



Reclassification of sedating antihistamines to remove ‘for the treatment of anxiety’ from the restricted medicine classification statements

Submission to the Medicines Classification Committee

Medsafe
January 2018



New Zealand Government

1. Purpose

The Medicines Adverse Reactions Committee recently recommended that 'for the treatment of anxiety' should be removed from the restricted medicine classification statements of sedating antihistamines.

This paper presents the background and data to support a recommendation that 'for the treatment of anxiety' should be removed from the restricted medicine classification statements of sedating antihistamines.

2. Background

Medicines Classification Committee (MCC)

At the 19th meeting on 20 May 1998, the MCC considered a submission from the National Toxicology Group for the reclassification from pharmacy-only to restricted medicine of sedating anti-histamines when sold as sleeping aids. The submission provided evidence of increasing intentional abuse of products marketed in this way.

At the 19th meeting the MCC recommended that:

- a. a sedating anti-histamine or any other over-the-counter product indicated for sedation or anxiety should be classified as a restricted medicine when in packs sufficient for five days' supply or less; those containing more than five days' supply should be classified as prescription medicines
- b. the Ministry be asked to review the classification of all oral sedating antihistamine products where the anti-histamine is not combined with another active ingredient
- c. the Ministry compose guidelines for all over-the-counter products indicated for insomnia or anxiety.

[The minutes of the 19th MCC meeting are available on the Medsafe website \(item 6iii\).](#)

At the 20th meeting on 19 November 1998 an update was provided to the MCC on their recommendations at the last meeting. Medsafe had not supported the recommendation on the grounds that most products on the market would become prescription medicines rather than restricted medicines. This would cause them to be removed from the market as they would not be prescribed. Companies had not been consulted on the possibility of their products being changed to prescription medicines. Nor did the recommendation harmonise with the Australian classification for these medicines.

The matter was resolved by means of a postal consultation held in October 1998. The five respondents agreed to limit the maximum pack size for sale as restricted medicine to 10 doses rather than to five days' supply. This would bring the pack size limits into line with those of Australia.

Medsafe wrote guidelines for medicines marketed for sedation or anxiety which harmonised with the proposed Australian guidelines for sedating antihistamines. The New Zealand guidelines were already on the website and would be incorporated into the new edition of The New Zealand Regulatory Guideline for Medicines which was currently under preparation.

The *Gazette* notice to implement the classification changes was published on 26 November 1998.

[The minutes of the 20th MCC meeting are available on the Medsafe website \(item 6.1\).](#)

New Zealand Regulatory Guidelines for Medicines (NZRGM)

Before the introduction of the Label Statements Database in 2011, specific packaging and labelling requirements for certain medicines were described in Part D of the NZRGM¹.

The following entry was included in Volume 1, Edition 6.3, 2011, of the NZRGM:

4.10.1 Anti-anxiety or anti-insomnia medicines	
Sedating antihistamines and any other over-the-counter medicines indicated for insomnia or anxiety may be sold as restricted medicines when the following conditions apply. Those medicines which are for insomnia or anxiety and which do not fulfil these conditions must be sold as prescription medicines.	
Pack size:	Not more than 10 doses
Use:	For short-term use only Not for children under 12 years Do not exceed maximum stated dose
Warning statements:	Consult a doctor if sleeplessness or anxiety persists
Note:	Normal sedation warnings apply for sedating antihistamines (see Medicines Regulations 1984, Regulation 22)

The NZRGM has now been replaced by the Guidelines on the Regulation of Therapeutic Products in New Zealand.

Medicines Adverse Reactions Committee (MARC)

At the 166th meeting on 26 June 2016, the MARC considered a report from Medsafe that provided a summary of the available information on the indications, contraindications and classifications of sedating antihistamines. The Medsafe paper for the MARC is attached in Appendix 1.

One of the recommendations from the 166th MARC meeting was that 'for the treatment of anxiety' should be removed from the restricted medicine classification statements of sedating antihistamines because there is little evidence for the use of sedating antihistamines for anxiety.

[The minutes from the 166th MARC meeting are available on the Medsafe website.](#)

Label Statements Database (LSD)

In September 2017, Medsafe published a consultation seeking comments from interested parties on proposed changes recommended by the MARC at the 166th meeting to labelling requirements for sedating antihistamines that are available without prescription. One of the proposed warning statement changes was to remove anxiety from the conditions.

[The closed consultation is available on the Medsafe website.](#)

One submission was received in response to the consultation which supported removing anxiety. The feedback provided was that the indication for anxiety has never been promoted as appropriate therapy in child mental health.

[The outcome of consultation is also available on the Medsafe website.](#)

Part A

3. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

In Schedule 1 to the Medicines Regulations 1984, the following sedating antihistamines have 'for the treatment of anxiety' in the restricted medicine classification statement and will therefore be included in this submission:

- brompheniramine
- chlorpheniramine
- cyclizine
- dexchlorpheniramine
- diphenhydramine
- doxylamine
- meclozine
- mepyramine
- pheniramine
- promethazine
- trimeprazine (British Approved Name) – alimemazine is the International Non-proprietary Name but is not included in Schedule 1.

Ketotifen was included in the MARC paper but is not included in the above list because it does not include 'for the treatment of anxiety' in the restricted medicine classification statement.

4. Proprietary name(s)

The list of products with the sedating antihistamines included in this submission, currently available in New Zealand are listed in Appendix 2. It appears that no sedating antihistamines are indicated for anxiety in New Zealand.

Ketotifen is not included in the list of products because it does not include 'for the treatment of anxiety' in the restricted medicine classification statement.

5. Present classification of the medicine

The current classification of the sedating antihistamines included in this submission is shown in Table 1.

Table 1: Current classification of sedating antihistamines included in this submission

Brompheniramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing brompheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Chlorpheniramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing chlorpheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Cyclizine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use other than in medicines used for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 6 dosage units; for oral use in medicines used for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p>
Dexchlorpheniramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night</p>

	<p>pack containing dexchlorpheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Diphenhydramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing diphenhydramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant; for oral use in a sealed container of not more than 10 tablets or capsules for the prevention or treatment of motion sickness in adults and children over 2 years of age except when sold at a transport terminal or aboard a ship or aircraft</p>
Doxylamine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing doxylamine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Meclozine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; in a pack size of up to 10 dosage units for the treatment of anxiety or insomnia</p> <p>Pharmacy-only; in a sealed container of not more than 12 tablets or capsules for the prevention or treatment of travel sickness except when sold at a transport terminal or aboard a ship or aircraft</p>
Mepyramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for dermal use</p>

	General sale; for external use in medicines containing 2% or less in packs not exceeding 25 grams
Pheniramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for ophthalmic use except when sold in practice by an optometrist registered with the Optometrists and Dispensing Opticians Board; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing pheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Promethazine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing promethazine or when at least 1 of the other active ingredients is a sympathomimetic decongestant; for oral use in a sealed container of not more than 10 tablets or capsules for the prevention or treatment of motion sickness in adults and children over 2 years of age except when sold at a transport terminal or aboard a ship or aircraft</p>
Trimeprazine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing trimeprazine or when at least 1 of the other therapeutically active ingredients is a sympathomimetic decongestant</p>

6. Classification sought

The classification sought for the sedating antihistamines included in this submission is shown in Table 1.

Table 2: Classification sought for the sedating antihistamines included in this submission

Brompheniramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing brompheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Chlorpheniramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing chlorpheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Cyclizine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use other than in medicines used for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 6 dosage units; for oral use in medicines used for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p>
Dexchlorpheniramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p>

	<p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing dexchlorpheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Diphenhydramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing diphenhydramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant; for oral use in a sealed container of not more than 10 tablets or capsules for the prevention or treatment of motion sickness in adults and children over 2 years of age except when sold at a transport terminal or aboard a ship or aircraft</p>
Doxylamine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing doxylamine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Meclozine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; in a pack size of up to 10 dosage units for the treatment of anxiety or insomnia</p> <p>Pharmacy-only; in a sealed container of not more than 12 tablets or capsules for the prevention or treatment of travel sickness except when sold at a transport terminal or aboard a ship or aircraft</p>
Mepyramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the</p>

	<p>manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for dermal use</p> <p>General sale; for external use in medicines containing 2% or less in packs not exceeding 25 grams</p>
Pheniramine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for ophthalmic use except when sold in practice by an optometrist registered with the Optometrists and Dispensing Opticians Board; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing pheniramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant</p>
Promethazine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing promethazine or when at least 1 of the other active ingredients is a sympathomimetic decongestant; for oral use in a sealed container of not more than 10 tablets or capsules for the prevention or treatment of motion sickness in adults and children over 2 years of age except when sold at a transport terminal or aboard a ship or aircraft</p>
Trimeprazine	<p>Prescription; except when specified elsewhere in this schedule</p> <p>Restricted; for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of anxiety or insomnia; for oral use for the treatment of anxiety or insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units</p> <p>Pharmacy-only; for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing trimeprazine or when at least 1 of the other</p>

	therapeutically active ingredients is a sympathomimetic decongestant
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7. Classification status in other countries (especially Australia, UK, USA, Canada)

In Australia, for the treatment of anxiety is not included in the classification statements of sedating antihistamines.

As one example, dexchlorpheniramine is classified as a:

- prescription medicine; except when included in Schedule 2 (pharmacy-only medicine) or 3 (restricted medicine)
- restricted medicine in oral preparations except
 - a. when included in Schedule 2; or
 - b. for the treatment of children under 2 years of age
- pharmacy-only medicine when combined with one or more other therapeutically active substances in oral preparations when:
 - a. at least one of the other therapeutically active substances is a sympathomimetic decongestant; or
 - b. in a day-night pack containing dexchlorpheniramine in the bed-time dose where the day and night doses are in the same immediate container or immediate wrapper, except in preparations for the treatment of children under 2 years of age.

Further information regarding products in Australia, UK, USA and Canada is attached in Appendix 1 (refer to section 2.5).

There is variation in the amount of information available for different sedating antihistamines in different countries, which is sometimes dependant on the classification. However, when the information is available there are no products indicated for the treatment of anxiety.

8. Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute

The list of products with the sedating antihistamines included in this submission, currently available in New Zealand are listed Appendix 2. It appears that no sedating antihistamines currently marketed are indicated for anxiety in New Zealand.

9. Labelling or draft labelling for the proposed new presentations(s)

The LSD currently has the following entry for sedating antihistamines:

Antihistamines, sedating Includes:	For oral use	<ul style="list-style-type: none"> • Do not use in children under 2 years old. • This medicine may cause drowsiness. 	1/06/2019
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Alimemazine Brompheniramine Chlorphenamine Cyclizine Dexchlorpheniramine Diphenhydramine Doxylamine Ketotifen Meclozine Mepyramine Pheniramine Promethazine		<ul style="list-style-type: none"> • Be cautious about driving a vehicle or operating machinery within 8 hours of taking this medicine. 	
	In cough and cold medicines	<ul style="list-style-type: none"> • Do not use in children under 6 years old. • Consult a healthcare professional before using in children aged six years and over. • Do not use with other antihistamines. • Do not use with other medicines intended to treat the symptoms of the common cold except on the advice of a healthcare professional. 	1/08/2011
	For the treatment of insomnia or anxiety	<ul style="list-style-type: none"> • Do not use in children under 12 years old. • Do not exceed the maximum stated dose. • This product is for temporary use only. [or] For short term use only. • Consult a doctor if sleeplessness (or anxiety) persists. 	1/08/2011

The following changes will need to be made to the LSD if the indication ‘for the treatment of anxiety’ is removed:

Antihistamines, sedating Includes: Alimemazine Brompheniramine Chlorphenamine Cyclizine Dexchlorpheniramine Diphenhydramine Doxylamine Ketotifen Meclozine Mepyramine Pheniramine Promethazine	For oral use	<ul style="list-style-type: none"> • Do not use in children under 2 years old. • This medicine may cause drowsiness. • Be cautious about driving a vehicle or operating machinery within 8 hours of taking this medicine. 	1/06/2019
	In cough and cold medicines	<ul style="list-style-type: none"> • Do not use in children under 6 years old. • Consult a healthcare professional before using in children aged six years and over. • Do not use with other antihistamines. 	1/08/2011

		<ul style="list-style-type: none"> Do not use with other medicines intended to treat the symptoms of the common cold except on the advice of a healthcare professional. 	
	For the treatment of insomnia or anxiety	<ul style="list-style-type: none"> Do not use in children under 12 years old. Do not exceed the maximum stated dose. This product is for temporary use only. [or] For short term use only. Consult a doctor if sleeplessness (or anxiety) persists. 	1/08/2014 1/06/2019

Part B

Reasons for requesting the classification change including benefit-risk analysis

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

It is potentially confusing having 'for the treatment of anxiety' in the classification statements of sedating antihistamines. The benefit of the proposed change is that the classification statements of sedating antihistamines would be less confusing.

11. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk

Little harm will result from removing 'for the treatment of anxiety' from the classification statements of sedating antihistamines.

There are no sedating antihistamines currently marked in New Zealand for the treatment of anxiety so there will be no need for any sponsor to submit a Self-assessable Change Notification, a Changed Medicine Notification or a New Medicine Application.

12. Local data of special considerations relating to New Zealand

There is limited information on the use of sedating antihistamines for the treatment of anxiety in New Zealand.

The paper presented to the MARC in Appendix 1 identified a Cochrane review regarding hydroxyzine for generalised anxiety disorder. The comments from Medsafe concluded the review indicate that there is limited evidence to support the use of sedating antihistamines for anxiety disorders.

Antihistamines have been used in the past in the treatment of generalised anxiety disorder because they have some anxiolytic effect and are not habit forming².

The New Zealand Formulary does not list any sedating antihistamines for the treatment of anxiety.

13. Discussion and conclusions

There are no sedating antihistamines currently marketed in New Zealand for the treatment of anxiety. There is little evidence to support the use of sedating antihistamines for anxiety.

Medsafe recommends that the MCC accepts the MARC's recommendation that 'for the treatment of anxiety' should be removed from the restricted medicine classification statements of the following sedating antihistamines:

- brompheniramine
- chlorpheniramine
- cyclizine
- dexchlorpheniramine
- diphenhydramine
- doxylamine
- meclozine
- mepyramine
- pheniramine
- promethazine
- trimeprazine.

If the MCC agrees to recommend that 'for the treatment of anxiety' should be removed from the restricted medicine classification statements of sedating antihistamines, the LSD should also be updated to remove the condition 'for the treatment of anxiety'.

References

1. Medsafe. 2011. *New Zealand Regulatory Guidelines for Medicines (Volume 1, Edition 6.13, 2011)*. Wellington: Medsafe.
2. Hoehn-Saric R. 1998. Generalised Anxiety Disorder: Guidelines for Diagnosis and Treatment. *CNS Drugs* 9(2) 85-98.
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