

5. Demonstrated efficacy (i.e. its ability to produce a wanted pharmacological effect at the proposed dosage)

The submission includes a study demonstrating bioequivalence to nicotine gum and therefore claims therapeutic equivalence also.

6. Is the product intended for treatment of a minor ailment or symptom readily identifiable by the user, which is capable of rapid spontaneous resolution and for which a medical consultation is not necessary?

The need/desire to stop smoking is well recognised by current smokers.

7. Likelihood of mis-diagnosing, masking or compromising the appropriate medical management of a disease

Nil.

8. Requirement for professional advice from a medical practitioner, dentist or pharmacist

Certainly smoking cessation rates are best when nicotine replacement therapy is accompanied by counselling. However a person may obtain this counselling from a number of sources not exclusively medical practitioners, dentists, and pharmacists, but also from smoking cessation clinics, specialist phone lines such as Quitline, physiotherapists, marae based health education.

Regarding safety concerns, these are on the labelling (serious heart disease, pregnant or breastfeeding), and any adverse effects must always be compared to the adverse effects of inhaling tobacco smoke and continued smoking.

9. Requirement for supervision of sale by a pharmacist

Nil.

10. Proposed labelling and warning statements

Proposed warning statements to appear on the label are “Nicotinell 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.”

11. Hazard potential, including likelihood for any adverse effects

Any hazard of nicotine replacement therapy (NRT) must be weighed against that of smoking cigarettes.

The submission includes a study evaluating the local and systemic tolerability of the lozenges. An equal number of male and female subjects were included, all smokers of at least 20 cigarettes a day. The local mucosal effects were assessed by ENT (ear, nose and throat) examinations by a specialist, as well as subjective symptoms. BP, heart rate recordings and ECGs were performed. 12 subjects participated in the acute phase study over 24 hours, which included 12 hours of 1 lozenge hourly. 29 participated in the in-use study where subjects used the lozenges daily as required for 15 days.

In the in-use study the average consumption was 12 lozenges daily. 10 subjects admitted to smoking during the in-use study, all at low levels: 1-5 cigarettes infrequently.

No mucosal abnormalities were detected in either part of the study. 2 in the acute group described a mild burning with the first lozenge only and a few in the in-use group complained of stinging and burning for the first few days, all resolved spontaneously. One ECG became abnormal in the acute study with non-specific T wave changes, which the cardiologist attributed to coronary insufficiency or spasm. A repeat ECG on day 6 was normal, as was a follow-up effort test. This person had a mildly elevated diastolic BP at baseline and was asymptomatic throughout. Otherwise, adverse effects were minor. 2 withdrew from the in-use group, one with insomnia and nervousness, and the other with gastralgia, the latter person had a history of a partial gastrectomy for peptic ulcer disease and a subsequent gastroscopy was normal.

Other factors (also considered with the application for reclassification of nicotine patches and gum to general sales) include:

1. Smoking cessation in itself can result in increased levels of some drugs. Hence there is the risk of subtle changes in medication effects and cardiac function on stopping smoking with or without NRT.
2. Studies in cardiovascular (CV) disease have not shown an increase in events with NRT. From an article in the journal of the American College of Cardiologists¹ it seems that doses of nicotine from cigarette smoking are generally higher and more rapid than from the slower NRT delivery. There are also other cardiotoxic substances apart from nicotine in cigarette smoke. They comment that because there is a flat dose-response curve then if one did smoke on top of NRT the effects should not exceed those of the cigarettes alone. Trials apparently suggest that NRT use in those with stable CV disease does not increase CV risk²³.
3. In pregnancy, harm may be caused to the foetus by the products of combustion rather than the nicotine. The supporting information with the NRT products does recommend against use in pregnancy and use of non-pharmaceutical measures first. If these fail then NRT should be considered and instructions followed closely.
4. Caution is advised in those with diabetes, hyperthyroidism, and phaeochromocytoma, as nicotine causes adrenaline release (so of course will cigarette smoking).
5. Chronic use is not recommended. [Although I do note that the datasheet recommends a *6 month course*. This is longer than other

¹ Benowitz NL & Gourlay SG. Cardiovascular toxicity of nicotine: implication for nicotine replacement therapy. *J Am Coll Cardiol* 1997; 29(7):1422-31.

² Keeley EC, Pirwitz MJ, Landau C, et al. Intranasal nicotine spray does not augment the adverse effects of cigarette smoking on myocardial oxygen demand or coronary arterial dimensions. *Am J Med* 1996; 101(4):357-63.

³ Nicotine replacement therapy for patients with coronary artery disease. Working Group for the study of transdermal nicotine in patients with coronary artery disease. *Arch Intern Med* 1994; 154(9):989-95.

NRT.] There is a substitute addiction potential and there can be other adverse effects. Meyler's side effects of drugs 13th edition suggests that accumulation may occur when the gum is taken daily causing chronic nicotine intoxication. A study of 20 controls and 20 long-term users of NRT chewing gum showed that the long-term use was correlated with insulin resistance and hyperinsulinaemia. They concluded that use of NRT should be transient and limited.

6. Continued smoking whilst on NRT is likely to cause adverse effects due to higher nicotine levels. These may include headache, heartburn, hiccoughs, nausea, vomiting, coughing, irritation in the mouth and throat, aphthous ulcers, acne, confusion, abdominal pain, back pain, myalgia, flatulence, more rarely - palpitations, sleep disturbance, dizziness.

Overdose: According to the datasheet the acute lethal dose is approx. 0.5-0.75 mg/kg of body weight, amounting around 40-60 mg for an adult. However even very small doses can be lethal in very young children, but this is also true for children eating cigarette butts and the lozenges will be in packaging.

12. Any relevant data on post-marketing experience

The company has submitted the first 3 periodic safety updates covering 17/7/98-16/1/2000. It is estimated that just over 1000 patients have used the lozenges. No serious/unexpected adverse events have been reported to the company.

13. Potential for inappropriate use of the medicine

Potentially could be used for weight reduction as NRT has been shown to avoid post-smoking cessation weight gain.

14. Potential for abuse of the medicine (e.g. non-therapeutic use of the medicine for self-gratification)

Potentially adolescents could try and get "high" on these products, they could even smoke on top of using the NRT. However it is unlikely to be seen to be a "cool" thing to do and they are more likely to feel sick and dizzy and stop.

The company has submitted a study examining the effects of swallowing the lozenges intact on pharmacokinetics, adverse events, cardiovascular and laboratory parameters, and gastric motility. This was an open single dose study with 3 groups of 8 volunteers (all smokers of at least 10 cigarettes per day), with equal numbers of both sexes. Group A consumed 3 lozenges, Group B consumed 6 lozenges, and Group C consumed 12 lozenges.

The nicotine was rapidly absorbed with a T_{max} of 2-3 hours (note absorption using the buccal method is less than an hour). Increasing doses caused nonproportional rises in C_{max} and AUC. [C_{max} was slightly higher than in a study that had subjects swallowing unchewed pieces of 4mg nicotine gum where the peak concentrations of nicotine were less than

10ng/ml.] Concentrations of nicotine obtained were within the range found with normal smoking.

Parameter mean (SD)	3 lozenges N=8	6 lozenges N=8	12 lozenges N=8
Tmax (h)	2.65 (2.76)	2.83 (1.95)	2.17 (1.39)
Cmax (ng/ml)	8.16 (7.58)	16.91 (11.76)	20.45 (8.79)
AUC (h.ng/ml)	37.03 (27.18)	84.90 (48.88)	103.07 (58.56)

There were no changes in BP, heart rate and ECGs. No serious adverse events. 6 in group C had transient stomach heaviness lasting up to an hour post ingestion. There were no effects on gastric motility for the 3 and 6mg doses. In group C the 2 subjects tested showed accelerated gastric clearance 1 hour post dosing, this had returned to normal by 11 hours. The only blood abnormality was an across the board decrease in Hb concentration by 10%, attributed to the blood letting.

The authors concluded that the simultaneous swallowing of 12 or less lozenges lead to a non-linear rise in serum nicotine concentrations, to levels in the range of those found in normal smoking, and was well tolerated.

15. Current availability of other products with similar benefits

- Other NRT in the form of patches, gum, inhalers, intranasal sprays, sublingual tablets.
- Nicobrevin (contains eucalyptus oil, menthyl valerate, quinine sulphate, camphor).
- Bupropion (Zyban) is a Prescription medicine indicated as an aid for smoking cessation, it acts centrally on noradrenergic and/or dopaminergic neurones. It has been marketed in other countries for some years as an antidepressant.

16. Any public health advantage associated with the availability of these medicines

Significant. There are an estimated 4500 deaths per year in NZ from smoking related diseases and 800 from passive smoking. It is proposed that greater availability of NRT would reduce the estimated 80000 premature deaths due to tobacco over the next 20 years in NZ. The World Bank has shown that significant savings can be made from NRT as a cost effective intervention in \$ per life year saved.

Several studies have been undertaken in the US to estimate the impact of OTC NRT, approved by the FDA in 1996. A study published in 1997 claims that use of NRT has increased by 152%. They estimate that this will yield from 114000-304000 new former smokers annually in the United States⁴.

⁴ Shiffman S, Gitchell J, Pinney JM, et al. Public health benefit of over-the-counter nicotine medications. *Tob Control* 1997; 6(4):306-10.

17. Patient convenience including geographical factors

A general sales classification would allow a wider range of providers of smoking cessation counselling and clinics to dispense NRT when appropriate. In view of the government's proposed subsidisation scheme this would further increase access. Pricing may decrease if supermarkets also sell NRT.

18. Monitoring

Not required.

19. Education

N/A.

20. Pharmacokinetics

The company have submitted a study comparing bioavailability of nicotine lozenges (1mg) with nicotine gum (2mg). This was an open, randomised, 2 way, within subject, crossover, multidose PK study. There were 2x 2 day trial periods, one for each product, with a 7-day washout in between. There was a 22-hour run in of smoking abstinence followed by 12 hour dosing and 23 hour sampling. Subjects were able to resume smoking during the washout.

24 subjects were in the study, all heavy smokers (averaging 28 cigarettes per day). Instructions were given on correct methods of sucking and chewing (the latter was timed and the gum removed after 30 minutes). Safety was tested with BP and heart rate recordings, blood tests, ECG and symptom recording.

Nicotine extraction from the lozenge was assumed to be 1mg after complete dissolution (target time was 30 minutes, the average was 29 minutes). The mean nicotine delivery for the gum was 1.061mg; this did increase slightly with increasing numbers of doses. For both products the Cmax at steady state was less than the expected value of 12-14ng/ml (with a single cigarette the peak plasma nicotine concentration ranges within 10 minutes between 25 and 50ng/ml), normal smoking levels are around 31ng/ml).

The gum achieved slightly higher plasma nicotine levels and AUC. Measurements were taken from the hour after the last dose as follows:

	Lozenge (mean ± SD)	Gum (mean ± SD)
Cmax (ng/ml)	10.58 ± 2.91	11.38 ± 3.79
Tmax (hr)	0.54 ± 0.21	0.47 ± 0.19
AUC (h.ng/ml)	9.23 ± 2.59	10.19 ± 3.41

According to the EU definition of bioequivalence the 90% confidence interval for the ratio of the PK variables (Cmax and Tmax for rate of absorption and AUC for extent of absorption) must be within a range of 80-125%. This was achieved (after adjustment for the rising nicotine dose with increasing numbers of doses of the chewing gum):

C_{max} 0.857-1.036
AUC 0.841-1.007

No serious adverse events were reported. Mild adverse events included headache, throat irritation, flatulence, and ear pain. No clinically relevant abnormalities were observed with cardiovascular monitoring.

Comparison to other NRT

Nicotine lozenges seem to relate most closely to sublingual nicotine and nicotine chewing gum.

The submission seems to indicate bioequivalence between the gum and lozenge when used according to instructions. However, I note that with regard to equivalent safety, the submission mentions that swallowing multiple pieces of gum resulted in nicotine concentrations of 10ng/ml, whereas swallowing 12 lozenges gave a concentration of 20ng/ml. This latter figure was a non-proportional rise, so a plateau level may be reached, but this was not determined. This may be important in considering the effects of overdose of the 2 forms and it tends to imply that the gum may be safer.

Nicotine sublingual tablets (2mg) were classified as Restricted Medicine at the MCC meeting 15/10/97. These have never been marketed in New Zealand. Concerns at the time were of irritation to the oral mucosa (though it was considered likely that consumers would cease to use the product if irritation were to occur), and the potential to abuse the sublingual product (particularly by simultaneous use with other nicotine-containing products).

The clinical expert report for sublingual nicotine states that the sublingual form is essentially similar to gum in pharmacokinetics, except for a lower bioavailability sublingually - thought to be due to a larger fraction being swallowed and absorbed through the gastro-intestinal tract (where nicotine is less well absorbed and undergoes first pass metabolism in the liver). Pharmacokinetic values were higher than those from this submission for gum and the lozenge, with C_{max} approx 13ng/ml, AUC approx 12-13, and T_{max} 0.33hr. Dose extracted was higher than the lozenge: 1.30mg for the gum and 1.99mg for the sublingual tablet.

There was no testing of "overdose"/pharmacokinetics in swallowing multiple sublingual tablets, but the report comments that there is small risk from overdose due to nicotine being a strong emetic and the reduced levels with GI absorption. A study tested pharmacokinetic differences when the tablet is consumed wrongly (i.e. not sublingually); the lowest C_{max} and bioavailability occurred when it was chewed and immediately swallowed (cf. chewed and delayed swallowing).

At the same MCC meeting, nicotine inhalers were reclassified from Prescription only to Restricted Medicine, after reviewing safety data submitted by the company in light of previous objections (potential for abuse with this route of administration, requirement for counselling so that

one does not create a substitute addiction). Concerns remained about psychological dependence.

Conclusion

The lozenge appears to result in similar or slightly lower concentrations of nicotine compared to the nicotine gum (General Sales) and sublingual tablet (Restricted Medicine). One would expect similar efficacy in smoking cessation. It does provide another alternative for NRT for those who do not like gum or find the patches uncomfortable.

There seems to be a low rate of adverse effects and, used appropriately, a low risk to the safety of consumers. My only concern is that, despite the swallowing of 12 tablets being well tolerated and nicotine being less well absorbed via the GI tract, there is a theoretically higher potential for a person to deliberately self-harm by swallowing a large number of lozenges. It also seems that higher nicotine levels are obtainable on swallowing multiple lozenges compared to gum. Also consumers are more likely to ingest multiple tablets (either accidentally or deliberately) than multiple pieces of gum or stick on multiple patches.

In the first instance I would consider classification as Restricted (like the sublingual tablet) or Pharmacy only medicine, in order to establish pattern of use and any risk of harm through overdose.