MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Proposed warning and advisory statement relating to the harm of opioid abuse

13 July 2022

Consultation outcome

Contents

Executive Summary

From 16 February to 4 April 2022, Medsafe sought feedback on proposed new warning statements for opioid medicines, to be implemented through the Label Statements Database (LSD). The LSD lists the warning and advisory statements that are required on the medicine and related product packaging labels under the Medicines Regulations 1984.

Minimising opioid-related harm is a topic that has been discussed in New Zealand and internationally. Warning statements on the product packaging of opioid medicines may provide additional information to consumers highlighting the risks associated with use.

This report is a summary of the submissions received. Part 1 is an overview of the respondents. Parts 2 to 6 summarise the general comments received for each consultation question and Medsafe's response. Part 7 is the final warning statement.

Medsafe received 41 valid responses to the consultation, and most respondents supported the labelling change. Respondents included health care professionals, industry members, and members of the public.

As a result of the consultation, the warning statement 'Use of this medicine has the risk of overdose and dependence' will be placed on the packaging of opioid medicines. This statement supersedes the currently required statements for codeine products.

The proposed implementation timeframe for the new warning statements was 12 months following the LSD update on the Medsafe website. However, based on feedback from industry, the implementation timeframe has been revised to 18 months following the update of the LSD. The LSD will be updated on 1 September 2022, and sponsors must update their opioid package labels by 1 March 2024. Medsafe encourages sponsors to update their labels before this date, if feasible.

About the consultation

Opioids are indicated to relieve moderate to severe acute pain, and for pain management in cancer or palliative care patients. Concerns over the long-term safety and efficacy of opioids have been raised when opioids are used for chronic non-cancer pain. Several countries have seen an increase in prescription opioid-related deaths and overdoses.

Medsafe presented a paper on opioid abuse, misuse, and dependence to the Medicines Adverse Reactions Committee (MARC) at their 184th meeting held on 3 December 2020. The MARC noted that from the global data, New Zealand is doing comparatively well with the issue of opioid abuse, misuse, and dependence. Nevertheless, the Committee agreed that there is some evidence of opioid related harm in New Zealand.

A second paper was presented at the 186th MARC meeting held on 10 June 2021. This paper discussed options for minimising opioid abuse, misuse, and dependence in New Zealand. The options presented were changes to product information, enhanced safety monitoring, labelling changes, prescribing changes, and communication activities.

The 184th and 186th MARC meeting minutes and reports are published online on the Medsafe website.

The MARC recommended Medsafe undertake a Label Statements Database (LSD) consultation to include warning and advisory statements on the manufacturer's original pack for opioid products in order to highlight the risks of abuse, misuse, and dependence.

Currently, opioid medicines do not have a required label statement except for codeine, which requires the phrase 'codeine is an addictive substance'. Therefore, information on the packaging label for opioid medicines is variable.

Table 1 outlines the proposed warning and advisory statements for opioid medicines, the proposed conditions and the proposed implementation date.

Table 1: Proposed warning and advisory statements for opioid medicines

Medicine/Group/Class	Conditions	Statement	Required by
Opioids Examples include: Alfentanil Buprenorphine Codeine Dextromethorphan Dihydrocodeine Fentanyl Methadone Morphine Oxycodone Pethidine Remifentanil Tramadol	For all classifications, including prescription, and all uses	• [*name of opioid*] is an addictive substance [*or*] • Use of this medicine has the risks of overdose and dependence [*or*] • Contains opioid	12 months from when the Label Statements Database is updated

As part of the consultation, Medsafe sought comments on:

- Whether the package labelling for opioids should include a warning and advisory statement relating to the harm of abuse, misuse, and dependence
- The preferred statement option (see Table 1)
- The proposed conditions and implementation date (see Table 1)

Consultation results

Thank you to everyone who responded to the survey.

We have analysed and summarised the survey results.

The results are divided into seven parts as follows:

1. Overview of respondents
2. Summary of responses: Should the package labelling for opioid medicines include a warning and advisory statement relating to the harm of abuse, misuse, and dependence?
3. Summary of responses: Which of the proposed statements should be including on the package labelling for opioid medicines?
4. Proposed conditions
5. Proposed timeframe for implementation
6. Other comments
7. Outcome: Statement to be included in the Label Statements Database

1. Overview of respondents

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

A total of 43 submissions were received via the consultation tool. Two submissions were not valid as the comments were not related to the topic of opioid misuse, abuse and dependence. Therefore, only the 41 valid responses will be discussed in this report.

As shown in Table 2, most responses were submitted by individuals (61%). There were 15 respondents (37%) who submitted on behalf of an organisation or group.

Table 2: Respondent type – individual or organisation

Respondent	Number	Percentage (%)
As an individual	25	61.0%
On behalf of an organisation or group	15	36.6%
Not answered	1	2.4%
Total	**41**	**100%**

Most respondents were based in New Zealand (85%), as shown in Table 3.

Table 3: Respondent location

Location	Number	Percentage (%)
New Zealand	35	85.4%
Australia	5	12.2%
Not answered	1	2.4%
Total	**41**	**100%**

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

- Healthcare professional (HCP), n=27
- Public, n=2
- Industry, n=10
- Other, n=3.

Table 4: Respondent category

Respondent	Categorised as	Number	Percentage (%)
Healthcare professional	HCP	24	58.5%
Professional body	HCP	4	9.8%
Member of the public	Public	2	4.9%
Sponsor	Industry	8	19.5%
Industry organisation	Industry	1	2.4%
Supplier	Industry	1	2.4%
Other	Other	1	2.4%
Total		**41**	**100%**

Most healthcare professional respondents were in the pharmacy profession (see Table 5).

Table 5: Health care professional respondents

Profession	Number	Percentage (%)
General practice	1	3.6%
General surgeon	1	3.6%
Anaesthetist and pain specialist	5	17.9%
Nurse practitioner	4	14.3%
Registered nurse	2	7.1%
Pharmacy	10	35.7%
Professional body	4	14.3%
Not answered	1	3.6%
Total	**28**	**100%**

2. Summary of responses – Should the package labelling for opioid medicines include a warning and advisory statement relating to the harm of abuse, misuse, and dependence?

Question

Should the package labelling for opioid medicines include a warning and advisory statement relating to the harm of abuse, misuse, and dependence?

Include warning statements – Agree Y/N

- Yes, n= 32
- No, n= 9

Table 6: Include warning statements for opioids – Summary of responses

		Respondent category									
		All (n=41)		HCP (n=28)		Public (n=2)		Industry (n=10)		Other (n=1)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Include warning statements	Yes	32	78.0	25	89.3	1	50.0	5	50.0	1	100
	No	9	22.0	3	10.7	1	50.0	5	50.0	-	-

Question

Please add your comments

There were 22 responses to this part of the question. Comments have been summarised by respondent category below.

Comments from healthcare professionals

Healthcare professionals were generally supportive of the consultation and agreed that a label statement should be added to the packaging of opioid medicines. Healthcare professionals felt that patients may appreciate any type of additional information on opioid harm, and the warning statement may serve as a reminder to discuss any concerns of the medicine with their doctor.

Two respondents commented on inappropriate medication sharing that occurs with pain medicines. Therefore, a warning statement may prompt individuals to think twice about sharing medicines that could have undesirable side effects.

One respondent was concerned with the amount of information that would be displayed on the dispensed product. A label statement may distract patients from the information on the dispensing label and cause confusion. A second respondent was concerned that a warning statement may discourage patients from taking opioids resulting in inadequate pain control.

Medsafe's response

The label statements are not intended to replace advice given by a healthcare professional. Healthcare professionals must discuss the benefits and risks of the medicine and advise patients on how to safely use opioid medicines for pain management. Label statements on the manufacturers packaging are intended to supplement the information found on the dispensing label, provided the medicine is dispensed in the original packaging. They may also act as a prompt to the pharmacist to discuss risks with the patient. Prescribers and pharmacists have a responsibility to ensure the directions of use for prescription medicines are clear and understandable.

Comments from public/other

Health consumers have the right to be fully informed, and a label statement would enable consumers to have access to additional information. However, this label would need to be simplified with clear wording to indicate opioid harm is a possibility rather than a guaranteed outcome.

Medsafe's response

Medsafe agrees that health consumers have the right to be fully informed about their health. The purpose of this consultation is to identify if a label statement is needed and if so, what a suitable statement would be.

Comments from industry

The industry raised concerns whether the addition of a warning statement would have any effect on reducing opioid harm. They noted that all opioid products in New Zealand are supplied via a prescription. Therefore, healthcare professionals should have adequately counselled patients on the adverse effects of a medicine.

Industry also commented that due to the PHARMAC tendering system, opioid products are supplied in large quantity pack sizes and repackaged down into smaller containers when dispensed to patients. In these cases, additional warning statements would not be seen by the patient and it would be more beneficial to adopt the use of a Cautionary Advisory Label (CAL) on the dispensed product.

Medsafe's response

Medsafe agrees that healthcare providers must discuss the benefits and risks of a medicine with the patient.

Medsafe and the MARC note that most medicines are repackaged down in community and hospital pharmacies but consider it helpful to have these statements available when the original manufacturer's pack is dispensed to patients.

The Pharmaceutical Society of New Zealand (PSNZ) is responsible for CALs. Medsafe will contact PSNZ to explore the feasibility of a CAL for opioids.

Outcome

The Label Statements Database will be updated to include a new warning statement for opioids.

3. Summary of responses: Which of the proposed statements should be included on the package labelling for opioid medicines?

Question

Which of the proposed statements should be included on the package labelling for opioid medicines?

Agree Y/N

- [Name of opioid] is an addictive substance, n=7
- Use of this medicine has the risk of overdose and dependence, n=19
- Contains opioid, n=4
- None of the above, n=10
- Not answered, n=1

Table 7: Proposed label statement – Summary of responses

	Respondent category									
	All (n=41)		HCP (n=28)		Public (n=2)		Industry (n=10)		Other (n=1)	
Preferred statement	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
[Name of opioid] is an addictive substance	7	17.0	4	14.3	1	50.0	2	20.0	-	-
Use of this medicine has the risk of overdose and dependence	19	46.4	16	57.2	-	-	2	20.0	1	100
Contains opioid	4	9.8	2	7.1	1	50.0	1	10.0	-	-
None of the above	10	24.4	6	24.4	-	-	4	40.0	-	-
Not answered	1	2.4	-	-	-	-	1	10.0	-	-

Question

If none of the above, please suggest an alternative statement, or why it should not be included

There were 19 responses received to this part of the question. Comments have been summarised by respondent category below.

Comments from healthcare professionals

Most healthcare professionals preferred the statement 'Use of this medicine has the risk of overdose and dependence'. Six suggested combining the statement options. The phrases 'Only take as directed by a medical professional' and 'Please discuss with your medical practitioner' were additional suggestions for the warning statement.

Some healthcare professionals were concerned about using medical jargon, particularly the term 'dependence', which patients may not understand. Healthcare professionals agreed that the statement needs to be simple and clear.

Medsafe's response

Medsafe agrees the label statement must be clear and understandable for consumers. Opioid dependence, long-term use and overdose are discussion points that should occur during patient counselling. Therefore, these terms should be familiar to patients when used in a label warning statement.

Medsafe acknowledges that a combination statement may better highlight the risk of opioid harm but notes the space restrictions on product labels. The addition of 'Only take as directed by a medical professional' or 'Please discuss with your medical practitioner' may be helpful, but we recognise that directions for use are clearly stated on the dispensing label and again must consider space restrictions on the product packaging.

Comments from industry

Industry recommended using simple lay terms and supported the concept of flexibility with the words used in the label statement. One sponsor expressed concern with 'Contains opioid', stating that the public may not know what an opioid is. Therefore, the public may not understand the risk of opioid-related harm.

Lastly, one sponsor suggested that different label statements should be used based on the indication of the product. For example, buprenorphine/naloxone products could have the phrase 'Contains opioid', and oxycodone products could have the phrase '[Name of this product] is an addictive substance'.

Medsafe's response

Statements can be altered and combined, providing the intent isn't changed. Medsafe is happy to work with sponsors to adopt suitable wording for their product's label statement. Differentiating statements by drug indication may be difficult as indications vary between products that contain the same active ingredient, and some products have multiple indications. However, see Part 4 'Proposed conditions' for products indicated for opioid dependence and products used solely in anaesthesia and post-operative analgesia.

Comments from public/other

None.

Outcome

Medsafe will adopt the statement 'Use of this medicine has the risks of overdose and dependence' as most respondents agreed with this proposed wording.

4. Proposed conditions

Question

Do you agree with the proposed conditions: 'For all classifications, including prescription, and all uses'?

Agree Y/N

- Yes, n=32
- No, n= 7
- Not answered, n=2

Table 8: Proposed conditions – Summary of responses

		Respondent category									
		All (n=41)		HCP (n=28)		Public (n=2)		Industry (n=10)		Other (n=1)	
Question	**Response**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Agree with proposed conditions	Yes	32	78.0%	26	92.9%	1	50%	4	40%	1	100%
	No	7	17.1%	1	3.6%	0	0%	6	60%	0	0%
	Not answered	2	4.9%	1	3.6%	1	50%	0	0%	0	0%

Question

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

There were 10 comments received in this section.

Comments from healthcare professionals

Some HCPs commented that tramadol can be described as an 'atypical opioid' because it does not represent the same degree of risk (for example, respiratory depression) as other opioids. Therefore, the statement should consider the distinction between stronger and weaker opioids.

Other HCPs commented that opioids used in a surgical setting should be exempt from the required statement, as the packaging would never be viewed by the patient. Similarly, medicines indicated for cancer pain should not be required to carry the warning.

Comments from industry

Industry commented that the warning statement should not be required for medicines indicated for opioid use disorder or medicines administered only in hospital settings, such as those combined with anaesthetics. One comment stated that the warning should apply only to opioid products that are dispensed to patients.

Medsafe comments and outcome

Medsafe agrees that products indicated for opioid dependence and products used solely in anaesthesia and post-operative analgesia do not need a warning statement.

Medsafe considers the proposed statement appropriate for all opioids.

The conditions will be 'For all classifications, including prescription, and all uses except when indicated solely for anaesthetic use or postoperative or obstetric analgesia, or for opioid dependence'.

5. 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=30
- No, n=10
- Not answered, n=1

Table 9: Proposed timeframe – Summary of responses

		Respondent category									
		All (n=41)		HCP (n=28)		Public (n=2)		Industry (n=10)		Other (n=1)	
Question	Response	No.	%	No.	%	No.	%	No.	%	No.	%
Agree with proposed timeframe	Yes	30	73.2%	25	89.3%	1	50%	3	30%	1	100%
	No	10	24.4%	3	10.7%	0	0%	7	70%	0	0%
	Not answered	1	2.4%	0	0%	1	50%	0	0%	0	0%

Question

If no, please suggest an alternative timeframe.

There were 13 responses received to this part of the question.

Comments from healthcare professionals

Most healthcare professionals indicated that the warning statement should be implemented as quickly as possible.

Comments from industry

Industry commented that a longer implementation timeframe is desirable to allow for manufacturing and supply lead times and sale of existing stock. The suggested timeframes were between 18 and 36 months.

Outcome

The implementation timeframe will be extended from 12 months to 18 months. The Label Statements Database will be updated on 1 September 2022. Therefore, the implementation date for updating package labels will be 1 March 2024.

6. Other comments related to label statements

Healthcare professional comments

Healthcare professionals supported having a warning statement on the labelling but said that this should not be at the expense of clear information on what can be a small label area. They also noted that more potent opioids have a higher risk of harm, but it is probably not useful to differentiate the risks via advisory warnings

Some HCPs commented that opioids are often repackaged for dispensing and therefore the patient would not see the warning statement in these situations. The dispensing label may also obscure information on the manufacturer's pack. To ensure that the patient sees the warning statement, HCPs suggested having a Cautionary and Advisory Label for the pack or the dispensing label.

HCPs commented that there is a balance between providing important safety information and the risk of making patients hesitant to take opioids despite requiring this type of pain relief. Opioids have potential harms other than abuse, misuse and dependence. They should be for short-term use where possible, except when used for cancer pain or palliative care.

Respondents also commented that the warning statement may prompt individuals to think twice about inappropriately sharing pain medicines.

There was concern that patients may not understand the term 'opioid'.

Some HCPs commented that although a label warning has merit, additional strategies are needed to mitigate the risk of opioid misuse, abuse and dependence. Examples included improving access to naloxone, investigating nasal administration, reviewing opioid pack sizes and indications and increasing awareness of pain management guidelines. However, some of this work would be outside of Medsafe's remit.

Medsafe's response

Medsafe agrees that the warning statement should be succinct so that it does not interfere with other information on the label. Medsafe considers one general statement to be suitable across the class of opioids, given that weaker opioids can contribute to dependence and overdose when combined with other medicines.

Comments from industry

Industry stated that the warning statement should align with Australian requirements for harmonised labelling. They noted patients would be more likely to see a Cautionary and Advisory Label than a warning statement on the pack. A warning statement may not fit on small containers and industry suggested it should only be required on the secondary packaging.

Industry noted that the Medicines Adverse Reactions Committee recommended the opioid warning statement to promote further engagement and discussion between the patient and their primary healthcare professional. Industry suggested having a prompt in the prescribing software for the prescriber to have the discussion at the time of prescribing. The pharmacist would supplement this discussion at the point of dispensing. Engagement with relevant medical and pharmacy groups would also be beneficial to explore options for patient education. Healthcare professional counselling at multiple time points in the prescribing and dispensing process may have more impact than simply adding a warning statement on the packaging.

Medsafe's response

There is no requirement in Australia for a warning statement on the manufacturer's packaging of opioid medicines. Therefore, the proposed statement does not pose a barrier to harmonisation. The Medicines Regulations 1984 also allow for warning statements to be included on the secondary packaging where it is impractical to put the warnings on the primary label because the container is too small.

At their 186th meeting, the Medicines Adverse Reactions Committee discussed options for minimising opioid abuse, misuse and dependence, including the proposed warning statement. In line with the Committee's recommendations, Medsafe has also:

- reviewed the risks and benefits of dihydrocodeine and restricted the indications
- developed a consumer information leaflet describing the risks of opioids
- requested data sheet updates for opioid products to align with the safety warnings in the Australian product information (search for a data sheet)
- contacted the New Zealand ePrescription Service about using the platform for a prescription drug monitoring programme for opioids.

The Pharmaceutical Society of New Zealand (PSNZ) is responsible for Cautionary and Advisory Labels (CAL). Medsafe will contact PSNZ to explore the feasibility of a CAL for opioids.

Implementing a prompt in practice management software is outside of Medsafe's remit.

Other comments

To make the warning statement highly visible on the pack, one respondent suggested a coloured box, large font or upper-case lettering.

Medsafe's response

Medsafe appreciates this suggestion. For information about labelling requirements, see the Guidelines on the Regulation of Therapeutic Products in New Zealand – Part 5: Labelling of medicines and related products (PDF, 326 KB, 18 pages).

7. Outcome: Statement to be included in the Label Statements Database

Table 10 shows the conditions, statement and required time frame for implementation.

The Label Statements Database will be updated on 1 September 2022. Affected products are required to have these statements by 1 March 2024.

The currently required statement for prescription codeine products is superseded by the new statement. The entry for over-the-counter codeine products will be removed from the Label Statements Database as codeine products are now available only on a prescription.

Table 10: Opioid statement for Label Statements Database

Medicine/Group/Class	Conditions	Statement	Required by
Opioids Examples include: Alfentanil Buprenorphine Codeine Dextromethorphan Dihydrocodeine Fentanyl Methadone Morphine Oxycodone Pethidine Remifentanil Tramadol	For all classifications, including prescription, and all uses except when indicated solely for anaesthetic use or postoperative or obstetric analgesia, or for opioid dependence	• Use of this medicine has the risks of overdose and dependence	1 March 2024