Johnson & Johnson Pacific

AUSTRALIA • FIJI • NEW ZEALAND

30th July 2010

The Secretary
Medicines Classification Committee
Medsafe
PO Box 5013
Wellington 6145

Dear Sir/Madam,

RE: APPLICATION TO AMEND THE NICOTINE ENTRY OF THE SCHEDULE OF CLASSIFICATIONS OF MEDICINES

Please find below an application by Johnson and Johnson (New Zealand) Limited to amend the nicotine entry of the Schedule of Classifications of Medicines.

Johnson and Johnson (New Zealand) Limited the sponsor of NICORETTE®/NICOTROL® products and with a long history in the research and development of Nicotine Replacement Therapy (NRT), requests amendment to the General Sale Classification of Medicines entry for nicotine to refer to *oromucosal absorption*, rather than specific dosage formats i.e. *chewing gum, lozenge, sublingual tablets*.

This application is intended to support the scheduling of nicotine mouth spray to General Sale (NICORETTE® QuickMist Mouth Spray 1mg/spray TT50-3763/14), as well as the down scheduling of nicotine inhaler (NICORETTE® Inhaler 10mg TT50-3763/4 and 15mg TT50-3763/4a), which both have an oromucosal mode of action, in line with other dosage formats currently included in the General Sale classification for nicotine. This application argues that these dosage formats do not differ significantly in their safety and efficacy compared to other oral NRT formats which are currently classified as General Sale.

The following Schedule of Classifications wording for General Sale is proposed.

*General: for preparations for **oromucosal** or transdermal **absorption***

We confirm that our application is for the General Sale classification only, and that the *Pharmacy Only* classification (which refer to inhaled products) and the *Prescription* classification, (which refer to nasal use products) **remain unchanged**.

JOHNSON & JOHNSON PACIFIC PTY. LTD A.B.N. 73 001 121 446
45 JONES STREET, ULTIMO NSW 2007, AUSTRALIA. TELEPHONE: 131 565, FACSIMILE: (02) 8260 8100
ADDRESS ALL COMMUNICATIONS TO: LOCKED BAG 5, BROADWAY, NSW 2007

To support this amendment please find enclosed our application.

Please contact the undersigned regarding any queries or correspondence concerning the above application.

Yours Sincerely,
Johnson & Johnson Pacific Pty Ltd

Dr. Michelle Gracanin
Regulatory Affairs Associate
phone: +61 2 8260 8393
fax: +61 2 8260 8518
email: mgracani@its.jnj.com

APPLICATION TO THE MEDICINES CLASSIFICATION COMMITTEE

NICOTINE

Application to amend the nicotine General Sale entry

30th JULY 2010

Johnson and Johnson (New Zealand) Ltd
P O Box 9222
Newmarket, 1149
Auckland, New Zealand

Contact person:

Dr. Michelle Gracanin
Regulatory Affairs Associate
Telephone: +61 2 8260 8393
Email: mgracani@its.jnj.com

PROPOSED CLASSIFICATION / CLASSIFICATION CHANGE

Johnson and Johnson (New Zealand) Limited the sponsor of NICORETTE®/NICOTROL® products and with a long history in the research and development of nicotine replacement therapy (NRT), requests amendment of the Classification of Medicines entry for nicotine to refer to exemption of preparations for oromucosal absorption, rather than specific dosage formats i.e. chewing gum, lozenge, and sublingual tablet.

Our application is intended to support the classification of nicotine mouth spray to General Sale (NICORETTE® QuickMist Mouth Spray 1mg/spray TT50-3763/14), as well as nicotine inhaler (NICORETTE® Inhaler 10mg TT50-3763/4 and 15mg TT50-3763/4a) which both have an oromucosal mode of action, in line with all the other oral dosage formats currently included in the General Sale classification for nicotine. Our application demonstrates that these dosage formats do not differ significantly in their safety and efficacy compared to other oral NRT formats currently under the General Sale classification. We confirm that the Pharmacy Only and Prescription entries **remain unchanged.**

CURRENT CLASSIFICATION WORDING

General:	for transdermal use or in chewing gum, lozenges or sublingual tablets.
Pharmacy Only:	for inhalation except when sold from a smoking cessation clinic run under the auspices of a registered medical practitioner, nurse, pharmacist or psychologist.
Prescription:	for nasal use except when sold from a smoking cessation clinic run under the auspices of a registered medical practitioner; in medicines other than for smoking cessation.

SUGGESTED CLASSIFICATION WORDING

General:	for preparations for **oromucosal** or transdermal **absorption**

The Pharmacy Only classification (which refer to inhaled products) and the Prescription classification, (which refer to nasal use products) **remain unchanged**.

Recently the National Drugs and Poisson Schedule Committee in Australia amended the scheduling of nicotine to exempt oromucosal spray use, as an aid in withdrawal from tobacco smoking, from scheduling. However, we feel a more logical approach is to group oromucosal preparations together and exempt them from scheduling.

OVERVIEW

Transdermal nicotine patches, chewing gum, lozenges and sublingual tablets are already considered to be suitable for sale without the supervision of a pharmacist and are classified as General Sale products. As the principle has already been established that currently available oral NRT can be classified as General Sale, and as the safety profile and abuse potential of both the nicotine mouth spray and nicotine inhaler are not significantly different from other NRT formats, it is proposed that the classification of nicotine mouth spray (NICORETTE® QuickMist Mouth Spray 1mg/spray TT50-3763/14), as well as nicotine inhaler (NICORETTE® Inhaler 10mg TT50-3763/4 and 15mg TT50-3763/4a) be General Sale given the mode of action for these two formats is buccal (oromucosal), in line with chewing gum, lozenges and sublingual tablets.

The proposed amendment is based on the following argument:

- Oromucosal preparations regardless of dosage format have comparable safety and efficacy profiles, therefore grouping them together is logical.
- The nicotine from the nicotine mouth spray and inhaler is absorbed buccally (oromucosally) in a similar way to the unscheduled nicotine gum, lozenge and sublingual tablet, the only difference being the dosage form of the products.

We maintain nicotine through inhalation, remain as Pharmacy Only classification given this route of absorption is different.

BACKGROUND

Smoking is common among New Zealanders, and confers significant morbidity and mortality risk, highlighting the clinical and public health importance of smoking cessation therapies like NRT. NRT is efficacious and well-established in New Zealand, being commonly used by smokers seeking to quit.

Currently all NRT formats on the New Zealand market are available OTC. NRT is available as chewing gum, lozenge, inhaler, patch and sublingual tablet in New Zealand. Nicotine from chewing gum, lozenge and inhaler is absorbed via the buccal mucosa, while for nicotine patch and nicotine sublingual tablet, nicotine is absorbed transdermally and sublingually/bucally respectively.

The principle is already established that oral NRT products may safely be sold unscheduled and do not require a pharmacist to supervise the sale. The statutory label warnings are present on the pack and the only instructions unique to each dosage form results from its administration. When administered in a pharmaceutical format, nicotine is practically devoid of the serious long-term adverse health consequences of smoking tobacco. There is also a low risk of NRT masking a serious disease or compromising medical management of a disease.

The MCC has previously considered the following regarding NRT (nicotine):

- The toxicity and safety of NRT (nicotine)

- The risks and benefits associated with the use of NRT (nicotine)
- The potential hazards associated with the use of NRT (nicotine)
- The extent and patterns of use of NRT (nicotine)
- The dosage and formulation of NRT (nicotine)
- The need for access to NRT (nicotine), taking into account its toxicity compared with other substances available for a similar purpose
- The potential for abuse or misuse of NRT(nicotine)
- The purposes for which NRT (nicotine) is to be used

The safety and efficacy profiles amongst buccal preparations regardless of the dosage format are comparable with each other, as well as with sublingual tablets. The pharmacokinetic profiles of nicotine chewing gum, nicotine lozenge and nicotine inhaler are similar[1]. Studies have also confirmed that the pharmacokinetic profile of the nicotine sublingual tablet is similar to that of nicotine chewing gum[2]. There are no significant differences regarding the safety of these formats. Hence, there is no reason to schedule oromucosal preparations based on their individual formats.

PRODUCTS FOR CLASSIFICATION/RECLASSIFICATION

OROMUCOSAL NICOTINE SPRAY (ONS) – NICORETTE® QuickMist Mouth Spray TT50- 3763/14

As part of our ongoing research and development into NRT, Johnson and Johnson (New Zealand) Limited have developed an ONS which we have applied for registration with Medsafe (TT50-3763/14) on the 20th May 2010.

Our classification proposal to refer to oromucosal absorption in general, thus including ONS as a General Sale medicine is considered appropriate for the following reasons:

- Studies demonstrate that nicotine from the ONS administered via oromucosal route will produce the desired efficacy with no incidents or trends indicating that the adverse event profile of the ONS might differ significantly from that of other NRT products available for use in the mouth e.g. chewing gum and lozenge.
- The plasma levels of ONS are comparable with those of existing NRT products. Data on file illustrates that plasma levels (C_{max} and AUC_{∞}) following a single-dose of ONS 1-2 mg are within the range of those for marketed buccal preparations such as nicotine 2 and 4 mg chewing gum and nicotine 2 and 4 mg lozenge.
- Oromucosal preparations regardless of dosage format have comparable safety and efficacy profiles', therefore grouping them together is logical.

The main difference between ONS and other forms of oral NRT is the speed of absorption. The Medsafe application contains data from four pharmacokinetic studies and a phase 2 pilot low intervention study. A placebo-controlled phase 3 study is ongoing, but no data are available at this point. We argue that the pharmacokinetic characteristics of ONS are similar to other already

approved oral NRT products, such as gums and lozenges, with regards to the extent of absorption after a single-dose as well as steady state blood levels of nicotine after multiple administrations. Thus, reference can be made to the safety and efficacy of other approved NRT products.

Given the justification above and the comparable safety and efficacy profiles of buccal (oromucosal) preparations with each other and with sublingual tablets, reference to preparations for oromucosal absorption in general is deemed acceptable and logical for this category.

NICOTINE INHALER – NICORETTE® Inhaler 10mg TT50-3763/4 and 15mg TT50-3763/4a

Inhalation route of administration is generally defined as taking into the lung by breathing through the nasal or oral respiratory route for local or systemic effect[3]. The Pharmacy Only entry for the aforementioned nicotine inhaler product does not accurately reflect the absorption/preparation for this product, thus the classification for this product is currently inappropriate.

We confirm that the major portion of the dose from the nicotine inhaler is deposited in the oral cavity, with less than 5% of absorption occurring in the lungs, absorbed buccally[4]. Thus, the route of administration is not "true" inhalation, but rather buccal (oromucosal). Therefore, this product is incorrectly included in the nicotine for inhalation (Pharmacy only) classification.

The registered product information for the inhaler states "*the major fraction of nicotine in the inhaler is deposited in the oral cavity*". Realising this, the nicotine from the nicotine inhaler is absorbed in a similar way to the unscheduled nicotine gum, lozenge and sublingual tablet, the only difference being the dosage format of the product.

In 2009 the MHRA rescheduled the nicotine inhaler from Pharmacy Only to General Sale. The MHRA acknowledged that the product was an "*inhalation cartridge for oromucosal use*".

The nicotine inhaler is an aid in withdrawal from tobacco smoking in an oromucosal preparation. The nicotine inhaler along with the nicotine chewing gum, lozenge, mouth spray and sublingual tablet can all be grouped under "preparations for oromucosal absorption". This is our reasoning for the proposed wording for the amendment to the current General Sale classification. If this approach is considered acceptable and the nicotine inhaler is rescheduled as a General Sale medicine, the Pharmacy Only entry for nicotine in preparations for inhalation will remain for those products that are for "true" inhalation. The nicotine inhaler will be captured under the entry for oromucosal absorption, and therefore no change is required to be proposed for the nicotine Pharmacy Only classification.

There has been no evidence from our data that inappropriate use is a problem with the nicotine inhaler. Since first marketed in the world in September 1996 there have been no reports of accidental or deliberate ingestion of nicotine cartridges. The inhaler also has a similar pharmacokinetic profile to the nicotine 2 mg gum[2]. Consumers can easily monitor and manage treatment with nicotine inhaler. The product is easy to use, and any relapse (in the form of

lighting up a cigarette) is easily recognized and may prompt the consumer to seek further advice and counseling from a pharmacist or healthcare professional.

The current scheduling of NRT indicates that the MCC has previously considered that NRT for smoking cessation fulfils the criterion for having an extremely low abuse potential. All currently marketed formats of NRT are unscheduled with the exception of the nicotine inhaler, which discussed above, is not a true inhaler. Johnson and Johnson (New Zealand) Limited considered that the abuse potential and safety profile of the nicotine inhaler is similar to the unscheduled NRT dosage forms.

In practice cigarettes, the most effective system of delivery of nicotine to the brain, are freely available from retailers. The relative ease of obtaining cigarettes and the ability to rapidly give pleasurable effects (effects not induced by the NRT) make them the more attractive and likely option for abuse.

Table 1 provides a brief comparison between nicotine chewing gum, inhaler and sublingual tablet demonstrating the similarities in the route of absorption, justifying grouping together oromucosal preparations.

Table 1. Brief comparison of Nicotine Gum, Nicotine Inhaler and Nicotine Sublingual Tablets (extracted from the registered product information).

Product	**NICORETTE® Gum** (TT50-3763, TT50-3763a, TT50-3763/2, TT50-3763/2a, TT50-3763/7, TT50-3763/7a, TT50-3763/8, TT50-3763/8a, TT50-3763/10, TT50-3763/10a)	**NICORETTE® Inhaler** (TT50-3763/4, TT50-3763/4a)	**NICORETTE® Sublingual Tablet** (TT50-3763/6, TT50-3763/9)
Scheduling	Unscheduled	Schedule 2	Unscheduled
Route of administration	Buccal (the gum is chewed in oral cavity and rested against check)	Buccal (as air is inhaled through the cartridge the nicotine is vapourised and absorbed in the mouth)	Sublingual (the tablet is placed under the tongue and nicotine is deposited in the oral cavity)
Dosage	12 week treatment period followed by a 12 week weaning period. Over time the amount of use per day declines 8-12 pieces (2 mg gum) or 4-6 pieces (4 mg gum). NMT 20 pieces (2 mg) or 10 pieces (4 mg) gum (equivalent to a daily dose of 40 mg) should be chewed in one day.	12 week treatment period followed by a 12 week weaning period. Over time the amount of use per day declines Inhaled air through cartridge for 20 mins. Self-titrate dose according to cigarette withdrawal symptoms; usually 6-12 cartridges/ day for 3 months, then reduce over 6-8 weeks; max duration 6 months	12 week treatment period followed by a 12 week weaning period. Over time the amount of use per day declines 1-2 tablets every 1-2 hours. NMT 40 tablets/day for 3 months then reduce over 2- 3 months; max duration 6 months.
Pharmaco-kinetics	Nicotine administered in chewing gums is readily absorbed from the oral mucosa membranes. Demonstrable blood levels are obtained within 5-7 minutes after starting chewing and reach a max. ~ 5-10 minutes after chewing is stopped. Blood levels are roughly proportional to the amount of nicotine released by chewing. The amount of nicotine absorbed depends on the amount extracted by chewing and the loss from the oral cavity due to swallowing or expectoration. Normally ~ 1.4 mg and 3.4 mg of nicotine will be extracted from the 2 mg and 4 gum respectively. **Steady state** trough levels of 10-14 ng/mL for 2 mg and 24-29 ng/mL for 4 mg Nicorette gum are achieved during standardised conditions I.e. chewing every two seconds for 30 minutes. A 12 week study found that 2 mg Nicorette chewing gum produced nicotine plasma levels of about 9 ng/mL, while 4 mg gum produced nicotine plasma levels of about 23 ng/mL.	The major fraction of the nicotine in Nicorette Inhaler is deposited in the oral cavity, absorbed buccally. Continuous, rapid inhalation over 20 minutes releases up to 40% (4 mg) of the nicotine from each cartridge and about 50% of the released nicotine is systemically available, i.e. about 2 mg. Self administration (ad lib. at clinical use) typically produces nicotine plasma concentrations of 8-10 ng/mL, The plasma concentrations following clinical use corresponded to once hourly chewing of Nicorette chewing gum 2 mg. Maximal plasma concentrations are reached within 15 minutes after the end of 20 minutes of inhalation. **Steady state** plasma levels of ~ 20-25 ng/mL are achieved with continuous, rapid inhalations during 20 minutes per hour for 12 hours at ambient room temperature in a laboratory setting.	Most of the nicotine absorbed from a Microtab tablet is absorbed through the buccal mucosa. The absolute bioavailability of nicotine after sublingual administration of the tablet is approximately 50%. The systemic bioavailability of swallowed nicotine is lower due to first pass elimination. The high and rapidly rising nicotine concentrations seen after smoking are rarely produced by treatment with the Microtab sublingual tablet. A maximum plasma concentration of about 7 ng/mL will be achieved after a single dose of a 4 mg tablet. The 2 mg strength of NICORETTE Microtab results in a plasma nicotine level of about 33% of normal smoking levels whereas a 4 mg tablet results in about a 66% level. Normal smoking level is defined as 20 cigarettes/day. **Steady state** trough nicotine plasma concentrations achieved after 10 hourly doses of one 2 mg tablet are about 10 ng/mL which is about 50% of normal smoking levels.
Adverse Events	There are few adverse event reposts suggestive of abuse or dependence	There are few adverse event reposts suggestive of abuse or dependence	There are few adverse event reposts suggestive of abuse or dependence
Transfer Dependence	Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.	Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.	Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

CONCLUSION

The safety profile of nicotine is well characterised and nicotine metabolism and elimination appear to be independent of the choice of nicotine formulation. The dosing regimens for oral NRT products are similar. However, the classification of nicotine is based on dosage format regardless of the mode of action, safety profile, abuse potential etc.

Tolerability, acceptance and safety of NRT are similar across all formats as demonstrated above. Widening the classification to include "preparations for oromucosal absorption" is logical as safety would not be compromised given the comparable safety and efficacy profiles across oromucosal formats. Appropriate labeling would bring attention to the standard warnings for use, and any specific warnings associated with individual dosage formats. Given that NRT is less harmful than smoking, safety concerns should not be a barrier to use, particularly as the consumers underlying health was likely to be much better than if they were to continue to smoke. There have been no indications from any market that non-smokers are abusing NRT in any currently available dosage form.

Given that ONS and nicotine inhaler have the same mode of action as the oral NRT products that are currently classified as General Sale, and the comparable safety and efficacy profiles of oromucosal preparations with each other, we trust that the classification committee will consider our request to amend the General Sale classification entry for nicotine to refer to "oromucosal" preparations in general rather than specify specific dosage formats.

We look forward to hearing the outcome after the 44th MCC meeting.

REFERENCES

1. Beradi, R.R, Kroon, L.A, McDermott, J.H, Newton, G.D, Oszko, M.A, Popovich N,G, Remington, T.L, Rollins, C.J, Shimp, L.A, Tietze, K.J. Handbook of Nonprescription Drugs An interatcitve approach to self-care. 15th Ed. 2006. Chapter 50.

2. Molander L, Lunell E. Pharmacokinetic investigation of a nicotine sublingual tablet. Eur J Clin Pharmacol 2001; 56: 813-819

3. Therapeutic Goods Administration Approved Terminology for Medicines. July 1999. Available at http://www.tga.gov.au/docs/pdf/aan/aan.pdf.

4. NICORETTE® Inhaler Data Sheet. Available on the Medsafe website.

APPENDICES

1. NICORETTE® QuickMist Mouth Spray 1mg/spray Medsafe TPDR (available on the Medsafe website)

2. NICORETTE® Inhaler 10 mg Medsafe TPDR (available on the Medsafe website)

3. NICORETTE® Inhaler 15 mg Medsafe TPDR (available on the Medsafe website)

4. NICORETTE® Inhaler Data Sheet. (available on the Medsafe website)

5. NICORETTE® Micortab Data Sheet.

6. Extract from NDPSC Records of Reasons of Meeting 58 – February 2010 (available on the NDPSC website)