasal spray reported few or no adverse events as a motivating reason. Of patients currently using sumatriptan nasal spray, tablet or injection, 90.9%, 74.2% and 70.6%, respectively, wanted to continue using Zomig Nasal spray. Most patients were satisfied with, and wished to continue using, Zomig Nasal spray[xv].

Patient preference and treatment satisfaction were also assessed in a large post marketing surveillance study conducted in Germany in 638 health care centres. The study aimed to evaluate the efficacy and tolerability and to assess the patient satisfaction with Zomig Nasal Spray among 1838 patients (84.8% female). Within 30 minutes of administration of Zomig Nasal spray, 85.0% of patients reported improvements in headache pain, with 25.1% reporting an improvement within 10 minutes. At 1 hour post-dose, 57.9% of patients were pain free and 61.7% were able to resume usual daily activities. Most patients (72.9%) rated Zomig Nasal spray as ‘better’ than previous therapy. The majority (88.8%) expressed a wish to continue using Zomig Nasal spray. Physicians evaluated the efficacy of Zomig Nasal spray as ‘excellent’ or

'good' in 89.4% of patients. Tolerability was evaluated as 'excellent' or 'good' in 91.6% of patients[xvi].

In the figure below, patients reasons are rated for wishing to continue using Zomig Nasal Spray 5mg.

Figure 2 - Patients' reasons for wishing to continue using Zomig Nasal spray for the acute treatment of migraine attacks (n=159)



Overall Zomig Nasal Spray has a good efficacy profile and undoubtedly would be of great benefit of making it available without prescription.

3. Ease of diagnosis

Self-diagnosis

In the minutes of the 35th Medicines Classification Committee meeting commenting on the sumatriptan OTC application, the committee noted that migraines once correctly diagnosed are easily recognisable by the consumer.

As with sumatriptan OTC it is proposed that the use of OTC Zomig be restricted to those patients who have been diagnosed with a history of migraine by either a doctor or by a Pharmacist using the Migraine Treatment Questionnaire.

Diagnosis by Pharmacist

The ability of a pharmacist to diagnose migraine is well established and further supported by the OTC reclassification of sumatriptan.

Pharmacy training and support materials will include the following.

Migraine Questionnaire

A questionnaire based on that for sumatriptan will be provided (refer to Appendix 3 for contents). This will allow pharmacists to confirm or establish a diagnosis of migraine and assess the suitability of the consumer for treatment with zolmitriptan.

Pharmacist Training

AstraZeneca will, in collaboration with relevant professional bodies, produce a package of educational materials to further assist pharmacist in the diagnosis and treatment of migraine. This will include a simple algorithm to differentiate patients with serious risk factors or symptoms from those who are suitable candidates for treatment with Zomig Nasal Spray. The algorithm and treatment guidelines will be based on the comprehensive Practice Guidelines developed for the introduction of OTC sumatriptan in the UK by the Royal Pharmaceutical Society of Great Britain (refer Appendix 4). This will ensure that pharmacists will be sufficiently trained to restrict sales to patients who can safely benefit from Zomig Nasal Spray.

Tfelt-Hansen[iii] raised potential issues of OTC use with triptans which included:

- Treatment of headaches that are not migraines
- Treatment too early or late to be effective
- Potential for overuse. Frequent intake of triptans (> 10 days per month) may, overtime lead to an increase in migraine attack frequency.

These issues are addressed with the use of the migraine questionnaire, CMI and clear diagnosis prior to treatment.

4. Relevant Comparative data for like compounds

Pharmacology

The pharmacological mechanisms of action of zolmitriptan and sumatriptan are similar. The bioavailability of 100 mg oral sumatriptan is less than that of 2.5 mg oral zolmitriptan (14% vs 39%, respectively) This can be partially explained by the more lipophilic nature of the zolmitriptan. LogDpH7.4 is a measure of lipophilicity and increasing values indicate greater lipid solubility[xvii].

All triptans are metabolised in the liver. Sumatriptan is metabolised by monoamine oxidase-A MAO-A which is found in the liver and gastrointestinal tract. Zolmitriptan is also metabolised by MAO-A; however, it is also metabolised by CYP1A2 isoenzyme. Zolmitriptan is metabolised to 3 major metabolites one of which (N-desmethyl metabolite) is 2-6 times more potent than the parent compound. It is very likely to contribute to the overall efficacy of zolmitriptan[i].

Efficacy

Zolmitriptan 5 mg had similar efficacy to sumatriptan 100 mg when used for the treatment of a single migraine attack, however it was generally more effective than sumatriptan 25 and 50 mg when given for the acute treatment of multiple attacks in single trials[ii].

In a meta-analysis of 53 trials, zolmitriptan 2.5 mg and 5 mg was shown to be equivalent in efficacy to oral sumatriptan 100 mg[xviii].

Safety

Zolmitriptan is well tolerated with an adverse event profile similar to that of all triptans. When compared with sumatriptan no important differences were evident[ii].

Triptans are vasoconstrictors and thus have the potential to cause serious cardiovascular events. Tfelt-Hansen[iii] reported that the incidence of serious cardiovascular events with triptans both in clinical trials and clinical practice was extremely low. This is more than likely explained by the craniovascular selectivity of of triptans.

Particular potential safety concerns with Zomig Nasal Spray arise due to known triptan class-effects. Sumatriptan is a restricted medicine in total doses of 100 mg over 24 hour period. In the datasheet for Zomig Nasal Spray, it is recommended that only one dose (5 mg) is given over a 24 hour period. The adverse event profile for oral zolmitriptan 5 mg and sumatriptan 100 mg are very similar.

Nappi et al reported that based on a very large population of patients tested during clinical trials and in post-marketing studies, triptans are safe and well tolerated when correctly used.

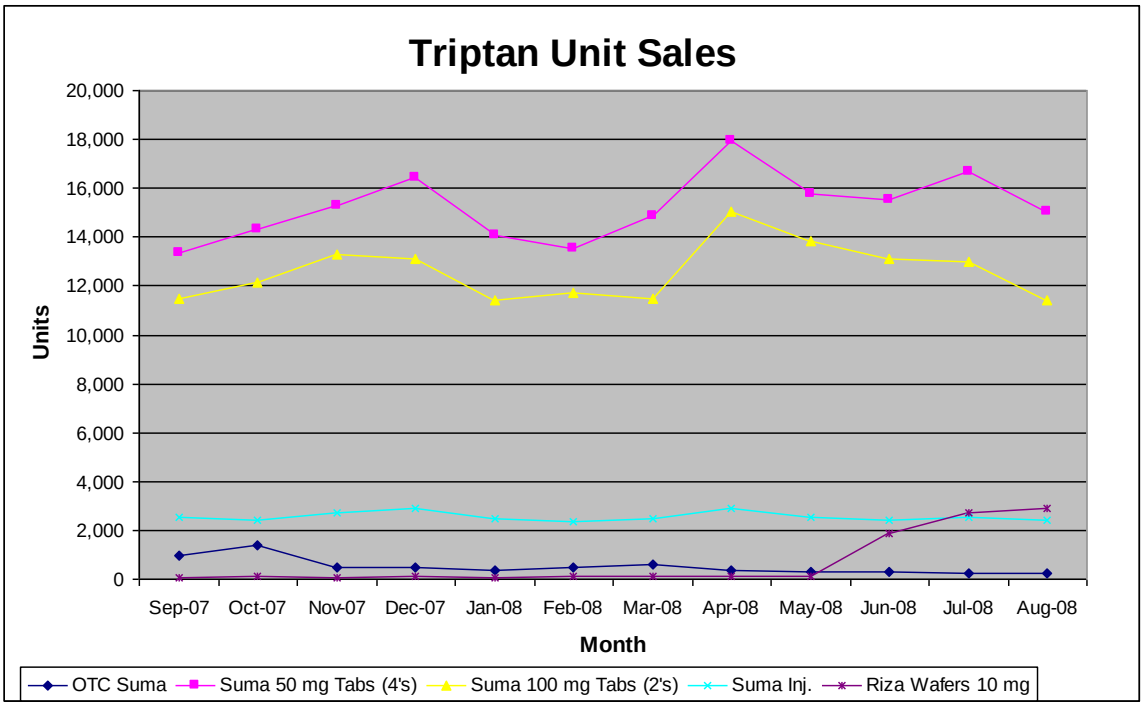
5. Local Data or special considerations relating to NZ

Feedback from NZ neurologists suggest that approximately 1/3 of patients currently taking sumatriptan tablets vomit regularly and therefore need an alternative triptan with a non-GI route of administration. In addition, feedback also suggest that 1/3 of patients currently taking the injectable form of sumatriptan don't like the side effects associated with the injection.

A report by Colmar Brunton[xi] evaluating Migraine in New Zealand noted that disorders such as migraine are not seen as "life threatening" and therefore receive low priority in the government health budget.

Since the introduction of an OTC pack in September 2007, sales of sumatriptan injection, 50 mg (4's) 100 mg (2s) have remained relatively constant indicating that the need for a non-oral formulation (See Figure 3 below). The impact of the introduction of sumitripatan OTC on the other prescription triptans is unremarkable. Rizatriptan wafers appear to impact on the prescription sumatriptan 50 and 100 mg tablet sales when after listing on the pharmaceutical schedule. Although they may appear to be easier to take than tablets, gastrointestinal disturbances will affect the absorption of the product.

Figure 3 – Triptan Sales (in units)



Oral formulations of sumatriptan are available OTC and without government restrictions on prescription. However as noted above the effectiveness of oral formulations is compromised in many migraine sufferers due to gastric disturbances. The only non-oral formulation currently available in NZ is sumatriptan injection which requires initial specialist consultation and hospital pharmacy dispensing. This product is also expensive at approximately $80.

Unit sales as displayed in Figure 3 indicate that oral formulations are currently the most widely used despite the limitations in the significant number of patients who experience gastric disturbances. This is likely due to the lack of willingness to self-inject despite a more rapid onset of action.

6. Interactions with Other Medicines

Zolmitriptan like other triptans have potential to interact with ergotamine derivatives, MAOIs and SSRIs. The proposed OTC datasheet is reflective of the interactions listed in the Practice Guidance: OTC sumatriptan published by the Royal Pharmaceutical Society

(Appendix 4), the NZ OTC sumatriptan datasheets and the prescription Zomig datasheet.

In addition the proposed Pharmacy Training Pack will include such information. The Migraine Questionnaire will also request that patients document all their current medications to ensure that appropriate consideration is given to concomitant medication when assessing patient suitability of Zomig Nasal Spray .

7. Contraindications

Contraindications are based on those already documented in the Zomig Prescription datasheet, as well as those indicated in the Practice Guidance: OTC sumatriptan published by the Royal Pharmaceutical Society (Appendix 4). They are also reflective of those in the NZ sumatriptan OTC product datasheets.

This information is included in the proposed OTC datasheet and CMI. In addition the proposed Pharmacy Training Pack will include such information as well as the Migraine Questionnaire.

8. Possible resistance

Not applicable

9. Adverse Events

Zomig Nasal Spray is well tolerated. Adverse reactions are typically mild/moderate, transient, not serious and resolve spontaneously without additional treatment.

Common adverse reactions associated with the Nasal Spray dose form are taste disturbance, epistaxis and discomfort of the nasal cavity. These are relatively mild and not serious and are common with nasal spray dose forms.

Despite the rapid appearance of the patient drug in the plasma and central nervous system after dosing with Zomig Nasal Spray, there are no significant differences in adverse effects compared to the oral formulation. This may be explained by the delayed

appearance of the active metabolite in the plasma associated with the nasal spray formulation compared to the oral tablet. Total patient exposure (AUC values) for the nasal spray and tablet formulation were similar.

Triptans have been available for over 15 years with substantial well-documented human exposure.

A significant concern with all triptans is their potential to cause coronary vasoconstriction. Ferrari et al[xviii] reviewed 53 triptan clinical trials and confirmed that there have been very few clinical reports of clinically significant myocardial ischaemia and invariably in patients with cardiovascular disease or risk factors. He concluded that triptans are very safe in appropriately selected patients.

The proposed Migraine Questionnaire together with the datasheet, CMI and Pharmacy Training tools will ensure that this at risk patient population is deemed unsuitable candidates for treatment with Zomig Nasal Spray.

Triptans are commonly also known to cause “chest-symptoms” which are characterised by tightness, heaviness, pressure and or pain in the chest, neck and or throat[i]. These can be of concern as they resemble symptoms of angina pectoris. The Pharmacy Training tools and CMI will counsel / advise patients of the possibility of these.

10. Potential for abuse or misuse.

Zolmitriptan is not a controlled-drug (psychotropic or narcotic) so no addiction or illegal use is anticipated. There is no evidence for zolmitriptan abuse and no evidence for zolmitriptan to potentiate the effects of ethanol or drugs of abuse.

The proposed Datasheet and CMI for Zomig Nasal will advise that the total intake of Zomig, in a 24 hour period, should not exceed 5 mg.

Nappi et al[i] reported that there is a potential of misuse of triptans in patients who have a high attack frequency as there had been several reports of drug-induced headache following frequent use. However Nappi et al also stated that triptans have a better

prognosis of with regard to the risk of relapse and no relationship between headache recurrence and triptan overuse has been documented.

The pack size of only one nasal spray per coupled with the migraine card issued after completion of the migraine questionnaire and the warning statements listed below limits the potential misuse in the non-prescription setting.

Patients will be advised to see their doctor if:

- their headache persists for more than 24 hours
- they experience 4 or more migraine attacks per month
- the pattern of their symptoms has changed
- their attacks have become more frequent, more persistent, or more severe, or if they do not recover completely between attacks.

11. Conclusion

Tfelt-Hansen's review of OTC triptans[iii] concluded that the availability of triptans OTC is a logical development for the better management of a common, benign, self-limiting but nonetheless burdensome condition that is grossly under treated.

The reclassification of sumatriptan in New Zealand confirms the suitability of triptans as OTC medicines considering the similarity across the class.

The availability of a non-oral triptan in the form of Zomig Nasal Spray 5 mg as a restricted medicine would further complement the currently available sumatriptan 50 mg tablets (2 pack). This will provide patients with a greater choice of dosage forms to meet the needs of patients

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