Australian Government
Department of Health
Therapeutic Goods Administration

Proposed changes to Required Advisory Statements for Medicine Labels (RASML): Triptans

Consultation paper

Version 1.0, July 2021

TGA Health Safety Regulation

Confidentiality
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Introduction

Purpose

The Therapeutic Goods Administration (TGA) is seeking comments from interested parties on proposed new advisory statements for labels of over the counter (OTC) medicines containing triptans (sumatriptan, zolmitriptan, rizatriptan, eletriptan), for inclusion in the Required Advisory Statements for Medicine Labels (RASML). The proposal to include advisory statements for triptan-containing medicines in RASML follows recent down-scheduling of triptans when supplied under specific conditions, from Schedule 4 to Schedule 3 of the Poisons Standard.

Background

Advisory statements

Consumers rely on information from their health practitioner, pharmacist and medicine label in order to use medicines safely and effectively. However, the enhanced access and availability of OTC medicines means that consumers may not always receive comprehensive advice from a practitioner or pharmacist.

In the context of self-medication, the medicine label is the primary source of information for the consumer; so the label must contain the directions and advisory statements that are needed for safe and effective use of these medicines.

The TGA Labelling Orders require medicine labels to include 'warning statements' where these apply to the medicines, including any advisory statements specified in the instrument made under subsection 3(5A) of the *Therapeutic Goods Act 1989* ('the Act'), as in force from time to time.

The Required Advisory Statements for Medicine Labels (RASML)

The RASML is registered on the Federal Register of Legislative Instruments under subsection 3(5A) of the Act, as the Therapeutic Goods (Medicines Advisory Statements) Specification 2019 ('the Specification'). The RASML sets out advisory statements that are required to be included on the labels of specified OTC and registered complementary medicines.

The most recent version of the Specification is the Therapeutic Goods (Medicines Advisory Statements) Specification 2019, which comprises RASML No. 5. The transition period for compliance with RASML No. 5 ended on 31 August 2020 and labels must now comply with the advisory statements specified in RASML No. 5.

Finalised advisory statements for the four triptans would be included in the next version, RASML No. 6. A transition period of 18 months from commencement of the new RASML is provided to allow for existing medicines that do not already comply with new requirements to have their labelling updated.

The advisory statements required by the RASML are designed to inform consumers about specific risks related to the use of medicines that have been identified during development and evaluation of new medicines, or subsequent pharmacovigilance activities, testing, adverse event reports or from other scientific or clinical information.

The RASML permits the wording of the actual statements that are included on medicine labels to differ from the wording set out in the RASML, as long as the intent is the same.

Scheduling of triptans in the Poisons Standard

The triptans sumatriptan, zolmitriptan, eletriptan and rizatriptan were recently down-scheduled from S4 to S3 with conditions as specified in the entries below, with effect on 1 February 2021 (Delegate's final decisions for sumatriptan and zolmitriptan were in May 2020, rizatriptan in August 2020 and eletriptan in Nov 2020).

The S3 schedule entries are as follows:

> SUMATRIPTAN when in divided oral preparations containing 50 milligrams or less per dosage unit and when sold in a pack containing not more than 2 dosage units for the acute relief of migraine in patients who have a stable, well-established pattern of symptoms.
>
> ZOLMITRIPTAN when in divided oral preparations containing 2.5 milligrams or less per dosage unit and when sold in a pack containing not more than 2 dosage units for the acute relief of migraine in patients who have a stable, well-established pattern of symptoms.
>
> RIZATRIPTAN when in divided oral preparations containing 5 milligrams or less per dosage unit and when sold in a pack containing not more than 2 dosage units for the acute relief of migraine in patients who have a stable, well-established pattern of migraine symptoms.
>
> ELETRIPTAN for oral use in tablets containing 40 mg or less per tablet and when in a pack containing not more than 2 dosage units for the acute relief of migraine in patients who have a stable, well-established pattern of symptoms.

Proposed RASML statements for OTC medicines containing triptans

There are currently no warning statements specified in RASML for triptans. Given the anticipated registration of triptan-containing OTC medicines following down-scheduling of triptans to S3, RASML warnings for these medicines are proposed. Proposed warnings are specified in the following table with the basis for each warning also included.

Warning statement	Basis for warning
Do not use:	
• without a previous diagnosis of migraine by a doctor	Triptans should only be used where there is a clear diagnosis of migraine in order to exclude other potentially serious neurological conditions

Warning statement	Basis for warning
• If you have previously had a heart attack or stroke or if you have heart disease, peripheral vascular disease (a blood vessel disorder) or high blood pressure	Consistent with contraindications listed in approved triptan Product Information (PIs) as follows (from sumatriptan PI, but similar for other triptans): - A history of myocardial infarction - Peripheral vascular disease or symptoms or signs consistent with ischaemic heart disease - Prinzmetal's angina/coronary vasospasm - Uncontrolled hypertension - Cerebrovascular accident or transient ischaemic attack
• if you have taken other migraine medications within 24 hours	Increased risk of vasospastic reactions. Consistent with approved triptan PIs and Martindale[1]
• if you have taken monoamine oxidase inhibitors (MAOIs; medicines used to treat depression) in the last 2 weeks	Consistent with the approved PI contraindication for sumatriptan/eletriptan (but not applicable for zolmitriptan or eletriptan - see 'Interactions with MAOIs' below).
• if you have liver or kidney problems, unless advised by your doctor	Contraindicated in severe liver disease (sumatriptan and eletriptan PIs) or dose restriction advised (zolmitriptan PI). Caution advised in those with hepatic impairment (sumatriptan PI). Potential impact on those with renal impairment (all triptan PIs). Sumatriptan PI advises caution.
Consult your doctor or pharmacist before use:	
• if you think you may be at risk of heart disease (including if you are post-menopausal or a male over the age of 40)	- Contraindicated in those with symptoms or signs consistent with ischaemic heart disease (triptan PIs). - Prior evaluation recommended in patients at risk of CV disease (triptan PIs). PI for sumatriptan strongly recommends it "not be given to patients in whom risk factors indicate a possibility of unrecognised coronary artery disease (CAD) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischaemic myocardial disease or other significant underlying cardiovascular disease. The risk factors include hypertension, hypercholesterolaemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age."

[1] Martindale: The Complete Drug Reference; March 2021

Warning statement	Basis for warning
• if you have any other medical conditions	To further ensure appropriate assessment of those with potential cardiovascular disease (eg. those with diabetes, hypertension, hypercholesterolaemia; consistent with warnings in triptan PIs).
• if you are taking medication for depression	Risk of serotonin syndrome (triptan PIs).
• if you are pregnant or breastfeeding	Consistent with pregnancy categories B3 (sumatriptan, zolmitriptan) and B1 (eletriptan, rizatriptan) and advice to exercise caution when breastfeeding (triptan PIs)
Speak to a doctor or pharmacist if your migraines become more frequent. Overuse of this medicine may worsen your condition.	Overuse of triptans may lead to medication overuse headache (MOH; triptan PIs).
This medicine may cause drowsiness. If affected, do not drive a vehicle or operate machinery.	Consistent with approved triptan PIs

Interaction with MAOIs – differences between triptans

Based on the approved PIs, there is less concern regarding MAOI interactions with zolmitriptan than for sumatriptan/rizatriptan. While the latter are contraindicated within 2 weeks of MAOI therapy, the approved PI for zolmitriptan (eg. Zomig tablets) advises dose restrictions in those taking MAOIs. Therefore, the above contraindication warning in relation to MAOIs is not appropriate for zolmitriptan. It is proposed for zolmitriptan that this warning be omitted and the additional antidepressant warning be modified for zolmitriptan as follows: "Consult your doctor or pharmacist before use…if you are taking or have recently taken medication for depression, including monoamine oxidase inhibitors".

There is no interaction between MAOIs and eletriptan – the MAOI warning can therefore be omitted for eletriptan.

Proposed RASML entries for triptans

In summary, the following RASML entries for sumatriptan, rizatriptan, zolmitriptan and eletriptan are proposed, with differences shown in bold/red for easy reference:

Column 1 Substance(s)	Column 2 Conditions	Column 3 Required statement(s)
Sumatriptan Rizatriptan* *(Entry 1 of 1)* * These would have individual but identical entries	In divided oral preparations for relief of migraine	• Do not use: - without a previous diagnosis of migraine by a doctor - if you have previously had a heart attack or stroke or if you have heart disease, peripheral vascular disease (a blood vessel disorder) or high blood pressure - if you have taken other migraine medications within 24 hours - **if you have taken monoamine oxidase inhibitors (MAOIs; medicines used to treat depression) in the last 2 weeks** - if you have liver or kidney problems, unless advised by your doctor • Consult your doctor or pharmacist before use: - if you think you may be at risk of heart disease (including if you are post-menopausal or a male over the age of 40) - if you have any other medical conditions - **if you are taking medication for depression** - if you are pregnant or breastfeeding • Speak to a doctor or pharmacist if your migraines become more frequent. Overuse of this medicine may worsen your condition. • This medicine may cause drowsiness. If affected, do not drive a vehicle or operate machinery.
Zolmitriptan *(Entry 1 of 1)*	In divided oral preparations for relief of migraine	• Do not use: - without a previous diagnosis of migraine by a doctor - if you have previously had a heart attack or stroke or if you have heart disease, peripheral vascular disease (a blood vessel disorder) or high blood pressure - if you have taken other migraine medications within 24 hours - if you have liver or kidney problems, unless advised by your doctor • Consult your doctor or pharmacist before use: - if you think you may be at risk of heart disease (including if you are post-menopausal or a male over the age of 40) - if you have any other medical conditions - if you are taking **or have recently taken** medication for depression**, including monoamine oxidase inhibitors** - if you are pregnant or breastfeeding • Speak to a doctor or pharmacist if your migraines become more frequent. Overuse of this medicine may worsen your condition. • This medicine may cause drowsiness. If affected, do not drive a vehicle or operate machinery.

Column 1 Substance(s)	Column 2 Conditions	Column 3 Required statement(s)
Eletriptan *(Entry 1 of 1)*	In divided oral preparations for relief of migraine	• Do not use: - without a previous diagnosis of migraine by a doctor - if you have previously had a heart attack or stroke or if you have heart disease, peripheral vascular disease (a blood vessel disorder) or high blood pressure - if you have taken other migraine medications within 24 hours - if you have liver or kidney problems, unless advised by your doctor • Consult your doctor or pharmacist before use: - if you think you may be at risk of heart disease (including if you are post-menopausal or a male over the age of 40) - if you have any other medical conditions - **if you are taking medication for depression** - if you are pregnant or breastfeeding • Speak to a doctor or pharmacist if your migraines become more frequent. Overuse of this medicine may worsen your condition. • This medicine may cause drowsiness. If affected, do not drive a vehicle or operate machinery.

Note: RASML permits the wording of the actual statements that are included on medicine labels to differ from the wording set out in the RASML, as long as the intent is the same.

Consultation questions and responses

The TGA is requesting comments that will help ensure that the proposed advisory statements are appropriate and support the quality use of the medicines and that any label changes that would be required for these medicines are made in the most convenient, efficient and cost-effective way.

Submissions must be relevant to warning statements for OTC medicines containing triptans and must be received by the closing date.

Question

Do you support the proposed conditions and wording of the advisory statements?

If there are aspects you do not support, please explain why you do not support them. You may make suggestions for alternative wording or additional statements that you think are suitable.

You may wish to include an assessment of how the proposed changes will impact on you; that is, what do you see as the likely benefits or costs to you (these may be financial or non-financial).

To provide your feedback click 'Make a submission' on the consultation page and include your response using the free text field and/or file upload function.

All feedback will be considered after the consultation period ends and will be published on the TGA website with your consent.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	OTC Medicines Evaluation Section	July 2021

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Reference/Publication #