Reclassification of sumatriptan 50 mg tablets in pack sizes of two or less tablets

Present Classification:	Prescription Medicine
Sought Classification:	Restricted Medicine (Pharmacist Only Medicine)

Submission to:
Medicines Classification Committee
Medsafe New Zealand

Submission from:

GlaxoSmithKline New Zealand Ltd
trading as GlaxoSmithKline Consumer Healthcare

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SPONSOR INFORMATION

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1 EXECUTIVE SUMMARY

1.1 Purpose of the application

This application seeks to change the scheduling status of sumatriptan 50 mg tablets from a Prescription Medicine to a Restricted Medicine (Pharmacist Only Medicine) in pack sizes of two tablets or less.

1.2 Justification for reclassification

1.2.1 The burden of migraine in the community

Migraine is a common neurovascular disorder that leads to significant functional impairment.[1] Attacks are episodic and characterised by severe, throbbing, often unilateral headaches, and may be accompanied by gastrointestinal symptoms (nausea, vomiting) and sensitivity to light, sound or movement. Based on a review of population-based studies, and using diagnostic criteria for migraine established by the IHS,[2] untreated or unsuccessfully treated attacks typically last from between a few hours up to a few days, with a median duration from 9 to 24 h.[3] The median frequency of attacks ranges from 0.4 to 1.5 attacks per month.[3]

Recent data suggest that migraine may affect over 400,000 New Zealanders. A report by research company Colmar Brunton, puts the annual economic cost of migraine to New Zealand's economy at $80 million, based on an estimated 700,000 lost working days. [4]

The results from a large survey show that for migraineurs, the three most important attributes for a migraine treatment are:[5]

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

Discussion with experts in migraine and related fields has revealed that ease of access to treatment and cost also figure highly on the list of desirable attributes.

1.2.2 Sumatriptan — extensive market experience

Imigran® (sumatriptan) is a 5-hydroxytryptamine 1B/5-hydroxytryptamine 1D (5-HT_{1B}/5-HT_{1D}) receptor agonist (triptan) widely used for the treatment of migraine. Sumatriptan is marketed in more than 110 countries: it was the first triptan to be launched in 1991 (injectable form) and it is estimated that over 600 million migraine attacks have been treated with the tablet formulation worldwide.

The injectable form and 100 mg tablets were first introduced in New Zealand in 1991, with the 50 mg tablets becoming available in 1995; and Imigran® is currently available as a Prescription Medicine in two forms — tablets (50 mg, 100 mg) and injectable (6 mg/0.5 mL).

1.2.3 Sumatriptan — excellent efficacy and tolerability profiles

The triptans have been specifically developed for the effective treatment of migraine (relieving both the headache and associated symptoms such as nausea and sensitivity to light and sound).

Sumatriptan has been widely studied in a clinical programme spanning almost two decades and an extensive body of efficacy and safety information is available for this product. Studies confirm that sumatriptan reduces pain and disability due to migraine attacks and improves migraine associated symptoms such as nausea and photophobia.[6-8] Post-marketing safety data derived from treatment of approximately 800 million migraine attacks worldwide (all formulations) confirm that sumatriptan has a well established tolerability profile.

The efficacy of sumatriptan 50 mg tablets, the lowest approved oral dose in New Zealand, in the management of migraine is very well supported and an extensive clinical database attests to a high degree of efficacy against the pain and disability of migraine and its associated symptoms.

There is an extensive body of experience from clinical trials and spontaneous reports to support the safety and tolerability of sumatriptan 50 mg. Published reports and real-world experiences illustrate that the triptans do not merit fears of cardiac consequences in appropriately selected individuals.[9] Commonly occurring adverse effects are generally mild, and severe adverse effects very rare. The safety profile of sumatriptan has been well established during more than 14 years since first launch (injectable form), and safety data are presented in this application.

GlaxoSmithKline proposes that, given the extensive market experience with sumatriptan and taking into account its wide therapeutic index, an alteration of its scheduling status from Prescription to Restricted Medicine in pack sizes of two 50 mg tablets would provide appropriate consumer accessibility to a migraine-specific product.

1.2.4 Indication

Imigran® Migraine Treatment is indicated for the acute treatment of migraine attacks, with or without aura. Imigran® Migraine Treatment relieves migraine headache and the associated symptoms of nausea and sensitivity to light and sound. The availability of Imigran® Migraine Treatment would provide those consumers who have a clear diagnosis of migraine with more convenient access to a migraine-specific medication that is a well tolerated treatment with proven efficacy.

1.3 Public health benefits

Migraine is a common condition and one which has a significant impact on those who suffer from it. Recent statistical data suggest that migraine may affect over 400,000 New Zealanders. A report by research company Colmar Brunton, puts the economic cost of migraine to New Zealand's economy at $80 million, based on an estimated 700,000 lost working days.[4]

The results from a large survey show that for migraineurs, the three most important attributes for a migraine treatment are:[5]

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

Discussion with experts in migraine and related fields has revealed that ease of access to treatment and cost also figure highly on the list of desirable attributes. Non-prescription availability of Imigran® Migraine Treatment would allow Pharmacists to recommend a specific migraine treatment when it is inconvenient for a patient to seek counsel from their doctor or when they are unable to do so because of the onset of a migraine attack. Furthermore, it ensures that the philosophy behind the quality use of medicines is upheld, providing Pharmacists with the ability to educate and guide consumers on the appropriate use of medicines in order to manage their condition effectively.

Provision of Imigran® Migraine Treatment as a Restricted Medicine in a pack containing two 50 mg tablets provides Pharmacists with a new option to recommend to patients with a history of acute migraine. This, in turn, has the potential to provide significant benefits in terms of the quality use of medicines.

1.4 Initiatives to enhance the Restricted Medicine status of sumatriptan

As part of its ongoing commitment to develop Pharmacy tools to support the Restricted Medicine status of sumatriptan, GSK has consulted with relevant external bodies including the Pharmaceutical Society of New Zealand. Input will continue to be sought to ensure that all materials meet the specific needs and requirements of the New Zealand market place.

These Pharmacy tools will likely include:

- A revised Data Sheet and a Consumer Medicine Information (CMI) leaflet to ensure safe and appropriate use of sumatriptan as a Restricted Medicine.
- A validated Migraine Questionnaire to allow the Pharmacist to establish or confirm a diagnosis of migraine and assess suitability for treatment with Imigran® Migraine Treatment.
- Pharmacist and GP training/education programmes.
- Consumer education materials.

1.4.1 Pharmacovigilance

Imigran® is not a new product and there is a wealth of experience based on current prescription use. The proposed revised Data Sheet for Imigran® Migraine Treatment will be more conservative than the Prescription Medicine Data Sheet. Moreover the proposed pack size is limited to two 50 mg tablets. The Global Product Safety Group within GSK Consumer Healthcare will engage in pharmacovigilance activities for the detection of risks to the health of this new Pharmacy-based population of users. For any medicinal product with a broader availability, a positive benefit-to-risk ratio for the user is paramount.

1.5 Minimal potential for misuse of the product

The Migraine Questionnaire will provide Pharmacists with a tool to screen customers with migraine and to ensure that sumatriptan is appropriate and that it is not supplied to subjects who are contraindicated based on the proposed Data Sheet.

The proposed Data Sheet, CMI and label for Imigran® Migraine Treatment will all state that no more than two 50 mg tablets (total dose 100 mg) may be taken in any 24 h period, or to treat the same migraine attack, and that the recommended dose of Imigran® Migraine Treatment should not be exceeded. The CMI and Data Sheet will provide clear information on what to do in the event of overdose. However, it is noted that oral doses in excess of 400 mg were not associated with side effects other than those listed in the overview of safety.

The Data Sheet also includes a specific warning about the occurrence of chronic daily headache/exacerbation of headache with overuse of sumatriptan. In addition, the CMI advises migraineurs to see their doctor if:

- their typical headaches persist for longer than 24 h
- they experience four or more migraine attacks per month
- they do not recover completely between attacks
- their attacks have worsened or become more frequent, more persistent, or their symptoms have changed.

Sumatriptan has a low abuse potential. Furthermore, there are few reports of overdose or abuse and little evidence of drug-induced chronic headache with sumatriptan.

2 PART A

2.1 International non-proprietary name of the medicine

Sumatriptan succinate:

3-(2-(DIMETHYLAMINO)ETHYL)-N-METHYL-1H-INDOLE-5-METHANE SULPHONAMIDE SUCCINATE 357 (GW ACN)

indole-5-methane sulphonamide, succinate (1:1)

GR 43175C

Chemical name:
3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulphonamide

2.2 Proprietary name

Imigran® Migraine Treatment

2.3 Name of company requesting reclassification

GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue
Ermington NSW
Australia 2115

2.4 Dosage form and strength for which a change is sought

Imigran® Migraine Treatment will be marketed as oral tablets; each tablet containing 50 mg sumatriptan (as succinate) in packs of two tablets.

2.5 Pack size and other qualifications

Imigran® Migraine Treatment will be supplied in packs comprising two tablets in foil blister contained in a cardboard carton.

2.6 Indications for which change is sought

The proposed indication for Imigran® Migraine Treatment is for the acute treatment of migraine attacks, with or without aura. Imigran® Migraine Treatment relieves migraine headache and the associated symptoms of nausea and sensitivity to light and sound. Imigran® Migraine Treatment should only be used where a clear diagnosis of migraine has been made by a doctor or Pharmacist.

2.7 Present classification of medicine

Prescription Medicine

2.8 Classification sought

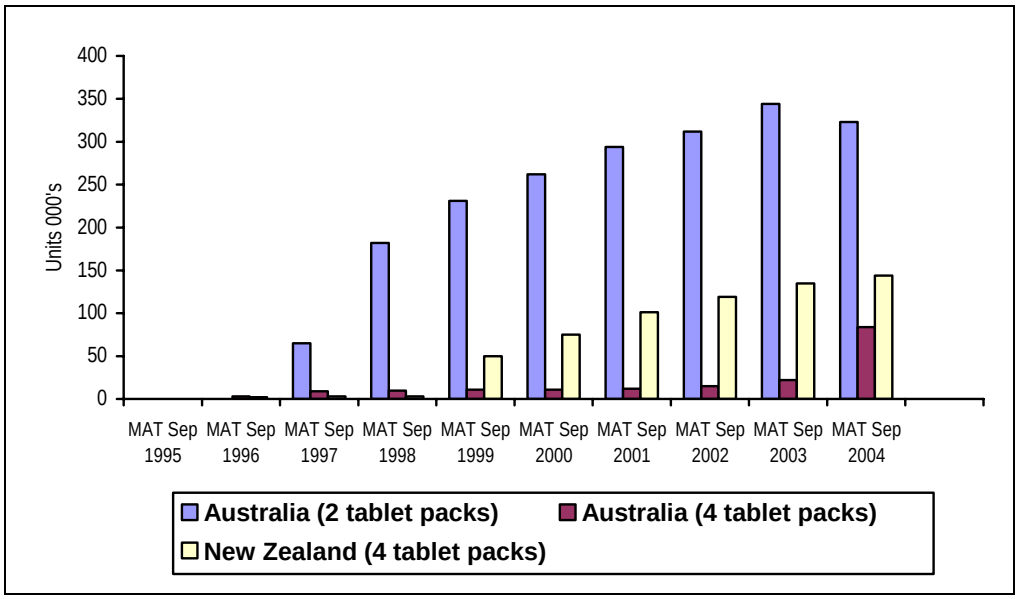
Restricted Medicine (also referred to as 'Pharmacist-Only Medicine').

2.9 Classification status in other countries

Re-scheduling applications for sumatriptan 50 mg tablets and naratriptan 2.5 mg tablets have been approved in the UK and Germany, respectively. *[Refer to Attachment 1.]*

2.10 Extent of usage in NZ and elsewhere and dates of original consent to distribute

Sales volumes by year since the launch of sumatriptan 50 mg tablets in New Zealand and Australia are as follows:



Data source: IMS audited units for Imigran 50mg sold in Australia and New Zealand (1995-2004). Note: In Australia during this time only the 2 tablet packs were available on the Pharmaceutical Benefits Scheme.

2.11 Labelling or draft labelling for the proposed new presentation

- Blister foil (primary packaging)
- Carton label (secondary packaging)
- CMI (to be contained in the carton)

[Refer to Attachment 2 for the draft text]

2.12 Proposed warning statements

Relevant warning statements advising patients of when not to take Imigran® Migraine Treatment will be included in both the Data Sheet and CMI for Imigran® Migraine Treatment. *[Refer to Attachment 2 for the draft text]*

2.13 Other products containing the same active ingredient that would be affected by the proposed change

None applicable.

3 PART B

3.1 A statement of the benefits to both the consumer and to the public expected from the proposed change

This submission contains relevant data to support a change in the scheduling status of sumatriptan 50 mg tablets to a Restricted Medicine (Pharmacist Only Medicine); in doing so it has accounted for the scheduling criteria summarized in the following table (see below). Each of these points is explained in further detail in this document.

Scheduling criteria	Key Issues	Proposed Solutions
Public health benefits	There is a clear, unmet consumer need for more effective, non-prescription migraine treatments. Optimal treatment outcomes with triptans (such as sumatriptan) are achieved with early use (when the migraine headache begins). Restricted Medicine availability, with the added support of Pharmacist intervention, promotes such use. Given that simple analgesics are commonly used for the initial treatment of migraine, Pharmacists are already intervening in requests for migraine treatment when customers present at the Pharmacy.	The wider availability of sumatriptan 50 mg tablets in pack sizes of two tablets would be accompanied by: ♦ training and educational programmes designed specifically for healthcare professionals and Pharmacy Assistants ♦ a revised Data Sheet and CMI for use specifically with Imigran® Migraine Treatment ♦ a Migraine Questionnaire that has been developed to help the Pharmacist to diagnose migraine and determine if Imigran® Migraine Treatment is suitable in accordance with the proposed revised Data Sheet. Consumers will be referred to their GP or recommended other treatment options if this product is not appropriate. The Migraine Questionnaire has been validated and user tested.
Safety considerations	Over 13 years' global post-marketing experience with sumatriptan tablets, equating to more than 600 million migraine attacks treated, reveals a benign adverse-effect profile.[9]	
Suitability of the ailment	Migraine is widely recognised as a self-limiting, self-recognisable condition.	

3.1.1 Public health benefits

Migraine is a common condition and one which has a significant impact on those who suffer from it. Recent statistical data suggest that migraine may affect over 400,000 New

Zealanders. A report by research company Colmar Brunton, puts the economic cost of migraine to New Zealand's economy at $80 million annually, based on an estimated 700,000 lost working days.[4]

The results from a large survey show that for migraineurs, the three most important attributes for a migraine treatment are:[5]

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

Discussion with experts in migraine and related fields has revealed that ease of access to treatment and cost also figure highly on the list of desirable attributes.

Most migraine sufferers self-medicate. Pharmacists are well used to providing advice to consumers on migraine and recommending over-the-counter (OTC) treatments for this condition. The availability of Imigran® Migraine Treatment would provide suitable migraine sufferers access to a migraine-specific treatment with fast onset of action. Imigran® Migraine Treatment has proven efficacy in migraine headache and other migraine symptoms such as nausea, photophobia and phonophobia and has a well established safety and tolerability profile. The availability of such a product could have potential benefits for migraine sufferers, their families and employers.

Clinical data in migraine are limited for most currently available non-prescription migraine medications and the studies that are available are often methodologically flawed. A systematic literature review of currently available non-prescription treatments in the management of migraine provided evidence that some treatments produced clinically meaningful relief compared with placebo.[10] However, clinical studies with non-prescription treatments had generally focused on patients with mild migraine by excluding those subjects experiencing disability in over 50% of attacks and/or vomiting with over 20% of attacks.[10] The authors concluded that over-reliance on current non-prescription agents resulted in avoidable patient suffering.

Non-prescription availability of Imigran® Migraine Treatment would allow Pharmacists to recommend a specific migraine treatment when it is inconvenient for a patient to seek counsel from their doctor or when they are unable to do so because of the onset of a migraine attack. Given the nature of migraine, such availability will facilitate access to an effective migraine-specific treatment, providing both immediate access (and hence faster relief) and optimal treatment outcome (maximal benefit is achieved when sumatriptan is taken at the first onset of headache). Furthermore, it ensures that the philosophy behind the quality use of medicines is upheld, providing Pharmacists with the ability to educate and guide consumers on the appropriate use of medicines in order to manage their condition effectively.

Provision of Imigran® Migraine Treatment as a Restricted Medicine in a pack containing two 50 mg tablets provides Pharmacists with a new option to recommend to patients with a history of acute migraine. This, in turn, has the potential to provide significant benefits in terms of the quality use of medicines. Availability of Imigran® Migraine Treatment as a Restricted Medicine provides a means by which Pharmacists can reduce the healthcare cost burden by counseling and treating those patients who would otherwise have to go to their GP for a script to treat an acute migraine episode.

3.1.2 Potential social benefits

A change in status for small packs of sumatriptan 50 mg from a Prescription Medicine to a Restricted Medicine has potential social benefits for migraine sufferers and their families and significant economic benefits for sufferers and their employers.

Migraine sufferers typically experience absence from work, reduced effectiveness whilst at work and disrupted home and social activities,[11] leading to a significant economic burden on society.[12] Migraine also has a personal cost for many individuals and their families — quality of life scores are significantly lower for migraineurs than matched controls and migraine has a detrimental effect on family life and relationships.[13;14] The ability to educate consumers, and ensure that they receive proper counseling and appropriate treatment, would also have particular benefits in terms of improved quality of life and reduced rates of absenteeism.

A work productivity assessment was conducted in the US among 101 full-time employees with migraine drawn from a health maintenance organisation population.[15] It was found that the mean cost associated with days missed from work and days of reduced productivity at work due to migraine were reduced by $435 per month per employee after initiation of treatment with sumatriptan. The authors note that the benefits of an effective treatment extend beyond work productivity outcomes. The indirect costs of migraine (personal, societal, economic) vastly outweigh the cost of treatment providing an important opportunity for cost-effective intervention.[12]

3.1.3 Potential to improve appropriate treatment choices

Given the wide variety of non-prescription medicines currently available in Pharmacy for the management of migraine, it is a reasonable assumption that Pharmacists are already managing this condition to some extent. The re-scheduling of sumatriptan 50 mg to Restricted Medicine status would be accompanied by comprehensive training initiatives to Pharmacists and GPs that would further enhance this current practice.

Lipton and colleagues have recently reported the results of a population-based survey conducted in 1999 that was designed to describe the patterns of migraine diagnosis and medication use in a representative sample of the US population and to compare results with a methodologically identical study conducted 10 years earlier.[16] They found that although the diagnosis of migraine has increased over the past decade, approximately half of migraineurs remain undiagnosed, and the increased rates of diagnosis of migraine had been accompanied by only a modest increase in the proportion using prescription medicines. This led them to conclude that given the availability of effective treatments, public health initiatives to improve patterns of care are warranted.

Whilst these data were generated in the US, they are reflective of the findings from New Zealand research – that is that consumers may try many different treatments but are not necessarily seeking healthcare advice and hence the products they use may not be the optimal choice for them.[4] It has recently been reported that of the many people exclusively taking OTC products for their condition only a minority obtain effective relief, leading to the suggestion that inappropriate drug use patterns could be avoided with proper education and monitoring.[9]

The wider availability of Imigran® Migraine Treatment would ensure that more consumers are aware of migraine, available treatment options and most importantly when and where to seek the expert advice of a healthcare professional to ensure that their particular condition is being optimally managed.

3.2 Evidence and rationale for reclassification

3.2.1 Treatment of migraine

Until the early 1990s, treatment options for migraine sufferers were limited to analgesics (paracetamol, aspirin and other non-steroidal anti-inflammatory drugs), ergot alkaloids and anti-emetics such as metoclopramide or domperidone. Aspirin, ibuprofen, paracetamol and paracetamol-aspirin-caffeine combinations are considered to be effective in the treatment of migraine,[17-23] but are less effective in moderate to severe episodes.[24]

Ergot alkaloids have been extensively used for the treatment of moderate to severe episodes of migraine but are now considered less suitable for prescribing than other anti-migraine treatments. Anti-emetics with antidopaminergic activity (metoclopramide, domperidone and phenothiazine anti-emetics) can improve headache, as well as attenuating autonomic dysfunction and speeding up gastric emptying.[24] Their major drawback is the risk of extrapyramidal effects or dystonic reactions, particularly in younger patients.

Development of potent, selective 5-HT_{1B}/5-HT_{1D} agonists such as sumatriptan that provide a specific treatment for migraine has significantly improved the outlook for sufferers. Clinical studies have provided unequivocal evidence that the severity and duration of migraine attacks can significantly be modulated by triptan treatment.[25]

Nevertheless, surveys in the UK and the US have shown that most migraine sufferers continue to self-medicate with OTC treatments.[26] Despite progress in understanding the pathophysiology of migraine and the development of the triptans, which provide a significant advance in the treatment of migraine, many migraine sufferers continue to be poorly served with their current treatments.

3.2.2 Rationale for Restricted Medicine status

The rationale for switching sumatriptan 50 mg from a Prescription Medicine to a Restricted Medicine is based on the following 3 key points:

- Migraine is a self-limiting, self-recognisable condition.
- There is a clear unmet consumer need for more effective over-the-counter migraine treatments.
- Optimal treatment outcomes with triptans are achieved with early use (consumers will be advised to treat as soon as possible after the onset of a migraine headache); restricted over-the-counter availability promotes such use.

The availability of Imigran® Migraine Treatment would provide suitable migraine sufferers access to a migraine-specific treatment with a fast onset of action. Imigran® Migraine Treatment has proven efficacy in migraine headache and other migraine symptoms such as nausea, photophobia and phonophobia and has a well established safety and tolerability profile.

Imigran® Migraine Treatment tablets contain sumatriptan at a dose of 50 mg per tablet, a dose chosen on the basis that it provides effective migraine relief while maintaining a wide safety margin. It is considered that Imigran® Migraine Treatment tablets meet the regulatory requirements for re-scheduling; details of which are provided in subsequent sections of this document.

3.2.3 Overview of efficacy of sumatriptan

The triptans have been specifically developed for the effective treatment of migraine (relieving both the headache and associated symptoms such as nausea and sensitivity to light and sound).

Sumatriptan has been widely studied in a clinical programme spanning almost two decades and an extensive body of efficacy and safety information is available for this product. Studies confirm that sumatriptan reduces pain and disability due to migraine attacks and improves migraine associated symptoms such as nausea and photophobia.[6-8] Post-marketing safety data derived from treatment of approximately 800 million migraine attacks worldwide (all formulations) confirm that sumatriptan has a well established tolerability profile.

Sumatriptan 50 mg tablets, the lowest approved oral dose in New Zealand, in the management of migraine is the dose that has been chosen as the most appropriate to reclassify to a Restricted Medicine. The efficacy of sumatriptan 50 mg is very well supported and an extensive clinical database attests to a high degree of efficacy against the pain and disability of migraine and its associated symptoms. *[Refer to Attachment 3]*

3.3 Ease of self-diagnosis or diagnosis by a Pharmacist for the condition indicated

Pharmacists currently manage consumers with headache, including migraine, on a regular basis. A recently published US survey has shown that Pharmacists, particularly those in community pharmacies, interact with headache sufferers multiple times daily (85% of respondents recommended 1-5 non-prescription headache treatments daily).[27] The Pharmacist is ideally placed to talk to and screen consumers wishing to purchase this product. This has a number of positive implications:

- Pharmacists are already managing migraine in the Pharmacy, drawing on a number of currently available non-prescription products. The availability of Imigran® Migraine Treatment provides them with an additional option, which

for suitable individuals can provide a safe and effective migraine specific treatment.

- Pharmacists are used to following treatment protocols and as such would ensure that only those people for whom this product is suitable would be given access to it through Pharmacy.
- Pharmacists are ideally placed to educate consumers on the correct use of this product and advise them if they need to be referred back to their GP for further evaluation.

Pharmacy training and support materials will include the following. *[Refer to Attachment 4]*

- Migraine Questionnaire

  A validated Migraine Questionnaire is in development for use in New Zealand to allow Pharmacists to establish or confirm a diagnosis of migraine and assess suitability for treatment with Imigran® Migraine Treatment. The Migraine Questionnaire is based on a similar questionnaire developed for use in other markets and has undergone considerable research including validation and user testing.

  Consumers are readily able to describe the pattern of their migraine headaches including associated symptoms and the extent of disturbance that these are causing. Using the proposed Migraine Questionnaire, the Pharmacist will be able to identify consumers with a clear diagnosis of migraine that is suitable for management by a Pharmacist prior to recommending Imigran® Migraine Treatment.

- Healthcare professional training

  Pharmacist and GP training/education programmes will also be developed to ensure the appropriate use of Imigran® Migraine Treatment. For the Pharmacist, this will cover use of the Migraine Questionnaire as well as counselling those customers who are not suitable for treatment with Imigran® Migraine Treatment (i.e. recommending other pharmacy treatments for migraine and referring customers to their GP if necessary).

- Consumer education

  In addition to the provision of a clearly written CMI (which will be performance tested), a consumer leaflet on migraine will be available from pharmacies. This will include information on migraine, advice on management and websites for consumer support groups.

  It is recognised that it is useful to keep a diary to monitor migraine frequency and treatment responses, a record card will be provided upon purchase of Imigran® Migraine Treatment and will need to be presented each time the product is purchased. This will enable consumers to keep a record to help the Pharmacist and GP track the frequency of purchase, frequency of migraine attacks and response to treatment.

3.4 Risk of masking a serious disease or compromising medical management of a disease that can be managed by a Pharmacist

The risk of masking a significant underlying condition is small. Imigran® Migraine Treatment as a Restricted Medicine would only be given to a consumer by a Pharmacist after consultation. Training and support materials will be put in place to ensure that factors associated with sinister causes of headache are identified and appropriate GP referral instigated.

Additionally, the 2 tablet-pack would only provide sufficient medication to treat one or two acute migraine episodes, and so it is highly unlikely that the use of Imigran® Migraine Treatment would present a risk of masking serious disease. The CMI recommends that consumers should talk to their doctor if the medication was ineffective, as this may indicate that they do not have migraine and that they may suffer from tension type headache or have an underlying condition which is causing their headache.

3.5 Relevant comparative data for like compounds

The triptans have been specifically developed for the treatment of migraine. There are no other like compounds.

A systematic literature review of non-prescription treatments in the management of migraine provided evidence that some treatments produced clinically meaningful relief compared with placebo.[10] However, clinical studies with non-prescription treatments had generally focused on patients with mild migraine by excluding subjects experiencing disability in over 50% of attacks and/or vomiting with over 20% of attacks.[10] The authors concluded that over-reliance on current non-prescription agents resulted in avoidable patient suffering.

There have been few published study that directly compare sumatriptan 50 mg and non-prescription medications. The authors of one meta-analyses noted the lack of high quality trials for simple analgesics and non-prescription preparations and consequently considered that NNTs (Number Needed to Treat) could not be calculated for any of the non-prescription products reviewed.[28] A Cochrane review of sumatriptan also found little comparative data with other products.[25] Among non-triptan drugs, the combination of ergotamine and caffeine was found to be significantly less effective than sumatriptan. Other drugs were considered to have been insufficiently studied to draw any firm conclusions.

A retrospective study conducted in the US assessed preference between triptans and analgesics in 663 patients with migraine.[29] Overall, 70% of patients preferred triptan (triptan alone or triptan plus an analgesic) over non-triptan therapy (prescription and non-prescription treatments; $p<0.001$). Most of these patients (71%) preferred to use the triptans alone. Greater efficacy was the main reason for the group preferring triptans alone (62%).

A large, open label, observational, four attack study involving 402 subjects who treated at least one migraine attack and submitted preference data was conducted to examine preference for and satisfaction with sumatriptan 50 mg tablets compared with usual non-triptan prescription or non-prescription treatment.[30;31] Overall, 73% of subjects preferred sumatriptan to their usual treatment whereas only 19% preferred their pre-study non-triptan therapy (most often non-narcotic analgesics or NSAIDs).[30] The most common reason for preferring sumatriptan was effective pain relief (cited by 98% of patients). Mean satisfaction score for overall effectiveness with sumatriptan tablets was 5.5 (where 5 = somewhat satisfied and 6 = satisfied) compared with 3.4 (where 3 = somewhat dissatisfied and 4 = neutral) for pre-study non-triptan therapy ($p<0.001$).[31]

3.6 Local data or special considerations relating to NZ

3.6.1 Support from the Pharmaceutical Society of New Zealand

As part of its ongoing commitment to develop validated Pharmacy tools to support the Restricted Medicine status of sumatriptan, GSK has consulted with relevant external bodies including the Pharmaceutical Society of New Zealand.

Input has been obtained in terms of developing draft materials for the Australian market place. Should this submission to re-classify sumatriptan be successful, further collaboration will be sought to ensure that the content of all training and educational materials meet the requirements of the New Zealand market place and that these materials are delivered in a suitable manner. [*See Attachment 5*]

3.6.2 Local data regarding the burden of migraine

A 1999 report published by the World Headache Alliance, cites the annual economic cost of migraine in New Zealand as NZ$80 million, based purely on working days lost.[4] This figure does not account for additional costs to the health system when migraine sufferers seek medical help. This report also demonstrated that only 1 in 3 migraine sufferers actually consulted their GP about their condition.

An earlier report investigating the overall and ethnic specific prevalences of bad headache including migraine, for the New Zealand population, found that 40.6% of the respondents suffered from bad headaches.[32] More than half (54.5%) of these had the characteristics of bad headache with features symptomatic of migraine. Trends in the prevalence of bad headache with features symptomatic of common migraine, peaked between the ages of 30-49 years in both men and women.

A more recent study investigated the functional impairment (work and social functioning and general health status) associated with migraine and tension-type headache among young adult members of the Dunedin Multidisciplinary Health and Development Study.[33] The 1-year prevalence for migraine headache was 7.4%, tension-type headache was 11.1%, and combined headache (coexisting migraine and tension-type headache) was 4.3%. Study members with combined headache had the poorest self-reported health, with significantly lower ratings on physical, vitality, and mental health measures than asthmatics currently using medication. The pervasive

impairment reported across multiple life domains among young headache sufferers illustrates the significant burden of illness associated with headache disorders.

3.7 Interactions with other medicines

Sumatriptan has a well recognised potential for interaction with ergotamine derivatives, MAOIs and SSRIs. The proposed Data Sheet and CMI contain adequate warnings of these interactions. Apart from the potential for interaction with SSRIs, no other drug interactions have been identified from the extensive post-marketing experience with this drug. *[Refer to Attachment 6]* These potential drug interactions are also addressed in the proposed pharmacy tools *[Refer to Attachment 4]*.

3.8 Contraindications

The proposed Data Sheet and CMI will include a comprehensive list of contraindications.*[Refer to Attachment 2]* These contraindications are also addressed in the proposed pharmacy tools *[Refer to Attachment 4].*

3.9 Possible resistance

Not applicable.

3.10 Adverse events

The last decade's experience with triptans in more than half a billion people worldwide reveals a benign adverse-effect profile.[9] Published reports and real-world experiences illustrate that these drugs do not merit fears of triptan-induced cardiac consequences in appropriately selected individuals.[9] *[Refer to Attachment 7]*

3.11 Specific safety issues of relevance to the rescheduling of sumatriptan

Specific tools, such as the proposed Migraine Questionnaire *[Refer to Attachment 4]*, as well as the Data Sheet and CMI *[Refer to Attachment 6]*, have been designed to identify consumers with contraindications for the use sumatriptan including those with a history of, or risk factors for, cardiovascular disease and hence will be used to screen out patients considered unsuitable for Imigran® Migraine Treatment. The pharmacy training materials will also aid Pharmacists in the counselling of patients regarding the possibility of “triptan sensations”.

3.12 Potential for abuse or misuse

Long-term clinical trials (up to 2 years) with sumatriptan have not shown any evidence of tolerance, misuse or reports of chronic daily headache.[34;35]

The proposed Data Sheet for Imigran® Migraine Treatment states that no more than two 50 mg tablets (total dose 100 mg) are to be taken in any 24 h period and that the recommended dose of Imigran® Migraine Treatment should not be exceeded. It also includes a specific warning about the occurrence of chronic daily headache/exacerbation of headache with overuse of sumatriptan.

In addition, migraineurs are advised to see their doctor if:

- their typical headaches persist for longer than 24 h
- they experience four 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.

These steps are expected to limit misuse in chronic daily headache or overuse (maximum number of tablets taken should not exceed six per month based on three attacks, each treated with two tablets) in the non-prescription setting and are considered to promote safe use of Imigran® Migraine Treatment. This guidance is in accord with a recent report suggesting that medication overuse and a high initial headache frequency are important risk factors for chronic headache.[36]

3.13 Overdose

A pack of Imigran® Migraine Treatment will contain only two 50 mg tablets in order to minimise the potential for deliberate or accidental overdose.

The proposed Data Sheet for Imigran® Migraine Treatment provides clear information to doctors on what to do in the event of overdose. It is noted that oral doses in excess of 400 mg were not associated with side effects other than those listed in the Data Sheet. The CMI provides clear advice on dosing and contact details for consumers to contact the Poisons Information Centre (or to speak to their doctor or Pharmacist) in the event of an overdose.

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