APPLICATION FOR RECLASSIFICATION OF PHENYLEPHRINE

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Submitted by:

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1. Cold, Cough, Allergy; Bronchodilator and Antiasthmatic Drug Products for over-the-counter Human Use; final monograph for OTC Nasal Decongestant Drug Products. Federal Register, Vol 59, No.: 162, Aug 23, 1994.

2. Adverse Drug Reaction – Medicine Summary for Phenylephrine (Source: ADRAC Database from 1972 – to date).

Part A

International non-proprietary name: PHENYLEPHRINE

Proprietary Name: Phenylephrine

Name of company requesting reclassification: Wyeth Consumer Healthcare

Dose Form: Inclusion of "Classification Conditions" for "Solid Dose Form For Oral Use".

Indications for which change is sought: No change is proposed.

The substance is indicated "for the symptomatic relief of nasal inflammation or congestion due to infection of the nasal mucosa, allergic conditions producing rhinitis, vasomotor rhinitis, sinus inflammation or congestion and inflammation or congestion associated with the Eustachian tube."

"Sympathomimetics may be used as adjunct therapy with analgesics, antibiotics, antitussives, antihistamines or expectorants in treatment of respiratory tract disease."

Present Classification:

Pharmacy only
Phenylephrine: for oral use in medicines containing more than 0.5%; for nasal use in medicines containing more than 1%; for ophthalmic use in medicines containing 5% or less and more than 1%.

Prescription
Phenylephrine: except when specified elsewhere in the Schedule.

General Sale
Phenylephrine: for nasal or ophthalmic use in medicines containing 1% or less, for oral use in medicines containing 0.5% or less.

Classification sought:

Pharmacy only
Phenylephrine: for oral use **in liquid form** containing more than 0.5% **and in solid dose form containing more than 10 milligram per dose form**; for nasal use in medicines containing more than 1%; for ophthalmic use in medicines containing more than 1% for ophthalmic use in medicines containing 5% or less and more than 1%.

Prescription
Phenylephrine: except when specified elsewhere in the Schedule.

General Sale
Phenylephrine: for nasal or ophthalmic use in medicines containing 1% or less, for oral use **in liquid form** containing 0.5% or less and **in solid dose form containing 10 milligram or less per dose form**.

History of Classification of Phenylephrine in New Zealand

5 June 1984 – The Medicines Regulations 1984

> Pharmacy only medicine
> Phenylephrine, and its salts, except when contained in medicines for nasal instillation.

9 December 1996 – The Medicines Regulations, 1984 – Amendment No.7

> Prescription Medicine
> Phenylephrine; for ophthalmological use in medicines containing more than 0.12%.
>
> Pharmacy only medicine
> Phenylephrine; except for nasal use when sold at an airport, except for ophthalmological use.

10 November 1999 – 22nd Meeting of Medicines Classification Committee decided to harmonize the classification with NDPSC, which is the present classification.

Classification status in other countries:

COUNTRY	STATUS
Australia	OTC
Austria	OTC
Belgium	OTC
Canada	OTC
Finland	OTC
France	OTC
Germany	OTC
Ireland	OTC
Italy	OTC
Mexico	OTC
New Zealand	OTC
Portugal	OTC
Spain	OTC
Switzerland	OTC
UK	OTC
United States	OTC
Denmark	Rx
Netherlands	Rx
Sweden	Rx
Hong Kong	OTC
Japan	OTC
Korea	OTC
Philippines	OTC
Singapore	OTC
Taiwan	OTC
Thailand	OTC

Extent of usage in NZ and elsewhere:

Phenylephrine contains oral dose products (both Liquid and Solid dose form) sold in Australia and New Zealand.

From l July 2002-30 June 2003 (12 months)

Total Units sold in Australia = 1,736,243

Total Units sold in New Zealand = 71,000

Proposed labelling: Not applicable

Proposed warning statements: Not applicable

Other products containing phenylephrine for oral use marketed in New Zealand:

Dimetapp Infant Drops

Dimetapp Elixir

Dimetapp Colour Free Elixir

Dimetapp DM Elixir

Dimetapp DM Colour Free Elixir

Dimetapp DM Colour Free Paediatric Drop

Demazin Drops

Demazin Syrup

Demazin Clear Syrup

Part B:

Statement of benefits:

- The proposed reclassification provides a clear and meaningful “Conditions” for the scheduling status for phenylephrine in solid dosage forms.

- To be eligible for the current “General Sale” status, a 10 milligram tablet or capsule of phenylephrine should weigh 2 grams or more. This is not an ideal weight for solid oral preparation. The proposed classification rectifies this situation, and

- The proposed classification will open the avenue for the introduction of phenylephrine-containing tablets. This will reduce the problem that exist with the diversion of pseudoephedrine-containing products for illicit purposes and help the community to have easy access to an alternate decongestant solid dose form.

Ease of self-diagnosis:

Most of the symptoms associated in the indicators listed for phenylephrine are easily identified and treated by the consumers. Labelling of these medicines always advises the consumers that these are for temporary relief. The consumers are also advised to seek medical advice if the symptoms persist or worsen.

Relevant Comparative Data for Like Compounds

Decongestants

Decongestants are vasoconstrictive drugs that reduce nasal congestion. However, decongestants have no effect on histamine or any other mediator involved in the allergic reaction. Therefore, decongestants are commonly administered in combination with antihistamines.

The decongestants that are available for oral (systemic) and topical (intranasal and ophthalmic) administration are listed in Table 1.

TABLE 1: Decongestants

Topical intranasal decongestants: **Short acting (4-to 6-h duration)** Ephedrine Epinephrine Naphazoline Phenylephrine Tetrahydrozoline **Intermediate acting (8-to10-h duration)** Xylometazoline **Long Acting** Oxymetazoline	**Ophthalmic decongestants** Epinephrine Naphazoline Oxymetazoline Phenylephrine Tetrahydrozoline **Systemic decongestants** Ephedrine Phenylephrine Pseudoephedrine **Inhalers** Desoxyephedrine Propylhexedrine

Pharmacology

Phenylephrine hydrochloride is a sympathomimetic (Table 2) with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity and is without significant stimulating effects on the central nervous system at usual doses. Its pressor activity is weaker than that of noradrenaline but of longer duration. Phenylephrine and its salts are most commonly used either topically or by mouth for the symptomatic relief of nasal congestion (Martindale – 32nd Edition, Page 1066).

TABLE 2: Classification of Cough/Cold Sympathomimetics

DRUG	DIRECT ACTION	INDIRECT ACTION	MIXED ACTION
Phenylephrine	✔ primary action		
Pseudoephedrine	✔	✔	✔

Receptor Affinity

In the physiological situation Noradrenaline is the natural adrenergic neuronal transmitter. Circulating adrenaline (from the adrenal medulla) as well as many other compounds (agonists) are capable of also eliciting an effector tissue response via direct stimulation of the adrenoreceptors. Many substances have been shown to antagonise neuronal responses at the adrenoreceptors. It has been demonstrated that many agonists as well as antagonists show a selectivity of receptor, i.e. some adrenoreceptors would be stimulated/blocked by some drugs but not by others. On the premise of the observed selectivity of the agonists and antagonists on the effector receptors, a concept of different classes of adrenoreceptor evolved.

The adrenoreceptors were designated as two major types, α or β. Further classification based on selective responses to specific agonists/antagonists has led to α_1 or α_2 and β_2 type receptor categories.

TABLE 3: Classification of Cough/Cold Sympathomimetics for Receptor Affinity

Sympathomimetic	α Adrenoreceptors	β Adrenoreceptors
Phenylephrine	✔ primary action	✔ no substantial effect except at higher doses
Pseudoephedrine	✔ primary action	✔ to a lesser degree

Pharmacokinetics

Phenylephrine has low oral bioavailability owing to irregular absorption and first-pass metabolism by monoamine oxidase in the gut and liver. When injected subcutaneously or intramuscularly it takes 10 to 15 minutes to act; subcutaneous and intramuscular injections are effective for up to about one hour and up to about two hours respectively. Intravenous injections are effective for about 20 minutes. Systemic absorption follows topical administration. The amount delivered by the oral route is hard to predict but systemic effectiveness has been demonstrated. Data on drug distribution and metabolite excretion are not known.

TABLE 4: Pharmacokinetics of Cough/Cold Sympathomimetics

Sympathomimetic	Half-life	Onset of Action (Oral)	Time to Peak Effect (Oral)	Duration of Action	
				Oral	Topical
Phenylephrine	2-3 hrs	15-20 min	30-90 min	2-4 hrs	30min-4hrs
Pseudoephedrine	5-8 hrs∗	15-30min	30-60min	4-6 hrs	No product

∗ The rate of renal elimination of basic sympathomimetics such as pseudoephedrine and phenylpropanolamine is significantly dependent upon urinary pH.

Dosages

Phenylephrine is commonly included as a decongestant for the relief of cough and cold symptoms. The recommended dose can be seen below.

TABLE 5: Oral Dosage

Sympathomimetic	FDA Recommended Dosage Range		
	Adult	**6-12 years**	**2-6 years**
Phenylephrine HCL	10 mg every 4 hrs not to exceed 60 mg/ 24 hrs	5 mg every 4 hrs not to exceed 30 mg/ 24 hrs	2.5 mg every 4 hr not to exceed 15mg/ 24hrs
Pseudoephedrine HCL/Sulphate	60 mg every 4-6 hrs not to exceed 240mg/ 24 hrs	30mg every 4-6 hrs not to exceed 120mg/ 24 hrs	5 mg every 4-6 hrs not to exceed 60mg/ 24 hrs

Source: Compiled from FDA. Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for OTC Human Use; Tentative Final Monograph for OTC and Nasal Decongestant Drug Products, Vol 59, No.:162(Aug 23, 1994 – page 43410 Column3).

Safety

Sympathomimetic drugs may produce a wide range of side effects. Many of these effects are similar to excessive stimulation of the sympathetic nervous system mediated via the agonist activity of the drug at that receptor site. Sympathomimetic therapy should not be continued or readministered to patients who have previously shown adverse symptoms.

These side effects indicate the need for medical attention. The incidence of serious side effects may be more frequent at higher doses.

TABLE 6: Serious Side Effects

Sympathomimetic	Serious Side Effects – Incidence Less Frequent
Phenylephrine	Chest discomfort or pain
Pseudoephedrine	Convulsions Hallucinations Irregular or slow heartbeat Shortness of breath or troubled breathing

SOURCE: Adapted from United States Pharmacopeial Convention, Inc. (1991) USP DI (11th ed.) Rockville, MD: USPC.

Cardiac Effects

Phenylephrine is mainly an α agonist with weak β-adrenoreceptor activity so there should be little or no cardiac activity. The vasoconstriction in the periphery causes an increase in both systolic and diastolic blood pressure. This pressor action is followed by a reflex bradycardia but there is little change in the contractile force of the heart. Phenylephrine has no direct effect on the $\beta 1$ receptors of the heart which control heart rate, conduction velocity and contractile force, so arrhythmias are not likely.

Less Serious Side Effects

These side effects indicate the need for medical attention only if they continue or are bothersome.

Less serious side effects may be more frequent at higher doses.

TABLE 7: Less Serious Side Effects

Sympathomimetic	**Less Serious Side Effects**	
	Incidence more frequent	**Incidence less frequent**
Phenylephrine		• Dizziness • Nervousness • Restlessness • Trembling • Troubled breathing • Unusual weakness △ Unusual paleness
Pseudoephedrine	Nervousness Restlessness Trouble in sleeping	▲ Difficulty or painful urination △ Fast or pounding heartbeat △ Unusual paleness • Headache • Dizziness or light-headedness • Increased sweating • Nausea or vomiting • Trembling • Troubled breathing • Weakness

The less serious side effects mainly result from unwanted vascular and cardiovascular effects or CNS stimulation.

△ Probably a vascular or cardiovascular effect (see serious side effects for explanation).

▲ Urinary retention due to contraction of the bladder sphincter and relaxation of the bladder muscle.

- Probably as a result of CNS stimulation.

SOURCE: Adapted from United States Pharmacopeial Convention, Inc. (1991) USP DI (11th ed.) Rockville, MD: USPC

Overdosage Symptoms

The table below compares the overdosage symptoms of phenylephrine and pseudoephedrine.

TABLE 8: Overdose

Sympathomimetic	Symptoms of Overdose
Phenylephrine	Fast, irregular, pounding heartbeat Hypertension (headache, continuing and/or slow heartbeat) Sensation of fullness in the head Tingling in the hands or feet Vomiting
Pseudoephedrine	Convulsions Hallucinations Increase in blood pressure Irregular heartbeat – continuing Shortness of breath or troubled breathing – severe or continuing Slow or fast heartbeat - severe or continuing Unusual nervousness, restlessness, or excitement

SOURCE: Adapted from United States Pharmacopeial Convention, Inc. (1991) USP DI (11th ed.) Rockville, MD:USPC

Local data or special considerations relating to NZ:

There is no local data separately available for phenylephrine, other than the extent of usage of phenylephrine-containing products in New Zealand.

Interactions with other medicines:

Furazolidone:
Furazolidone, an antibacterial agent with monoamine oxidase inhibitory (MAOI) activity, may increase the pressor response of mixed or indirect-acting sympathomimetics in a manner similar to the other MAOI's, which would result in hypertension.

Methyldopa:

Methyldopa may increase the pressor response to sympathomimetics, resulting in hypertension. However, the effect of this interaction may depend on the degree of direct-, mixed- or indirect-acting activity of the sympathomimetic.

MAO Inhibitors

Many studies report that the coadministration of monoamine oxidase (MAO) inhibitors and indirect- or mixed-acting sympathomimetics results in severe headache, hypertension and hyperpyrexia, possibly resulting in a hypertensive crisis. Sympathomimetics with direct-acting effects do not appear to interact, or interact to a small extent, with MAO inhibitors.

Tricyclic Antidepressants

Tricyclic antidepressants appear to increase the pressor response to direct-acting sympathomimetics and decrease the sensitivity to the indirect-acting agents.

Alpha-adrenergic blocking agents

α blockade either directly (e.g. labetalol, phenoxybenzamine, phentolamine, prazosin) or by agents with some α-adrenergic blocking action (e.g. haloperidol, phenothiazines, thioxanthines) may block or decrease the pressor effect of the sympathomimetics (i.e. vasoconstriction could be reduced)

Antihypertensives and diuretics used as antihypertensives

The pressor effects of sympathomimetics may interfere with the antihypertensive therapy. Blood pressure monitoring may be required.

Beta-adrenergic blocking agents

β blockade may result in unopposed α stimulation. Hypertension, excessive bradycardia and heart block are possible.

CNS stimulants

Other medications with CNS stimulating properties plus sympathomimetic therapy (especially pseudoephedrine and phenylpropanolamine) may result in excessive CNS activity, e.g. nervousness, irritability, insomnia, convulsions, cardiac arrhythmias.

Digitalis glycosides

Concurrent use with sympathomimetics may increase the risk of cardiac arrhythmias.

Levodopa

Concurrent use with sympathomimetics may increase the risk of cardiac arrhythmias.

Sympathomimetics

Concurrent use of two sympathomimetics may increase CNS stimulation, increase cardio-vascular effects or increase the potential for other side effects.

Thyroid hormones

Concurrent use with sympathomimetic therapy may increase the effects of either of the medications. Thyroid hormones enhance the risk of coronary insufficiency when sympathomimetics are taken by patients with coronary artery disease.

Ref: Drug Information for Community Pharmacists, OTC Drugs: Coughs & Colds (1992) Dept of Pharmacy, The University of Queensland.

<u>Contraindications for Sympathomimetics</u>:

- Sympathomimetics should be used with caution in patients who are susceptible to its cardiovascular actions.

- Care is needed in conditions which predispose a patient to adverse effects on the heart, such as hyperthyroidism.

- Pre-existing hypertension.

- Elderly patients who may have pre-existing coronary or cerebrovascular disease.

Adverse events: Summary of ADR report from ADRAC, Australia on phenylephrine.

		ALL REPORT DATES Causality Unclear Excluded Total Suspected	Sole
- **Cases Including Medicine**		10	3
- **Occurrences of Medicine**		10	3
- **Reactions Related to Medicine**		29	8
Cardiac disorders	Palpitations	1	1
Eye disorders	Glaucoma NOS	2	0
	Conjunctivitis	2	0
	Keratitis	2	2
Infections and Infestations	Blepharitis	1	0
Nervous System disorders	Dystonia	1	0
	Oculogyric crisis	1	0
	Syncope	1	0
Psychiatric disorders	Agitation	1	0
	Confusion	1	0
	Delirium	1	0
	Hallucination NOS	1	0
	Insomnia	1	1
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema NOS	1	1
Skin and subcutaneous tissue disorders	Periorbital oedema	2	0
	Dermatitis bullous	1	0
	Rash vesicular	1	0
	Rash Erythematous	1	0
	Pruritus NOS	1	0
	Rash maculo-papular	1	0
	Sweating increased	2	0
	Vasospasm	1	1
Vascular disorders	Hypotension NOS	1	1
	Hypertension NOS	1	1

This summary includes ADR reports received by ADRAC (TGA) from 1972 – to date on phenylephrine-containing products.

Potential for abuse or misuse:

Although other sympathomimetic agents such as pseudoephedrine, have been reported to be misused, Wyeth Consumer Healthcare is not aware of any abuse or misuse related to phenylephrine.

Conclusion:

- Phenylephrine-containing products are already available on General Sale. This submission only requests for a more elaborate "Conditions" of the classification status of phenylephrine in Solid Oral Dosage forms.

- Phenylephrine-containing products are available in Australia for many years. The Medicine Summary which includes ADR reports received by ADRAC on phenylephrine-containing products from 1972 – to date indicates that phenylephrine is safe to use by self-selection by consumers.

- The data contained in this application supports the availability of phenylephrine in solid dose forms for General Sale and Pharmacy only depending on the level of phenylephrine in the product.

References:

1. Cold, Cough, Allergy; Bronchodilator and Antiasthmatic Drug Products for over-the-counter Human Use; final monograph for OTC Nasal Decongestant Drug Products. Federal Register, Vol 59, No.: 162, Aug 23, 1994.

2. Adverse Drug Reaction – Medicine Summary for Phenylephrine (Source: ADRAC Database from 1972 – to date).