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**THIRD REPORT OF THE
EXPERT ADVISORY COMMITTEE
ON
NONPRESCRIPTION COUGH AND COLD REMEDIES
TO THE
HEALTH PROTECTION BRANCH
HEALTH AND WELFARE CANADA**

PHENYLPROPANOLAMINE, LOZENGES AND COMBINATIONS

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Canada

REPORT OF THE EXPERT ADVISORY COMMITTEE ON NONPRESCRIPTION COUGH AND COLD REMEDIES TABLE OF CONTENTS

		PAGE
INTRODUCTION		5
RECOMMENDATIONS		5
1.	PHENYLPROPANOLAMINE HYDROCHLORIDE, ORAL NASAL DECONGESTANT	5
2.	LOZENGES	4
	2.1 Introduction	4
	2.2 General Recommendations	5
	2.3 Specific Recommendations	5
	2.3.1 <u>Eucalyptus Oil (or Eucalyptol) as a Nasal Decongestant in Lozenge Dosage Forms</u>	5
	2.3.2 <u>Eucalyptus Oil (or Eucalyptol), Alone or in Combination with Menthol, as an Antitussive in Lozenge Dosage Forms</u>	6
	2.3.3 <u>Eucalyptus Oil or Eucalyptol as an Expectorant in Lozenge Dosage Forms</u>	7
	2.3.4 <u>Menthol as a Nasal Decongestant in Lozenge Dosage Forms</u>	7
	2.3.5 <u>Menthol, Alone or in Combination with Eucalyptus Oil, as an Antitussive in Lozenge Dosage Forms</u>	8
	2.4 Lozenge Combinations	9
3.	COMBINATIONS	9
	3.1 Introduction	9
	3.1.1 <u>Analgesics</u>	9
	3.1.2 <u>Bronchodilator Combinations</u>	11
	3.1.3 <u>Anticholinergic Combinations</u>	11
	3.1.4 <u>Antihistamine and Expectorant Combinations</u>	11
	3.2 Criteria for Acceptability of Nonprescription Cough and Cold Combination Products	11
	3.3 Criteria for Lack of Acceptability of Nonprescription Combination Cough and Cold Products	13
	3.4 Recommendations on Aromatic Combination Drugs Which Are Applied Topically to the Skin or	

	Inhaled in Steam		14
	3.4.1	<u>Nasal Decongestant Effectiveness of Combination Aromatic Topical Rubs</u>	14
	3.4.2	<u>Nasal Decongestant Effectiveness of Combination Aromatic Products Inhaled in Steam</u>	16
	3.4.3	<u>Antitussive Effectiveness of Combination Aromatic Topical Rubs</u>	17
	3.4.4	<u>Antitussive Effectiveness of Combination Aromatic Products Inhaled in Steam</u>	19
3.5	Cough and Cold Combinations by Pharmacological Category		20
	3.5.1	<u>Acceptable Combinations</u>	20
	3.5.2	<u>Unacceptable Combinations</u>	21
	3.5.3	<u>Combinations For Which No Recommendations Have Been Made</u>	21
	3.5.4	<u>Combinations For Which Additional Information Is Required</u>	22
	LIST OF REFERENCES		24
	APPENDIX Names and Affiliations of Members of The Expert Advisory Committee		32

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INTRODUCTION

This report is the third of three reports of the Expert Advisory Committee on Nonprescription Cough and Cold Remedies. It summarizes the Committee's recommendations to the Health protection Branch on phenylpropanolamine, lozenge dosage forms and combinations of ingredients in nonprescription cough/cold remedies. Cold ingredients (antihistamines, nasal decongestants and anticholinergics) and cough ingredients (antitussives, expectorants and bronchodilators) were dealt with in the Committee's first and second reports, respectively.

The terms of reference of the Committee were published in Information Letter No. 658 on February 29, 1984 and were reiterated in the introductory section of the Committee's first report. In addition, the manner in which the Committee has gone about its task was described in the introduction of the first report and will, therefore, not be repeated here.

Following a detailed review of each drug, the drug was assigned to one of three categories, as follows:

- | | |
|--------------|---|
| Category I | Generally recognized as safe and effective. |
| Category II | Not generally recognized as safe and effective. Drugs demonstrated to be either unsafe and/or ineffective were placed in this category. |
| Category III | Available data insufficient to permit final classification. |

RECOMMENDATIONS

1. PHENYLPROPANOLAMINE HYDROCHLORIDE, ORAL NASAL DECONGESTANT

Although phenylpropanolamine (PPA) is an oral nasal decongestant, it was not included in the Committee's report on antihistamines, nasal decongestants and anticholinergics as the Committee was waiting for additional safety data on the cardiovascular effects of the drug. The safety and efficacy of PPA were assessed following an extensive review of the published literature, a review of adverse drug reactions reported to the Health protection Branch from 1965-1986,¹ and a review of three text books on PPA.²⁻⁴ In addition, the Committee reviewed three written submissions from industry on PPA,⁵⁻⁷ one of which was also presented orally to the Committee.⁷

The safety of PPA came into question following reports of marked pressor effects in humans following the use of a product called Trimolets.⁸⁻¹³ These reports originated in Australia and caused considerable anxiety in the scientific community. However, it later became apparent that the drug

contained in Trimolets was either d-pseudoephedrine or d-norpseudoephedrine, not phenylpropanolamine (which is d,l-norephedrine).² Furthermore, although advertised as a timed release preparation, Trimolets actually contained 85 mg of immediate release d-PPA, approximately 3.5 times the conventional 25 mg dose of PPA.²

The results of 20 clinical trials¹⁴⁻³³ and one epidemiologic study³⁴ were evaluated by the Committee. The trials involved approximately 2000 subjects and included normotensive, hypertensive, and obese individuals, as well as asthmatics, patients with hyperglycaemia and patients with severe autonomic impairment. Overall, these studies showed that PPA used in Canadian formulations poses no significant health hazard as far as cardiovascular side effects are concerned. Considering the pharmacological activity of PPA (sympathomimetic), adverse cardiovascular reactions would be expected to be the most serious side effect experienced by users of this drug.

The pressor effects of PPA (dl-norephedrine) were studied in an 881 subject, multicentre, randomized, double blind, one day clinical trial¹⁵ in which sustained release (75 mg), immediate release (25 mg thrice daily) and placebo were compared. Statistically significant but clinically unimportant (2-2.5 mmHg) pressor effects were observed. In this study the pressor response to PPA was inversely related to the degree of obesity and was less in subjects with higher baseline diastolic blood pressures. Thus, individuals who might be considered to be most at risk (mildly hypertensive and obese patients) would have a safety margin equal to or even greater than normal individuals. On the other hand, subjects with the rare disorder of severe autonomic dysfunction, manifested as orthostatic hypotension, experience an exaggerated pressor response to PPA.³⁰

The Committee also reviewed three recent studies³¹⁻³³ performed by SmithKline Consumer Products and CIBA Consumer Pharmaceuticals which were initiated at the request of the FDA to study the cardiovascular effects of PPA. In a double blind, placebo controlled, parallel dose range study in 15 health volunteers, the cardiovascular effects of single oral doses of PPA (50, 75, 150, 250 mg) were determined.³² The average peak increases in supine blood pressure for PPA compared to placebo were 17/7 mmHg at 50 mg, 24/7 mmHg at 75 mg, 42/12 mmHg at 150 mg and 78/32 mmHg at 250 mg, suggesting that significant pressor responses to PPA are associated with single immediate release doses of 75 mg and higher, a dose 3 times the usual 25 mg dose. No significant arrhythmias or

changes in cardiac rate were noted following 24 hour Holter monitoring of subjects. When present, the pressor response was transient, lasting a matter of minutes, while plasma levels of PPA persisted at or near peak values for more than 4 hours.

In a 17 day, double blind, placebo controlled, parallel tachyphylaxis study, 15 subjects were given placebo for days 1-3 to eliminate placebo responders, and either 100 mg immediate release PPA on days 4 through 15, 50 mg PPA twice daily with challenge with 100 mg on days 4, 10 and 15, or placebo with challenge with 100 mg PPA on days 4, 10 and 15.³¹ This study established that tolerance to the pressor response to PPA develops after multiple dosing, an attribute of PPA which is considered favourable.

The response of 12 healthy volunteers to increasing single oral doses of PPA (12.5, 25, 50, 75, 100, 125 and 150 mg) was evaluated in a recent single blind study.³³ PPA was given in ascending doses until subjects met withdrawal criteria (systolic BP \geq 180 mmHg, diastolic BP \geq 110 mmHg, heart rate \geq 150 \leq 45 bpm or increases of \geq 40 mmHg in systolic BP or \geq 30 mmHg diastolic BP, or significant sympathomimetic complaints or EKG changes). Two subjects met vital sign criteria at 100 mg, 5 at 125 mg, 3 at 150 mg; 2 did not meet the criteria at 150 mg. This study clearly demonstrated a dose response relationship between PPA and elevations in BP, with the BP elevating effects most prominent when subjects were in the supine position. The dose of PPA found to cause potentially clinically significant BP increases was 125 mg or higher.

The Committee was also provided with a detailed analysis of 333 serious putative adverse reactions associated with PPA use from the published literature and the FDA's Spontaneous Reporting System.³⁵ According to this review, the risks of death or any serious adverse reaction associated with the use of PPA alone appears to be very, very small.

Based on its review of data outlined briefly above, the Committee concluded that PPA, at the doses specified below, is a safe and effective oral nasal decongestant.

Recommendation:	Category I as an oral nasal decongestant.
G.P. Availability:	Recommended for inclusion in proprietary medicines (is currently available).

Dosage: 25 mg every 4 hours or 37.5 mg every 6 hours, not to exceed a maximal daily dose of 150 mg.

Labelling
Recommendations: As for other oral nasal decongestants, see section 2.6, the Committee's first report.

2. LOZENGES

2.1 Introduction

When a review of marketed lozenge products was undertaken, it became apparent that this class of OTC drug products contained a wide variety of active ingredients from various pharmacological groups. At least 62 separate active ingredients were identified, most of which had not been reviewed previously by the Committee. These ingredients possessed diverse pharmacological actions, such as antiseptic, local anaesthetic, counterirritant, analgesic, demulcent, antihistaminic, nasal decongestant or antitussive. The Committee, following consultation with the Health Protection Branch, decided to focus its efforts on drug ingredients previously encountered, as to do an exhaustive review of all ingredients would greatly enlarge the Committee's mandate and extend the review process. As a consequence, only a partial review of lozenge ingredients was carried out. It was recommended that a separate Committee should be formed to review this product category, if so desired by the Health Protection Branch.

Ingredients in lozenges fall into two basic groups: those acting systemically (e.g. dextromethorphan) and those acting locally (e.g. glycerin). There was virtually no information available in the published literature on the pharmacology of ingredients found in nonprescription lozenge dosage forms. However, at the Committee's request, industry (via the Nonprescription Drug Manufacturers' Association of Canada) provided a number of unpublished studies which were reviewed by the Committee and which formed the basis of a number of recommendations.

The Committee was aware that their dosage recommendations for lozenges were not consistent throughout. In some cases dosages were expressed as per cent concentrations, in other cases by weight (mg/lozenge). This discrepancy arose because of the nature of the data submitted to the Committee for review. It has been suggested to the Committee that aromatics in lozenge dosage form are topical drugs and should therefore, be expressed as per cent concentrations (as for other topical drugs), rather than by weight per lozenge.³⁶

It was assumed by the Committee that under normally recommended usage conditions, throat lozenges are designed to deliver their systemically active ingredients via the gastrointestinal route, following dissolution in saliva. Lozenges are not considered to be effective buccal or sublingual dosage forms as only a small proportion of the medication would be expected to be absorbed through the oral mucosa.^{37,38}

2.2 General Recommendations

The following general recommendations were made concerning ingredients found in lozenge dosage forms:

2.2.1

The dosage and dosage interval for any Category I systemically acting drug previously reviewed by the Committee, and which is contained in a lozenge dosage form, should be the same as that approved for conventional oral dosage forms (e.g. diphenhydramine, phenylpropanolamine, phenylephrine, dextromethorphan and guaifenesin).

2.2.2

A drug previously reviewed by the Committee and placed in Category II or III should remain in the same category, as appropriate, when present in a lozenge dosage form, unless acceptable data are provided to permit a category change.

2.2.3

When taken as directed, lozenges must provide appropriate doses for both systemically and locally acting drug ingredients.

2.3 Specific Recommendations

2.3.1 Eucalyptus Oil (or Eucalyptol) as a Nasal Decongestant in Lozenge Dosage Forms

No published or unpublished studies were available on eucalyptus oil or eucalyptol as a single ingredient nasal decongestant in lozenge dosage form. The effects of a combination lozenge containing eucalyptus oil (4 mg) plus menthol (5 mg) were compared with placebo in an unpublished, investigator blinded, randomized crossover study of 8 patients with nasal congestion due to a common cold.³⁹ Changes in nasal airway flow and

changes in nasal surface temperature were measured for 30 minutes after drug ingestion. As the active lozenge was significantly superior ($p < 0.05$) at only one time point, using the more objective method of measurement (nasal airflow), and because this difference was in part due to a decrease in airflow in the placebo group, it was concluded that this combination of ingredients had not been shown to possess significant nasal decongestant activity.

Recommendation: Because of insufficient evidence of efficacy, either alone or in combination with menthol, eucalyptus oil or eucalyptol was placed in Category III as a nasal decongestant when present in a lozenge dosage form.

2.3.2 Eucalyptus Oil (or Eucalyptol), Alone or in Combination with Menthol, as an Antitussive in Lozenge Dosage Forms

The Committee reviewed a number of unpublished studies on the antitussive effectiveness of eucalyptus oil 0.15% w/w, either alone or in combination with menthol 0.25% w/w, in a lozenge dosage form.⁴⁰⁻⁴⁵ These studies were investigator blinded only, as it was impossible to blind subjects because of the unique, potent flavouring of the two aromatics.

In a citric acid aerosol challenge study of 36 subjects, the superior antitussive effectiveness of eucalyptus oil (0.15%), menthol (0.26%) and the combination of the two was demonstrated over that of an unmedicated lozenge.⁴⁰ Furthermore, this combination of ingredients was shown to be statistically significantly superior to an unmedicated control lozenge in reducing cough in 48 chronic bronchitic patients.⁴¹ Two further studies in 96 chronic bronchitic patients were supportive of the efficacy of eucalyptus oil as an antitussive: one study compared eucalyptus oil (0.15%) in combination with menthol (0.26%) with an unmedicated lozenge control,⁴² the other study compared eucalyptus oil (0.15%) alone with an unmedicated lozenge.⁴³ Two other studies in chronic bronchitic patients failed to demonstrate statistically significant superiority of eucalyptus oil either alone⁴⁴ or in combination with menthol^{44,45} over an unmedicated control lozenge. One of the studies was a pilot study of

only 9 subjects.⁴⁵ In the other study, great subject-to-subject variability, as well as the complexity of a four-treatment crossover study, were considered to have prevented the achievement of statistical significance.⁴⁴

Recommendation: From the above, it was concluded that eucalyptus oil (0.15% w/w) and the combination of eucalyptus oil (0.15% w/w) plus menthol (0.26% w/w) are effective antitussives when available in a lozenge dosage form. Category I classification was, therefore, recommended for eucalyptus oil alone or in combination with menthol, at the concentrations specified. Inclusion in proprietary medicines was also recommended.

2.3.3 Eucalyptus Oil or Eucalyptol as an Expectorant in Lozenge Dosage Forms

Recommendation: As no studies, either published or unpublished, were available on the expectorant efficacy of eucalyptus oil or eucalyptol in lozenge dosage forms, Category III classification was recommended.

2.3.4 Menthol as a Nasal Decongestant in Lozenge Dosage Forms

The Committee reviewed three unpublished studies on the nasal decongestant effectiveness of menthol when present in combination with eucalyptus oil³⁹ or when present as a single active ingredient.^{46,47} No published studies were available for review.

As outlined under section 2.3.1, the combination of menthol (5 mg) with eucalyptus oil (4 mg) in a lozenge dosage form³⁹ was not considered to have effective nasal decongestant activity. Some support for the nasal decongestant action of menthol (20 mg), as a single active ingredient, was provided by a randomized, double blind, parallel design study of 30 subjects suffering from either a cold or allergic rhinitis.⁴⁶ However, this study was not considered sufficiently convincing to permit Category I classification. According to a third randomized, double blind, parallel design, single dose study of 40 patients suffering from colds, a medicated

lozenge containing menthol (11 mg) was statistically significantly superior to a placebo lozenge in decreasing nasal congestion for up to 2 hours after a single dose.⁴⁷ It would appear that the appropriate dosage interval would be not more than every 2 hours. However, it was not possible to specify a dosage interval with any certainty based on the data provided.

Recommendation: It was, therefore, recommended that menthol should be given Category I classification as a nasal decongestant when present in a lozenge dosage form at a dose of 11 mg. Inclusion in proprietary medicines was also recommended.

2.3.5 Menthol, Alone or in Combination with Eucalyptus Oil, as an Antitussive in Lozenge Dosage Forms

The Committee reviewed a number of unpublished studies on the antitussive effectiveness of menthol 0.26% w/w, either alone or in combination with eucalyptus oil 0.15% w/w, in a lozenge dosage form.^{40-42,44,45,48} With the exception of reference 48, these studies are reviewed under section 2.3.2, and provide support for the effectiveness of menthol (0.26% w/w) as a nasal decongestant in lozenge dosage form.

In a randomized, single blind, crossover study of 50 patients with chronic bronchitis, menthol (0.26%) was shown to be statistically significantly superior to an unmedicated placebo lozenge in reducing numbers of recorded coughs. Both lozenges provided statistically significant cough reduction compared to pretreatment cough frequency.⁴⁸

Recommendation: From the submitted data, it was concluded that menthol (0.26% w/w), either alone or in combination with eucalyptus oil (0.15% w/w), is an effective antitussive when available in a lozenge dosage form. Category I classification was, therefore, recommended for menthol alone or in combination with eucalyptus oil, at the concentrations specified above. Inclusion in proprietary medicines was also recommended.

2.4 Lozenge Combinations

Aside from specific recommendations on the antitussive combination of menthol and eucalyptus oil in lozenge dosage form, (see sections 2.3.2 and 2.3.5), the Committee did not make any other recommendations on combinations of ingredients in lozenges. As mentioned in the introductory section to lozenges (section 2.1), it was recommended that a separate Committee should be formed to review this product category and to make recommendations concerning the suitability of individual active ingredients as well as combinations of ingredients.

3. COMBINATIONS

3.1 Introduction

After reviewing individual active ingredients from 6 different pharmacological categories, the Committee discussed combinations of ingredients. With the exception of aromatic ingredient combinations (i.e. menthol, camphor and eucalyptus oil), the approach taken on combinations was a "generic" one, with recommendations being restricted to combinations of drugs by pharmacological category (e.g. an antihistamine plus a nasal decongestant). The Committee considered written submissions supplied by industry,⁴⁹⁻⁵⁴ as well as published data from the FDA.^{55,56} In addition, the Nonprescription Drug Manufacturers' Association of Canada and the Pharmaceutical Manufacturers' Association of Canada made a joint oral and written presentation to the Committee.⁵⁷ All this information formed the data base on which the Committee made its recommendations.

The Committee was well aware of the advantages associated with the use of combination products. However, it was recommended that single ingredient products from each pharmacological category should also continue to be available to the consumer.

3.1.1 Analgesics

An Expert Advisory Committee was formed to study and make recommendations on nonprescription analgesics. Their recommendations were published on October 10, 1979 in Information Letter 565. This was followed by two further Information Letters - 622 (May 5, 1982) and 659 (February 20, 1984) based on further comments from interested parties. The Expert Advisory Committee on Nonprescription Cough and Cold Remedies briefly reviewed the analgesic recommendations referred to

above and agreed in general terms with the lists of acceptable and unacceptable analgesics, as well as the recommendations concerning combinations of analgesic ingredients.

There are factors favouring the inclusion of analgesics in cough and cold preparations. Combination products cost less than if several separate products have to be bought separately, and have enjoyed considerable consumer popularity. A number of epidemiological studies and surveys have been done which provide evidence for the existence of multiple concomitant symptoms which would benefit from multiple ingredient preparations including those containing analgesics.⁵⁷⁻⁶²

Despite the foregoing, the Committee did not favour the inclusion of analgesics in cough and cold remedies, particularly in the case of children. Consumers are often unaware of the existence of an analgesic in a combination product and may then take another analgesic resulting in "double dosing", which is clearly undesirable. The association of acetylsalicylic acid and Reye's syndrome, and the possibility of cumulative toxicity with chronic use of acetaminophen were also a concern. Use of analgesics may mask symptoms of a serious underlying disorder, such as meningitis, and increasingly pediatricians are advocating against the routine use of analgesics/antipyretics to treat fever.

Fixed dose combinations intended for children pose a particularly difficult problem. Doses for analgesics have been developed and published in the Canadian Food and Drug Regulations⁶³ based on the Analgesic Expert Advisory Committee's recommendations. However, the doses stipulated in the regulations are for very circumscribed age groups, whereas those recommended by the Expert Advisory Committee on Cough and Cold Remedies for other ingredients found in cough and cold remedies are for much broader age ranges. Reconciliation of these differing dosage statements is obviously very difficult and would require more study.

Finally, the Committee was unwilling to recommend analgesics in cough and cold remedies as they had not been provided with any data to support their effectiveness in treating symptoms associated with and specific to the common cold.

3.1.2 Bronchodilator Combinations

Bronchodilators per se were considered to be inappropriate in cough and cold remedies in combination with other ingredients. While they may be of value in an asthmatic with a cold, they were considered to be of limited value in nonasthmatics. In any case, they should only be used under medical supervision and were not considered suitable for inclusion in nonprescription products.

The Committee supported the initiative of the Health Protection Branch to place methylxanthines, exclusive of caffeine and pamabrom, on Schedule F.

3.1.3 Anticholinergic Combinations

As there were no Category I anticholinergic drugs reviewed by the Committee, combinations containing an anticholinergic were also considered unacceptable. Even if there were a Category I anticholinergic available, the combination of an oral expectorant and an oral anticholinergic would be questionable because of the opposing actions of the drugs on bronchial secretions. Also, the combination of oral anticholinergic and oral nasal decongestant would be questionable because of the theoretical possibility of additive cardiovascular and central nervous system effects.

3.1.4 Antihistamine and Expectorant Combinations

As many antihistamines have some anticholinergic activity, the combination of antihistamine and expectorant would appear to be counterproductive. However, a number of authors have reported no clinically significant drying effect of antihistamines on lower airway secretions (see section 1.1.4 of the Committee's first report on antihistamines, nasal decongestants and anticholinergics). As a result, the Committee did not object to an antihistamine - expectorant combination.

3.2 Criteria for Acceptability of Nonprescription Cough and Cold Combination Products

The Committee recommended that the following criteria should be applied in the evaluation of the acceptability of combinations of ingredients in cough and cold products:

3.2.1

Each active ingredient must contribute to at least one of the claimed effects of the product.

3.2.2

When combining active ingredients, each must not decrease the safety or efficacy of any of the other individual active ingredients.

3.2.3

Only ingredients (including both active and inactive ingredients) which serve a demonstrable or recognized pharmacological activity or pharmaceutical purpose should be included in a combination product.

3.2.4

Only one medicinal ingredient from each therapeutic category should be included, unless the two ingredients from the same therapeutic class have different mechanisms of action (e.g. menthol and dextromethorphan in an antitussive) or have been shown to provide a therapeutic advantage. Examples of acceptable advantages are enhanced effectiveness or safety. The inclusion of more than two active ingredients from the same therapeutic class is unacceptable (with the exception of certain aromatic combinations).

3.2.5

Each active ingredient must be safe and effective (i.e. Category I) when used alone and must be used in the combination product within the established dose range. In some cases data may be available to support the use of an ingredient only when present in a specific combination but not as a single ingredient. In such cases, the ingredient will be placed in Category I for use only in the acceptable combination.

3.2.6

The combination must provide rational concurrent therapy.

3.2.7

The label must reflect the anticipated major pharmacological effect or symptomatic benefit pertinent to the intended use of the product for each active ingredient so that the consumer fully understands the purpose of the product.

The label should recommend use of the product only when at least one symptom for each medicinal ingredient is present. Cautions to be included on the label should be a succinct composite of the cautionary statements developed for each single active ingredient. A statement should appear (preferably immediately after the Trade Name of the product) listing each of the basic pharmacological groups present in the product as well as the claimed symptomatic benefits.

3.2.8

The directions for use of the combination product may not exceed any maximum dosage limits established for any of the individual active ingredients.

3.3 Criteria for Lack of Acceptability of Nonprescription Combination Cough and Cold Products

The following criteria for rejecting a combination cough and cold product were agreed upon:

3.3.1

Contains an "active" ingredient not reviewed by the Committee. Any new ingredients should be reviewed by the Health Protection Branch for acceptability or lack thereof, using the same criteria as those developed by the Committee.

3.3.2

Contains an acceptable active ingredient at less than the minimum effective dose established by the Committee, unless a therapeutic advantage has been demonstrated for such a dose.

3.3.3

Contains an active ingredient deemed unacceptable by the Committee.

3.3.4

If more than two active ingredients from the same pharmacological group are combined, the combination is considered unacceptable (with the exception of certain aromatic combinations).

3.4 Recommendations on Aromatic Combination Drugs Which Are Applied Topically to the Skin or Inhaled in Steam

The Committee made a number of recommendations on individual aromatic ingredients (e.g. menthol, camphor and eucalyptus oil), applied topically or inhaled in steam, in their first and second reports. The Committee also reviewed data on combinations of aromatic ingredients and decided to make specific recommendations for some combinations as in some cases the combination could be categorized as Category I, yet the individual active ingredients could not.

3.4.1 Nasal Decongestant Effectiveness of Combination Aromatic Topical Rubs

A statistically significant ($p < 0.05$) nasal decongestant superiority of a combination product containing the following aromatic ingredients: menthol 2.6% w/v, camphor 4.73% w/v, eucalyptus oil 1.2% w/v, spirits of turpentine 4.5% w/v, cedar leaf oil 0.4% w/v, thymol 0.07% w/v and myristica oil 0.5% w/v, over a petrolatum control was demonstrated in 4 studies.⁶⁴⁻⁶⁷ Two of these studies also demonstrated the superiority of the combination over no treatment at all.^{66,67} In these studies, the duration of the effect lasted up to 8 hours and subjective relief of symptoms correlated well with objective changes in nasal airway resistance.

While two further studies failed to convincingly demonstrate the nasal decongestant effectiveness of menthol (2.8% w/w)¹, camphor (5.2% w/w)¹ or eucalyptus oil (1.3% w/w)¹ as single active ingredients, these studies did show that these 3 ingredients are active and contribute to the overall effect of the combination product.^{68,69} The other four aromatics have no support for being nasal decongestants.

1 Menthol, camphor and eucalyptus oil at 2.8% w/w, 5.2% w/w and 1.3% w/w are equivalent to menthol, camphor and eucalyptus oil 2.6% w/v, 4.73% w/v and 1.2% w/v, respectively.

Recommendation:	It was, therefore, recommended that the combination of menthol (2.6% w/v), camphor (4.73% w/v) and eucalyptus oil (1.2% w/v) be placed in Category I as a topical rub for the relief of nasal congestion associated with the common cold. Furthermore, these 3 ingredients, at the concentrations given, should be identified as the active ingredients on the label. Their effectiveness, as single active nasal decongestants, however, remains to be established (see section 2.5 of the Committee's first report).
G.P. Availability:	Recommended for inclusion in proprietary medicines (is currently available).
Dosage: -	Adults and children 2 to under 12 years of age: rub on the throat, chest and back as a thick layer. The area of application may be covered with a warm, dry cloth if desired, however, clothing should be left loose about the throat and chest to help the vapours rise to reach the nose and mouth. Application may be repeated up to three times daily or as directed by a physician.
-	Children under 2 years of age: consult a physician.
Labelling Recommendations:	Statement of Identity and Indications For Use - as for other nasal decongestants, see sections 2.6.2 and 2.6.3, Committee's first report. Warning Statement: For external use only. Do not take by mouth or place in the nose (see section 1.6.3.5, the Committee's second report).

3.4.2 Nasal Decongestant Effectiveness of Combination Aromatic Products Inhaled in Steam

A statistically significant ($p < 0.05$) nasal decongestant superiority of a combination product containing the following aromatic ingredients: menthol 3.65% w/v, camphor 7.0% w/v, thymol 0.12% w/v, turpentine 6.26% w/v, myristica oil 0.92% w/v, eucalyptus oil 1.7% w/v, oil of cedar leaf 0.6% w/v and tincture of benzoin 5.0% w/v, following inhalation in steam from a hot steam vaporizer, over a steam control was demonstrated in two studies.^{70,71} The duration of effect was found to last up to 8 hours⁷¹ and subjective impressions correlated well with objective findings.⁷⁰

In a study of single active ingredients, the nasal decongestant efficacy of menthol (0.05%)², camphor (0.1%)² and eucalyptus oil (0.025%)² was compared in each case to that of steam alone.⁷² While this study was not considered sufficient to allow Category I classification of the individual ingredients (see section 2.5, Committee's first report), it did permit a determination that menthol, camphor and eucalyptus oil should be considered the active ingredients in a combination product. No studies were found with respect to the other 5 ingredients' nasal decongestant effect, nor are they suspected of such activity.

Recommendations:	Category I classification was recommended for the combination of menthol (0.05%) ² , camphor (0.1%) ² and eucalyptus oil (0.025%) ² when inhaled in steam from a hot steam vaporizer for the relief of nasal congestion associated with the common cold. These 3 ingredients' effectiveness as single active nasal decongestants remains to be established (see section 2.5, Committee's first report).
G.P. Availability:	Recommended for inclusion in proprietary medicines (is currently available in Canada)

2 The concentrations given in brackets represent the concentrations of ingredients following dispersal in vaporizer water.

- Dosage: - Adults and children 2 to under 12 years: add 15 mL of solution, for each litre of water, directly to the water in a hot steam vaporizer. Breathe in the medicated vapours. May be repeated up to three times daily or as directed by a physician.
- Children under 2 years of age: consult a physician.

Labelling

Recommendations: Statement of Identity and Indications For Use - as for other nasal decongestants, see sections 2.6.2 and 2.6.3, Committee's first report.
Warning Statement: For external use only. Do not take by mouth or place in the nose (see section 1.6.3.5, Committee's second report)

3.4.3 Antitussive Effectiveness of Combination Aromatic Topical Rubs

A statistically significant ($p < 0.05$) antitussive superiority of a combination product containing the following aromatic ingredients: menthol 2.6% w/v, camphor 4.73% w/v, eucalyptus oil 1.2% w/v, spirits of turpentine 4.5% w/v, cedar leaf oil 0.4% w/v, thymol 0.07% w/v and myristica oil 0.5% w/v, over a petrolatum control was demonstrated in 5 unpublished clinical trials.⁷³⁻⁷⁷ Two of these studies were of patients with chronic bronchitis s^{73,77}; the remaining three studies were of citric acid aerosol-induced cough.⁷⁴⁻⁷⁶

The Committee had previously reviewed studies of the antitussive effectiveness of individual aromatic ingredients in topical rub preparations and had placed camphor and menthol in Category I, whereas eucalyptus oil/eucalyptol was placed in Category III (see sections 1.3.1, 1.3.6 and 1.5.6, respectively, of the Committee's second report).

Two subcombinations of ingredients were studied by the citric acid aerosol method.⁷⁴ One combination was of menthol, camphor and eucalyptus oil; the other was of turpentine, thymol, cedar leaf oil and myristica oil. In both cases, the concentrations of ingredients were the same as those given for the total product cited above.

Both of these combinations showed statistically significant cough reductions compared to placebo, with menthol, camphor and eucalyptus oil demonstrating greater activity than the second mixture. However, turpentine, thymol, cedar leaf oil and myristica oil have not been shown individually to make a contribution and have only been shown together to have an effect in one study.

Based on the above, it was concluded that aromatic topical rubs, at the concentrations cited, are safe and effective antitussives. It was recommended that menthol, camphor and eucalyptus oil should be identified as the active ingredients on the product label. The other

ingredients need further study, probably as a combination, to be considered contributors to the antitussive effect.

Recommendation:	Category I classification was recommended for the combination of menthol 2.6% w/v, camphor 4.73% w/v and eucalyptus oil 1.2% w/v, when applied as a topical rub as an antitussive.
G.P. Availability:	Recommended for inclusion in proprietary medicines (is currently available).
Dosage:	- As for combination aromatic topical rubs as nasal decongestants, see section 3.4.1.
Labelling Recommendations:	Statement of Identity, Indications For Use and Warning Statements - as for other antitussives, see section 1.6, the Committee's second report.

3.4.4 Antitussive Effectiveness of Combination Aromatic products Inhaled in Steam

A statistically significant ($p < 0.05$) antitussive superiority of a combination product containing the following aromatic ingredients: menthol 3.65% w/v, camphor 7.0% w/v, thymol 0.12% w/v, turpentine 6.26% w/v, myristica oil 0.9% w/v, eucalyptus oil 1.7% w/v, oil of cedar leaf 0.6% w/v and tincture of benzoin 5.0% w/v, following inhalation in steam over a steam control was demonstrated in three clinical studies.⁷⁸⁻⁸⁰ Two of the studies were of cough induced by citric acid aerosol challenge,^{78,79} the third was a study of patients with acute upper respiratory tract infections.⁸⁰ A fourth study, using citric acid aerosol methodology, failed to demonstrate significant cough reductions probably because the closed room used in the study was premoisturized with steam before aromatics were added and subjects placed in the room.⁸¹ The high moisture level appeared to prevent statistically significant further effects either by steam alone or steam plus aromatics.

Based on data previously reviewed by the Committee, camphor and menthol were placed in Category I as single ingredient antitussive agents; however, eucalyptus oil/eucalyptol was placed in Category III (see the Committee's second report, sections 1.3.1, 1.3.6, and 1.5.6, respectively).

Based on the above, it was concluded that a combination aromatic product containing ingredients as specified above, is safe and effective as an antitussive following inhalation in steam. The data support the conclusion that menthol and camphor are the principal antitussive ingredients. The other ingredients need further study to be considered as contributors to the antitussive effect.

Recommendation: Category I classification was recommended for the combination of menthol (0.05%)³ and camphor (0.1%)³ when inhaled in steam from a hot steam vaporizer as an antitussive.

3 The concentrations given in brackets represent the concentrations of ingredients following dispersal in vaporizer water.

G.P. Availability:		Recommended for inclusion in proprietary medicines (is currently available in Canada)
Dosage:	-	As for combination aromatic products inhaled in steam as nasal decongestants, see section 3.4.2.
Labelling Recommendations:		Statement of Identity, Indications For Use and Warning Statements - as for other antitussives, see section 1.6, the Committee's second report.

3.5 Cough and Cold Combinations by Pharmacologic Category

The following recommendations regarding combinations of drug categories were made by the Committee:

3.5.1 Acceptable Combinations

- oral antihistamine and oral antitussive, provided the antitussive is also not an antihistamine and vice versa, and provided the label cautions that the product may cause marked drowsiness
- oral antihistamine and oral nasal decongestant
- oral antihistamine and oral antitussive and oral nasal decongestant
- oral antitussive and oral expectorant
- oral antitussive and oral nasal decongestant
- oral antitussive and oral nasal decongestant and oral expectorant
- oral expectorant and oral nasal decongestant
- oral antihistamine and oral expectorant
- menthol (0.05%)⁴, camphor (0.1%)⁴, eucalyptus oil (0.025%)⁴ in a suitable vehicle for steam inhalation as a nasal decongestant

4 These concentrations represent final concentrations following appropriate dilution.

- menthol (2.6%), camphor (4.73%) and eucalyptus oil (1.2%) in a suitable ointment vehicle for topical use as a nasal decongestant
- menthol (0.05%)⁴, camphor (0.1%)⁴ in a suitable vehicle for steam inhalation as an antitussive
- menthol (2.6%), camphor (4.73%), eucalyptus oil (1.2%) in a suitable ointment vehicle as a topical antitussive
- menthol (0.26%) and eucalyptus oil (0.15%) in a lozenge as a topical antitussive

3.5.2 Unacceptable Combinations

- any combination of ingredients one of which is a bronchodilator
- any combination of ingredients, one of which is an anticholinergic (note - this does not include antihistamines, some of which have anticholinergic properties)
- combinations containing Category I ingredients from different pharmacological groups if any ingredient is present at less than the minimum effective dose
- combinations containing a corrective (an active ingredient specifically intended to counteract a side effect of other ingredients in the product)
- combinations containing caffeine as a stimulant per se
- phenylpropanolamine plus ephedrine plus caffeine
- caffeine plus ephedrine or pseudoephedrine or PPA

3.5.3 Combinations For Which No Recommendations Have Been Made

- combinations containing analgesics
- combinations of ingredients in lozenge dosage form, except as specified above

4 These concentrations represent final concentrations following appropriate dilution.

3.5.4 Combinations For Which Additional Information Is Required

- oral antitussive (if the antitussive is also a Category I antihistamine, such as diphenhydramine) and an oral antihistamine. This would result in two antihistamines in one product for which a therapeutic advantage should be demonstrated.
- oral antihistamine (if the antihistamine is also a Category I antitussive, such as diphenhydramine) and an oral antitussive. This would result in two antitussives in one product for which a therapeutic advantage should be demonstrated.
- oral antihistamine, oral nasal decongestant, oral antitussive and oral expectorant. A target population for this combination of ingredients should be demonstrated.
- any other combinations containing four or more ingredients from differing pharmacological groups, except for combinations specified as acceptable. A target population for any such combination should be demonstrated. (The Committee noted that significant target populations for the following four ingredient combinations have been demonstrated: antitussive, analgesic, expectorant and nasal decongestant; antitussive, analgesic, antihistaminic and nasal decongestant. However, these combinations were not considered because they contained an analgesic, and analgesic use per se in colds was not reviewed by the Committee.)
- two agents from differing pharmacological groups may be acceptable when used to treat the same symptom as long as there is no decrease in safety.
- combinations containing two Category I ingredients from the same pharmacological group may be acceptable to treat the same symptom if they have differing mechanisms of action, or if a therapeutic advantage can be shown.
- combinations containing two Category I ingredients from the same pharmacological group if either or both ingredients are present at less than the minimum effective dose may be acceptable if a therapeutic advantage can be demonstrated.

- combinations of herbal ingredients, whether present as active or inactive, with Category I drugs reviewed by the Committee. Such combinations should be demonstrated to be safe and effective for the proposed claims, should meet the requirements for acceptable combinations and should meet acceptable standards for potency and purity.

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APPENDIX

NAMES AND AFFILIATIONS OF MEMBERS OF THE EXPERT ADVISORY COMMITTEE

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