

# NICOTINE LOZENGES

**Nicotine 1mg Lozenges**

## **APPLICATION FOR CLASSIFICATION**

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Prepared for:- The New Zealand Medicines Classification Committee

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## **SUMMARY**

This application for classification of a medicine relates to the active ingredient nicotine, in the form of nicotine lozenges, providing 1mg nicotine per lozenge for the relief of nicotine withdrawal symptoms in nicotine dependency as an aid to smoking cessation.

Currently nicotine lozenges do not fall into any specific classification category in New Zealand, as the only nicotine presentations classified are chewing gum, transdermal use, sublingual tablets, and for inhalation and nasal administration. However the submission for classification demonstrates that Nicotine 1mg lozenges are bioequivalent to Nicorette<sup>®</sup> 2mg chewing gum and have the same usage characteristics as nicotine chewing gums. Thus, it is proposed that nicotine lozenges should also have the same classification as nicotine chewing gums ie: Pharmacy Medicine. It is acknowledged that this classification may change in the near future to General Sales Medicine, and Novartis would support the lozenge following the classification status of the chewing gums. As there are no lozenge presentations currently available in New Zealand, classification of this presentation will not affect any products currently marketed here.

Nicotine lozenges would currently be classified as a Prescription Medicine in Australia, as the prescription category for nicotine in Australia is a “catch-all” classification for anything that is not elsewhere classified. Novartis Consumer Health in Australia is putting forward a similar application to the NDPSC to have nicotine lozenges classified in Australia as a Pharmacy Medicine. This application will be submitted by the end of August 2000, in time to be placed on the agenda for the November 14<sup>th</sup> – 16<sup>th</sup>, 2000 meeting of the NDPSC.

Nicotine lozenges have been classified as an OTC medicine in many other countries, including Denmark, Ireland, The Netherlands, Sweden and the United Kingdom.

The application demonstrates that nicotine lozenges have the same usage characteristics as nicotine chewing gums, provide the same pharmacological effects as nicotine chewing gum (and by inference the same therapeutic effect) and represents no greater abuse potential than the chewing gums (being a controlled release formulation). Thus, classification as a Pharmacy Medicine is considered appropriate.

The lozenge presentation is noted as having a number of advantages over the current range of presentations available in New Zealand for nicotine replacement therapy – they offer a very good alternative for consumers that do not like chewing

gum or transdermal patches or for those consumers that have tried chewing gum or patches before, and having failed would like to try something different. Additionally, some consumers may see these lozenges as a better tasting alternative and they are environmentally friendly in that they are completely consumed (no chewed gum or used patches, containing residue nicotine, to be safely disposed of). The development of a new delivery format for nicotine replacement therapy also fits well with current Governmental initiatives to reduce the levels of smoking amongst the New Zealand population by offering consumers another alternative for smoking cessation.

## **PART A**

### **1. International Non-Proprietary Name of the Medicine**

This application for classification of a medicine relates to the active ingredient Nicotine.

### **2. Proprietary Names**

The proprietary name of the product is Nicotinell<sup>®</sup>. There are already two Nicotinell<sup>®</sup> products available in New Zealand – transdermal patches and chewing gum. This application refers to a new presentation, lozenges, which are not currently classified.

Novartis understands that while there are other brands of nicotine products available in New Zealand, no other company has a lozenge presentation. Thus, this application does not affect any other products marketed in New Zealand.

### **3. Company Requesting Classification**

Classification of nicotine lozenges is requested by Novartis Consumer Health (Australasia) Pty Ltd.

4. Dose Forms and Strengths

The dose form for which a classification is sought is lozenges. At this stage only one strength of lozenge is proposed – 1mg per lozenge.

5. Pack Size and Other Qualifications

The proposed pack size to be marketed is 12 lozenges.

6. Indications for Which Change is Sought

The proposed indication for Nicotine lozenges is:-

“Nicotinell® 1mg lozenge provides an effective aid to combat the unpleasant withdrawal symptoms caused by giving up smoking. Relief of nicotine withdrawal symptoms, in nicotine dependency as an aid to smoking cessation.”

7. Present Classification of the Medicine

Nicotine is currently classified in New Zealand according to type of presentation or delivery system. Classifications as of July 2000 are:-

PHARMACY MEDICINE	Nicotine in chewing gum, for transdermal use
RESTRICTED MEDICINE	Nicotine in sublingual tablets, for inhalation
PRESCRIPTION MEDICINE	Nicotine for nasal administration

Clearly, a lozenge presentation does not fit into any of the current classification categories for nicotine, and as such needs to be classified in its own right.

## 8. Classification Sought

In Part B of this application, the lozenge will be demonstrated to utilise the same delivery system as nicotine chewing gum (buccal route of administration, controlled release) and achieve comparable bioavailability to chewing gum presentations. On this basis, Novartis considers that the lozenge presentation should be classified as chewing gum presentations are currently classified. Thus, the classification sought for nicotine lozenges is PHARMACY MEDICINE.

Novartis understands that the classification of nicotine chewing gum and nicotine for transdermal use may change in New Zealand in the near future to General Sales Medicines. Should such a reclassification occur, Novartis would support the lozenges maintaining comparability with the chewing gum presentations.

## 9. Classification Status in Other Countries

### **Australia**

Currently in Australia nicotine lozenges would be classified under Schedule 4, Prescription Medicine. Schedule 4 states: NICOTINE for use as an aid in withdrawal from tobacco smoking (including preparations for nasal administration) except when included in Schedule 2 or 3. As in New Zealand, Schedule 2 and 3 encompass chewing gums, transdermal use, sublingual use and inhalation - thus, a lozenge presentation is not included in Schedules 2 or 3 and so, unlike New Zealand where the Prescription Medicine classification is not a 'catch-all', falls into the Prescription Medicine classification.

The New Zealand Medicines Classification Committee should note that Novartis intend to submit an application for reclassification of nicotine lozenges in Australia for consideration by the NDPSC. This application will be submitted in August 2000 in time to be considered at the November 14<sup>th</sup> – 16<sup>th</sup>, 2000 meeting of the NDPSC.

### **Other Countries**

Nicotine lozenges have been approved for distribution in the following

countries as an over-the-counter (ie: not prescription) medicine:-

Austria  
Denmark  
Finland  
Ireland  
Italy  
The Netherlands  
Portugal  
Sweden  
United Kingdom

10. Extent of Usage in New Zealand and Elsewhere

Data is available on the usage of nicotine replacement therapy in New Zealand as a whole. Currently, chewing gums, nasal sprays, transdermal patches and capsules are available for this type of therapy in New Zealand. For the 12 months to May 2000 220,000 units of these products were sold in New Zealand. Assuming that each unit represented approximately one week's treatment, and on average each patient was treated for 8 weeks, this represents 27, 500 people being treated to aid smoking cessation in the last 12 months. Given recent Governmental policy that has

increased the price of cigarettes and is likely to provide significantly more support for people attempting to stop smoking, these figures are expected to increase considerably in the next 12 months.

The figures provided above suggest there is a considerable need for smoking cessation products in New Zealand. Given the difficulty of permanent smoking cessation, and that many people make more than one attempt, Novartis believes any new product that offers these consumers choice and variety in their attempts to stop smoking is important, and should be as freely available to these consumers as possible.

#### 11. Labelling

Please see Appendix 1 for proposed labelling.

#### 12. Proposed Warning Statements

Proposed warning statements are included on the label. They are:-

“Nicotine lozenges are not suitable for children. Do not use the lozenge if you have serious heart disease, are pregnant or breastfeeding. Not to be used by non-smokers.”

These are the same warnings that currently apply to Nicotine Chewing Gum.

#### 13. Other Products Affected by Proposed Change

As has already been discussed, due to the way nicotine products are classified (presentation based), this proposed classification will not affect any other products currently available in New Zealand.

## **PART B**

### **Reasons For Requesting Classification Change**

The primary reason for requesting a classification change for nicotine lozenges is that it is not clear in New Zealand at present how these lozenges would be classified, and Novartis desired to present reasons for such lozenges to be classified as PHARMACY MEDICINE. This application will demonstrate that nicotine lozenges have the same usage characteristics as nicotine chewing gum, provide the same pharmacological effects as nicotine chewing gum (and by inference the same therapeutic effect) and represent no abuse potential. As such, Novartis believes that it would be appropriate for the Medicines Classification Committee to classify nicotine lozenges as the chewing gum is classified as present ie: Pharmacy Medicine.

### **Usage Characteristics**

Nicotine lozenges deliver nicotine systemically through a controlled release buccal delivery system. In order to achieve such buccal delivery, a specific sucking technique is recommended, as follows (see also proposed label):-

1. Suck one lozenge slowly until taste becomes strong
2. Rest Nicotine lozenge between the gum and cheek
3. Suck again when taste has faded
4. Suck the lozenge slowly so it remains whole for about 30 minutes

Clearly this is not the usual way in which people would suck a lozenge, the more usual technique being continuous sucking in the middle of the mouth.

Nicotine chewing gum also utilises a controlled release buccal delivery system – the chewing technique for Nicotine gum is:-

1. Chew one piece of gum slowly until taste becomes strong
2. Rest Nicotine gum between gum and cheek
3. Chew again when taste has faded
4. Repeat chewing routine for about 30 minutes

To Novartis' knowledge, this chewing technique is successfully utilised by consumers and nicotine is delivered to the user as intended. As such, Novartis expects that the sucking technique recommended for the lozenges can be successfully performed by lozenge users, and the lozenges also will deliver nicotine to the consumer as desired.

Secondly, nicotine chewing gum has been shown to have no significant influence on oral health parameters such as plaque, stained pellicle, gingivitis, calculus, or general oral pathosis when compared to placebo gum. Clearly these health parameters are important for on-going oral health, and nicotine lozenges should likewise have little or no influence on oral health. In order to investigate this, a local and systemic acute and in-use tolerability study was conducted in healthy smokers to assess local mucosal and systemic tolerability<sup>1</sup>. During the acute phase, subjects were administered one lozenge every hour for 12 hours. During the in-use phase subjects were given a two week supply of lozenges where consumption was required to be from 10 to 24 lozenges per day with a recommended dosage of not more than one lozenge every hour. Twelve subjects completed the acute phase of the trial and 27 subjects complete the in-use phase.

During the acute phase, there were no significant changes from baseline for heart rate, although one subject had an abnormal ECG (the subject was asymptomatic). In the opinion of a co-investigator the T-wave abnormalities observed were either due to coronary insufficiency or to a coronary spasm possibly related to nicotine absorption. However, absorption of nicotine from the lozenges was calculated to be less than the subject's normal absorption from smoking, and the adverse event had spontaneously resolved by the time of recheck (6 days later).

Two subjects complained of a mild burning sensation on sucking the first lozenge, one subject reported two episodes of headache and one subject reported dizziness during the acute phase. All adverse events resolved spontaneously. There were no changes in the oral mucosa observed during the acute study.

During the in-use phase of the trial two subjects experienced elevated diastolic pressure – however, these subjects had diastolic blood pressure readings at baseline which were at the upper limits of normal. One subject had an anaphylactic reaction, with food allergy as the suspected cause. Two subjects withdrew – one due to gastralgia (patient had previously had a partial gastrectomy) and one due to insomnia (patient had previously experienced insomnia with nicotine chewing gum). Safety data indicates that most adverse events that occurred during this in-use study could be expected from a nicotine-containing lozenge administered for two weeks. Most adverse events were mild or moderate in intensity and resolved spontaneously. There were no changes observed in the oral region mucosa upon repeated applications of lozenges.

In summary the authors concluded that the lozenges appear to have been well-tolerated upon multiple exposures based on ENT examination, cardiovascular evaluations and the nature of the adverse events reported and observed.

In terms of longer-term oral health, the committee should note that the lozenges are non-cariogenic.

Lastly, nicotine 1mg lozenges were specifically developed to offer consumers a discrete and better tasting alternative to nicotine gum.

### **Pharmacological Effects**

In order to ascertain the pharmacological effects an open randomised two-way multiple dose pharmacokinetic trial in 24 healthy volunteers comparing the Nicotine lozenge 1mg and Nicorette® gum 2mg was conducted<sup>2</sup>. One dose of the lozenge or gum was administered every hour for 12 hours during each trial period. In this way, steady state is assumed to be achieved after the last of the twelve hourly doses, keeping the short elimination half-life of nicotine in mind.

At steady state conditions, after the last dose, the two products showed an equivalent rate and extent of bioavailability as assessed by the  $C_{max}$  and  $AUC_{\tau}$  values.  $T_{max}$  values were comparable also.

No serious adverse events were reported. The incidence of adverse events that occurred during this study was comparable for both test medications. Most were

considered minor and not related to test medications. The Nicotine 1mg lozenge was well-tolerated.

The authors concluded “1mg lozenges exhibited similar pharmacokinetic parameters when compared with those of Nicorette® 2mg gum. In addition, at steady state conditions both products were bioequivalent in terms of the 0.80-1.25 90% confidence interval for the test/reference ratio when dose adjustment for the 2mg gum was performed (this adjustment was justified because the amount of nicotine released from the gum increased with increasing dose number)”. They also concluded that the lozenge was safe in comparison with the Nicorette® 2mg gum.

As with all medicines containing the same active ingredient, demonstration of bioequivalence is considered to also demonstrate therapeutic equivalence. As such, this study demonstrates that Nicotine 1mg lozenges are as effective as Nicorette® 2mg gum as an aid to smoking cessation.

### **Abuse Potential**

Previous experience and studies with nicotine gum have shown that because nicotine is released slowly from the gum in the gastrointestinal tract and undergoes extensive presystemic metabolism, true nicotine intoxication is highly unlikely after swallowing nicotine gum.

To check that the same is true for nicotine lozenges, and predict the safety and tolerability of possible accidental or intentional swallowing of a large number of Nicotine lozenges, 27 healthy smokers completed a trial to assess these parameters<sup>3</sup>. The subjects intentionally swallowed 3, 6 and 12 lozenges at once. After swallowing 3 lozenges, one subject reported a mild headache, which lasted approximately one hour. No subjects reported any complaints after swallowing 6 lozenges. Six subjects reported transient stomach heaviness (full feeling) for approximately one hour after ingestion of 12 lozenges.

The simultaneous swallowing of up to 12 lozenges was followed by an increase in nicotine serum concentrations to levels which were in the range of those found in normal smoking. Mean C<sub>max</sub> values after swallowing 3, 6 and 12 lozenges were 8.16, 16.91 and 20.45 ng/ml respectively. There was no correlation between nicotine levels and safety parameter variations. Moreover there were no serious adverse events reported and no clinically significant abnormalities for cardiovascular parameters, laboratory tests or gastric motility were observed.

Safety data indicate that if one intentionally swallows up to 12 lozenges at a time there will be insignificant adverse consequences. It can be concluded that swallowing nicotine lozenges, similar to nicotine gum, appears not to be of concern for development of toxicity or abuse potential.

### **Other Considerations**

Nicotine replacement therapy is well-established as an aid to smoking cessation in New Zealand. Additionally, the relative appropriateness of such therapy being available without prescription is also well-established in this country, as such therapies have been available as Pharmacy Medicines for a number of years. Over this time consumers have demonstrated that they can self-diagnose their requirements for such therapy, and indeed self-diagnosis is important as a significant part of the therapy is the patient's relative determination to 'do it'.

Over the time nicotine replacement therapy has been available in New Zealand without prescription there has been no cause for concern or reason to rethink this situation in terms of interactions with other medicines, contraindications, adverse events or possible resistance or abuse.

The development of a lozenge presentation of nicotine replacement therapy is considered an important progression in nicotine replacement therapy. Lozenges offer the following benefits to the consumer:-

- an alternative for those consumers that do not like chewing gum or patches
- an alternative for those consumers that have tried chewing gum or patches before, and failed, and would like to try something different
- a better tasting alternative
- an alternative that is completely used ie: no chewed gum or used patches to dispose of

Thus, this new lozenge presentation is considered an important step forward to offer consumers greater choice in the nicotine replacement therapy market, particularly for those consumers that have found the current choices do not suit, or they have tried them and are looking for something different. The advent of a new presentation for nicotine replacement therapy fits in well with current Government initiatives to reduce levels of smoking within the New Zealand population by offering consumers another alternative for smoking cessation.