MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Proposed warning and advisory statements for ocular decongestants

26 January 2023

Consultation outcome

Contents

Executive Summary

In June 2021, the Medicines Adverse Reaction Committee (the Committee) noted that the package label for Clear Eyes (naphazoline) 0.01% eye drops did not have a lower age limit for use. The Committee expressed concerns that because Clear Eyes is a pharmacy-only medicine, it could be used in children under 12 years of age inappropriately without further investigation or adequate input from a healthcare professional.

The New Zealand Formulary for Children has an age restriction for naphazoline of 12 years and older. Therefore, the Committee recommended that Medsafe undertake a Label Statements Database (LSD) consultation to include this age limit on the package labelling.

There are a range of ocular decongestant products currently available as pharmacy only medicines that contain naphazoline, tetrahydrozoline (tetryzoline) or phenylephrine. Not all product labels for these medicines include an age restriction for use. There is potential for such products to be inappropriately used in children. Following the recommendation from the MARC, the LSD consultation was extended to include all ocular decongestants when used for eye redness and/or minor eye irritation.

From 11 July to 23 September 2022, Medsafe consulted on whether a proposed warning statement for all ocular decongestants when used for eye redness and/or minor eye irritation to include an age restriction of 12 years and older should be included in the LSD.

This report is a summary of the submissions received.

Medsafe received 10 valid submissions to the consultation. Respondents included health care professionals and industry members.

Most respondents agreed that the LSD should include a warning statement for ocular decongestants with an age restriction for use. However, it was suggested that each ocular decongestant should have a separate age restriction.

As a result of the consultation, a new warning statement for ocular decongestants will be added to the LSD, with separate age restrictions for use for naphazoline and tetrahydrozoline.

The LSD will be updated on 1 August 2023. Affected products are required to have these statements by 1 February 2025.

We would like to thank everyone for their contribution to this consultation.

About the consultation

Ocular decongestants are medicines that provide temporary relief from redness, burning and minor irritation of the eyes. They reduce eye redness by constricting dilated blood vessels through activation of alpha-adrenergic receptors.

In New Zealand, there are a range of ocular decongestant products containing naphazoline or tetrahydrozoline (tetryzoline) that are sold as pharmacy-only medicines. Ocular decongestants containing phenylephrine <1% are classified as general sale, and higher strengths are available in pharmacies. At present, only naphazoline and tetrahydrozoline products are available and indicated for use in eye redness and/or minor eye irritation.

Ocular decongestant products, when sold as general sale or pharmacy-only medicines, are not required to have a data sheet or a consumer medicine information leaflet. In addition, there is no requirement for a health professional to be involved in the sale of the medicine. Therefore, consumers and caregivers must rely on the information on the package labelling to take the medicine safely.

In June 2021, the Medicines Adverse Reaction Committee (the Committee) noted that the Clear Eyes (naphazoline) 0.01% eye drops package label did not have a lower age limit for use, and recommended a LSD consultation to include an age limit. The Label Statements Database lists the warning and advisory statements that are required on medicines and related package labelling. Currently, there are no LSD warning and advisory statements for ocular decongestants.

Without adequate warnings on the label, there is a risk that these products could be used in young children. Safety concerns relating to use of ocular decongestants in young children include the possibility of systemic effects and lack of safety and efficacy information. In addition, continual use of these products for eye redness may delay caregivers from seeking healthcare professional advice for more serious eye-related conditions.

At present, a lower age restriction for use is included on some ocular decongestant package labelling.

- Naphazoline: some package labels of naphazoline-containing products state that they should not be used in children under 12 years of age, while other products do not have an age limit.
- Tetrahydrozoline: the package labels of tetrahydrozoline-containing products state that they should not be used in children under 6 years of age.
- Phenylephrine: there are no phenylephrine eye drops used for eye redness and/or minor eye irritation that are approved in New Zealand. Phenylephrine is also used for diagnostic procedures; products used for this purpose will not be required to have the proposed warning and advisory statement.

Medsafe proposed that a lower age recommendation of 12 years old should be reflected across all ocular decongestant product labels. Table 1 below shows the proposed warning and advisory statement for ocular decongestants. The proposed conditions and the date for implementation are also outlined below.

Table 1: Proposed warning and advisory statement for ocular decongestants

Medicine/Group/Class	Conditions	Statement	Required by
Decongestant, ocular: Examples include: Naphazoline Tetrahydrozoline (tetryzoline) Phenylephrine	For ophthalmic use When used for eye redness and/or minor eye irritation only. When used in combination with another medicine(s), the age limit for the combination product should reflect the highest age limit overall from each medicine.	Do not use in children under 12 years of age.	12 months from when the Label Statements Database is updated.

As part of the consultation, Medsafe sought comments on:

- whether the package labels for ocular decongestants should contain a warning and advisory statement for an age restriction of use
- whether the proposed age restriction of 12 years and under for all ocular decongestants is appropriate
- the conditions the label statements will be applied to
- the required by (implementation) date
- whether there are any other statements relating to use of ocular decongestants in children that should be included on the package labelling.

Consultation results

Thank you to everyone who responded to the survey.

We have analysed and summarised the survey results.

The results are divided into eight parts as follows:

1. Overview of respondents
2. Summary of responses: Should ocular decongestants include a warning statement for an age restriction of use?
3. Summary of responses for proposed statement: 'Do not use in children under 12 years of age' should be applied to all ocular decongestants.
4. Summary of responses: Other Label Statements to be considered
5. Proposed conditions
6. Proposed timeframe for implementation
7. Other comments
8. Outcome

Part 1 summarises the respondent demographics by individual or organisation, location, respondent category, and by health profession.

Parts 2 to 6 contain a tabulated summary of respondents' agreement or disagreement with the proposed statement. This table is broken down by respondent category. Comments from respondents are grouped, and a response from Medsafe and the final outcome for each part is included at the end.

Part 7 contains other comments raised by respondents in this consultation.

Part 8 contains the overall outcome and the final statements, as they will appear in the Label Statements Database.

1. Overview of respondents

You can view the submissions that we have permission to publish.

A total of 10 submissions were received via the consultation tool.

As shown in Table 2, most responses were submitted on behalf of an organisation, group or industry (70%). The remaining responses were submitted by individuals (30%).

Table 1: Respondent type – individual or organisation

Respondent	Number	Percentage (%)
As an individual	3	30
On behalf of an organisation or group	7	70
Total	**10**	**100.0**

All respondents were based in either New Zealand or Australia, as shown in Table 3.

Table 2: Respondent location

Location	Number	Percentage (%)
New Zealand	5	50
Australia	4	40
Other *(Australia + NZ)*	1	10
Total	**10**	**100.0**

For the analysis, respondents have been categorised into one of two categories (see Table 4):

- Healthcare professional (HCP), n=5
- Industry, n=5

Table 3: Respondent category

Respondent	Categorised as	Number	Percentage (%)
Healthcare professional	HCP	3	30
Professional body	HCP	2	20
Sponsor	Industry	4	40
Industry organisation	Industry	1	10
Total		**10**	**100**

Of the 3 healthcare professional respondents, 2 were optometrists, and one was a pharmacist.

2. Summary of responses – Should ocular decongestants include a warning statement for an age restriction of use?

Question
Should the package labelling for ocular decongestants such as naphazoline, tetrahydrozoline or phenylephrine – containing eye drops include a warning statement for an age restriction of use?

Include warning statements – Agree Y/N

- Yes, n=9
- No, n=1

Table 5: Include warning statements for ocular decongestants – summary of responses

		Respondent category					
		All (n=10)		HCP (n=5)		Industry (n=5)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Include warning statements	Yes	9	90	5	100	4	80
	No	1	10	0	0	1	20

Question
Please add your comments

There were 6 responses to this part of the question. Comments have been summarised by respondent category below.

Comments from Industry

Overall, respondents supported an age restriction to advise consumers on the safe and appropriate use of the products. However, the age restriction should be evidence based and reflect best practice guidance.

Other comments included the following.

- Medsafe did not provide evidence for why the same age limit would be applied to all ocular decongestants. However, there may be evidence to support different age restrictions for different active ingredients.
- Was the proposed age restriction for boron-containing medicines (as discussed in the June 2021 MARC meeting) or based on the safety of ocular decongestants?
- The warning statements for age restriction vary as to whether included in the warning section or in dosing information, however, convey the same information.
- One respondent commented that that the proposed statement was consistent with approved labelling. In contrast, another respondent did not agree with the proposed advisory statement as it was not supported by evidence.
- Fitting all the required information on ophthalmic products, typically in small volume containers, would be challenging.

Medsafe's response:

Medsafe proposed the same age limit for ocular decongestants due to limited efficacy and safety information to support use in children and the potential for adverse events. Self-treatment of red eyes in children may mask underlying eye conditions. Inclusion of a similar age restriction for use of all ocular decongestants is therefore justified.

Tetrahydrozoline was first approved in New Zealand in 1969, and naphazoline in 1970, before the current legislation was passed in 1981.Therefore, it is likely there is limited information on the safety and efficacy of these medicines, particularly in children.

Younger children may experience systemic effects from ocular decongestants. Adverse effects may include central nervous system depression, bradycardia, coma, hypotension and hypothermia. These effects are related to alpha agonist toxicity. Such serious adverse events have been reported in younger children who have accidently taken ocular decongestants orally. [1]

Some ocular decongestant products already have an age restriction on their package label. However, the age restriction varies depending on the medicine. Medsafe had reviewed other international labelling and prescribing resources for tetryzoline products and is aware of consistent recommendations for use in children aged 6 years and above. However, it is not clear what evidence was used to inform this recommendation. Medsafe agrees that age restrictions for ocular decongestants should be evidence based where this exists. Some respondents provided evidence for age restrictions as part of their consultation submissions. Medsafe considered this evidence before finalising the proposed labelling statement.

Medsafe considers that a warning statement for age restriction on use is preferred to having age restrictions in the dosing information only. Package labels with an age restriction currently include this statement in the warning section and/or dosing section.

Medsafe notes potential confusion in relation to the background for this LSD consultation from a respondent. In June 2021, the MARC discussed boron-containing excipients and fertility concerns. The report for the MARC included information on medicines containing boric acid and borax, which included Clear Eyes. On reviewing the information, although not directly related to the topic of boron, the MARC noted an additional safety concern that the Clear Eyes packaging had no lower age limit for use. An LSD consultation was therefore recommended to allow a lower age limit to be mandated for such products. Other decongestant eye drop products were not part of the report presented to the MARC, as they do not contain boron-containing excipients.

Medsafe acknowledges that containers for eye drops are small, and that including additional information might be challenging. The warning statement may be printed on a separate information sheet, which is supplied to the consumer with the medicine (for example, a package insert). Given that information on age restrictions on use are present on some eyedrop containers, and/or the product outer packaging, the inclusion of this information is possible. In addition, an age restriction for use is required to ensure that the medicine is used safely and appropriately. It is advantageous that such warnings be visible at point of purchase.

[1] Food & Drug Administration. 2012. FDA Drug Safety Communication: serious adverse events from accidental ingestion by children of over-the-counter eye drops and nasal sprays. URL:https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-serious-adverse-events-accidental-ingestion-children-over-counter-eye, (accessed 3 June 2022)

Comments from Healthcare Professionals

- When prescribing ocular decongestants in children, it is important to consider the risks and benefits.
- Add "unless prescribed by a health practitioner" to the statement, or words to that effect.

Medsafe's response:

Medsafe agrees that there are risks related to the use of ocular decongestants in children below 12 years of age, and that if such medicines were to be used in this age group, healthcare professional advice should be sought.

Outcome

There will be a new LSD warning statement for ocular decongestants.

3. Summary of responses for Statement

Question
Do you agree that the proposed statement 'Do not use in children under 12 years of age' should be applied to all ocular decongestants?

Agree Y/N

- Yes, n=7
- No, n=3

Table 6: Statement: Do not use in children under 12 years of age – Summary of responses

		Respondent category					
		All (n=10)		HCP (n=5)		Industry (n=5)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Agree with proposed statement	Yes	7	70	5	100	2	40
	No	3	30	0	-	3	60

Question
If no, please suggest an alternative statement, or why it should not be included

There were 4 responses received to this part of the question. Comments have been summarised by themes below:

Addition of 'unless under medical advice/prescribed by health practitioner'

- The proposed statement should advise against use in children under 12 years of age, unless on medical advice.
- Adding this text means there is flexibility for doctors to prescribe the products when clinically necessary and consumers will not be confused if a doctor prescribes a product for a child younger than the age restriction.

Medsafe's response

Medsafe acknowledges that in certain circumstances, as with other medicines, a benefit risk assessment for use of ocular decongestants in young children may be required by an expert health professional. A patient or patient's family may be confused if recommended a product with age restriction warnings.

The ocular decongestant products that already contain an age restriction on the label do not include 'unless on medical advice'. It would be appropriate to keep warning statements consistent with current labelling.

In such circumstances, where a health professional prescribes an ocular decongestant for a child, the patient and family should be appropriately counselled on the reasons for using the medicine, so that there is no confusion with warnings labels that recommend against use in that age group.

Different lower age limit for tetrahydrozoline versus naphazoline

The proposed statement for an age restriction of 12 years and over was not supported for tetrahydrozoline. However, it was supported for naphazoline.

- Information was provided in relation to tetrahydrozoline and use in children over 6 years of age. The information supported the current age for use, given no safety concerns have been identified.
- Medsafe should consider different age restrictions for the different active ingredients, reflecting current labelling, and based on evidence.
- This LSD consultation should focus on naphazoline and tetrahydrozoline as separate medicines only, and not on all ocular decongestants.

Medsafe's response:

Medsafe recognises that that there are different lower age limits included on the package labelling of some naphazoline and tetrahydrozoline ocular decongestant products in Australia and New Zealand.

Use in children and infants may result in central nervous system depression, due to an increased risk of systemic adverse events. Medsafe proposes that the age limit warning statement for naphazoline should be 12 years and over. The naphazoline products in New Zealand that already include an age limit have this age recommendation. In addition, this age limit was supported in the consultation.

Submissions as part of this consultation, mostly from health professionals, supported the proposed warning statement for both naphazoline and tetrahydrozoline. However, Medsafe acknowledges that a change in the age restriction for tetrahydrozoline was not supported by industry respondents in the consultation.

Medsafe is aware that current age restrictions for tetrahydrozoline in Australia and United States of America are 6 years of age and above. Safety concerns for ocular decongestants also include accidental oral ingestion. Most of these cases have been reported in younger children. To manage this safety concern, the package labels of tetrahydrozoline products advise seeking medical attention immediately if swallowed. These products also have child-resistant caps, to manage this safety concern.

Medsafe has reviewed the information provided for tetrahydrozoline and use in children as part of this consultation. The age of use for tetrahydrozoline products will remain consistent with current product labelling, and international labelling.

Phenylephrine eye drops used as ocular decongestants are not approved in New Zealand. As a result, there is not enough information to recommend an appropriate lower age restriction for use.

Outcome

There will be separate statements for naphazoline and tetrahydrozoline, to reflect the different age limits.

- Naphazoline: 'Do not use in children under 12 years of age'
- Tetrahydrozoline: 'Do not use in children under 6 years of age'

4. Other Label Statements to be considered

Question
Are there any other warning and advisory statements relating to use of ocular decongestants in children that should be included on the package labelling?

Table 7: Other statements that should be included – Summary of responses

		Respondent category					
		All (n=10)		HCP (n=5)		Industry (n=5)	
Question	Response	No.	%	No.	%	No.	%
Other statements	Yes	5	50	2	40	3	60
	No	5	50	3	60	2	40

Other Label Statements to be considered

Australian statements

Three respondents suggested that the LSD should including all/some of the Australian required labelling statements.

These statements are included in the Australian Regulatory Guidelines for Over-the-Counter Medicines (ARGOM) and in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021. These statements, or similar wording, are already included in the labelling of products that are marketed in both countries, as they are mandated in Australia.

The LSD should also include the following statements for ocular decongestants.

- 'Prolonged use may be harmful' – this warning statement can help mitigate against the risk of rebound hyperaemia, associated with prolonged use of ocular decongestants, and can also lead to over-use.
- 'Consult a doctor or pharmacist if using other eye drops' – this warning statement will assist consumers by advising them that they should not self-treat with ocular decongestants if they also use other eye drops, whether prescribed or self-selected, without first consulting a doctor or pharmacist.
- 'Do not use if you have glaucoma or other serious eye conditions' – this warning statement addresses the known contraindication regarding use by people who have glaucoma, due to the risk of acute angle closure crisis.
- 'If symptoms persist consult a doctor or pharmacist' – ocular decongestants / vasoconstrictors are for short-term use for self-limiting redness and discomfort of the eye.

Other suggested statements

- 'Not for long-term use'.
- Add further information to explain why naphazoline and tetrahydrozoline should not be used in infants and children. These medicines may cause severe slowing down of the central nervous system (CNS), which may lead to unconsciousness.
- 'Do not use with contact lenses'.

Medsafe's response:

Medsafe is aware of the required warning statements for ocular decongestants in the Australian Regulatory Guidelines for Over-the-Counter Medicines (ARGOM) and in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.

Medsafe has reviewed the New Zealand package labelling of currently approved and marketed naphazoline and tetrahydrozoline ocular decongestants. Mandatory Australian warnings (or words of similar meaning) are included on the package labels. Likewise, information about contact lenses is also included.

Outcome

The warning statements required in Australia for ocular decongestants included above, are acceptable for use in NZ, providing the NZ statements are also included.

5. Proposed conditions

Question

Do you agree with the proposed conditions:

'For ophthalmic use'

'When used for eye redness and/or minor eye irritation only'

'When used in combination with another medicine(s), the age limit for the combination product should reflect the highest age limit overall from each medicine'

Agree Y/N

- Yes, n=9
- No, n=1

Table 8: Agree with proposed conditions – Summary of responses

		Respondent category					
		All (n=10)		HCP (n=5)		Industry (n=5)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Agree with proposed conditions	Yes	9	80	5	100	4	80
	No	1	20	0	0	1	10

Question

Do you agree with the proposed conditions? If no, please suggest alternative conditions.

There was one comment received in this section. The respondent commented that it is unclear if the condition "When used for eye redness and/or minor eye irritation only" includes allergic conjunctivitis.

Medsafe's response:

Allergic conjunctivitis symptoms usually include red, watery, itchy or gritty eyes. The above condition would cover these symptoms.

Outcome:

The condition 'when used for eye redness and/or minor eye irritation only' will be updated to 'when used as an ocular decongestant for eye redness and/or minor eye irritation only'. This change is because marketed phenylephrine products available for pharmacy only and restricted sale are currently indicated for diagnostic or therapeutic procedures. They are not indicated for use as ocular decongestants.

6. Proposed timeframe for implementation

Question
Do you agree with the proposed implementation timeframe of 12 months following the update of the Label Statements Database on the Medsafe website?

Agree Y/N

- Yes, n=5
- No, n=5

Table 9: Agree with proposed timeframe – Summary of responses

		Respondent category					
		All (n=10)		HCP (n=5)		Industry (n=3)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Agree with proposed timeframe	Yes	5	50	5	100	0	0
	No	5	50	0	0	5	100

Question
If no, please suggest an alternative timeframe.

There were five responses received to this part of the question.

Comments

Respondents generally preferred a longer time frame.

Outcome

The usual timeframe for implementation of LSD changes is one year after the outcome is published on the Medsafe website. However, Medsafe also notes the pressures faced by the industry in the context of a global pandemic with regards to supply chain issues. Therefore, Medsafe considers a timeframe of 18 months to be appropriate.

The LSD will be updated on 1 August 2023. Affected products are required to have these statements by 1 February 2025.

7. Other comments

Disagreement for same age restriction across all ocular decongestants

One respondent commented that the advisory statement should not be extended to all ocular decongestants, and that the proposed age limit is not justified for tetrahydrozoline. For this consultation, Medsafe did not provide specific evidence or safety concerns for use of tetrahydrozoline, naphazoline or phenylephrine in the paediatric population.

Medsafe's response

Medsafe acknowledges that no specific safety concerns for each ocular decongestant were included in the initial consultation.

The main goal of this consultation was to propose that an age restriction for use is added to all ocular decongestant product labels. Currently, some ocular decongestants do not have an age limit and may be used in younger children. Without appropriate warnings in place, use of such products in younger children may lead to harm.

Potential safety concerns identified, but not specifically listed in the consultation, include the risk of alpha agonist toxicity due to systemic absorption or accidental oral administration of ocular decongestants. Symptoms associated with toxicity include central nervous system depression, bradycardia, hypotension, hypothermia and respiratory depression

Medsafe plans to amend the proposed statement to account for different age recommendations for different ocular decongestant medicines.

Safety concerns in children

One respondent questioned the efficacy of ocular decongestants for allergic eye disease. They also commented on safety concerns including rebound redness/inflammation on discontinuation and masking of symptoms of more serious disease. Patients may present later with more advanced disease and potentially have worse outcomes.

In children, there does appear to be evidence of toxicity and side effects with these medicines, particularly when used in infants/young children. Children may not complain of symptoms, and ocular decongestants may mask signs of ocular inflammation or infection.

Medsafe's response

Medsafe agrees with the above comments.

Safety concerns in children noted by this respondent include toxicity, side effects, lack of efficacy and masking of more serious eye-related conditions. All of which reinforce the requirement to have a mandatory label statement for age restriction for use of ocular decongestants.

8. Outcome: Ocular decongestant statements to be included in the Label Statements Database

Tables 10 and 11 shows the conditions, statements and required time frame for implementation.

The Label Statements Database will be updated on 1 August 2023. Affected products are required to have these statements by 1 February 2025.

Table 10: Naphazoline warning statements for Label Statements Database

Medicine/Group/Class	Conditions	Statement	Required by
Naphazoline	• For ophthalmic use • When used as an ocular decongestant for eye redness and/or minor eye irritation only • When used in combination with another medicine(s), the age limit for the combination product should reflect the highest age limit overall from each medicine	• Do not use in children under 12 years of age	1 February 2025

Table 11: Tetrahydrozoline warning statements for Label Statements Database

Medicine/Group/Class	Conditions	Statement	Required by
Tetrahydrozoline (tetryzoline)	• For ophthalmic use • When used as an ocular decongestant for eye redness and/or minor eye irritation only • When used in combination with another medicine(s), the age limit for the combination product should reflect the highest age limit overall from each medicine	• Do not use in children under 6 years of age	1 February 2025