Proposed package insert for NICORETTE® ICY WHITE 2 mg and 4 mg

SCHEDULING STATUS

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PROPRIETARY NAME AND DOSAGE FORM

NICORETTE® 2 mg gum

NICORETTE® 4 mg gum

NICORETTE® MINT 2 mg gum

NICORETTE® MINT 4 mg gum

NICORETTE® ICY WHITE 2 mg gum

NICORETTE® ICY WHITE 4 mg gum

NICORETTE® FRESHFRUIT 2 mg gum

NICORETTE® FRESHFRUIT 4 mg gum

NICORETTE® FRESHMINT 2 mg gum

NICORETTE® FRESHMINT 4 mg gum

COMPOSITION

NICORETTE® 2 mg: each piece contains 10 mg nicotine-resin complex 20 %, equivalent to 2 mg nicotine.

List of excipients: chewing gum base, sorbitol, sodium carbonate anhydrous, flavour, glycerol, sodium hydrogen carbonate.

NICORETTE® 4 mg: each piece contains 20 mg nicotine-resin complex 20 %, equivalent to 4 mg nicotine.

List of excipients: chewing gum base, sorbitol, sodium carbonate anhydrous, flavour, glycerol, D&C yellow No. 10.

NICORETTE® MINT 2 mg: each piece contains 10 mg nicotine-resin complex 20 %, equivalent to 2 mg nicotine.

List of excipients: chewing gum base, xylitol, sodium carbonate anhydrous, peppermint oil, levomenthol, magnesium oxide light, sodium bicarbonate.

NICORETTE® MINT 4 mg: each piece contains 20 mg nicotine-resin complex 20 %, equivalent to 4 mg nicotine.

List of excipients: chewing gum base, xylitol, sodium carbonate anhydrous, peppermint oil, levomenthol, magnesium oxide light, quinoline yellow (E104).

NICORETTE® ICY WHITE 2 mg: each piece contains 10 mg nicotine-resin complex 20 %, equivalent to 2 mg nicotine.

List of excipients: chewing gum base, xylitol, peppermint oil, sodium carbonate anhydrous, sodium hydrogen carbonate, acesulfame potassium, levomenthol, magnesium oxide light, Winterfresh, hypromellose, sucralose, polysorbate 80, starch, titanium dioxide (E171), carnauba wax.

NICORETTE® ICY WHITE 4 mg: each piece contains 20 mg nicotine-resin complex 20 %, equivalent to 4 mg nicotine.

List of excipients: chewing gum base, xylitol, peppermint oil, sodium carbonate anhydrous, acesulfame potassium, levomenthol, magnesium oxide light, quinoline yellow (E104), Winterfresh, hypromellose, sucralose, polysorbate 80, starch, titanium dioxide (E171), carnauba wax.

NICORETTE® FRESHFRUIT 2 mg: each piece contains 10 mg nicotine-resin complex 20 %, equivalent to 2 mg nicotine.

List of excipients: chewing gum base, xylitol, sodium carbonate anhydrous, sodium hydrogen carbonate, magnesium oxide light, acesulfame potassium, peppermint oil, levomenthol, acacia, tuttifrutti (QL84441), hypromellose, sucralose, polysorbate 80, titanium dioxide (E171), and carnauba wax.

NICORETTE® FRESHFRUIT 4 mg: each piece contains 20 mg nicotine-resin complex 20 %, equivalent to 4 mg nicotine.

List of excipients: chewing gum base, xylitol, sodium carbonate anhydrous, acesulfame potassium, magnesium oxide light, peppermint oil, levomenthol, acacia, titanium dioxide (E171),

quinoline yellow (E104), tuttifrutti (QL84441), hypromellose, sucralose, polysorbate 80 and carnauba wax.

NICORETTE® FRESHMINT 2 mg: each piece contains 10 mg nicotine-resin complex 20 %, equivalent to 2 mg nicotine.

List of excipients: chewing gum base, xylitol, sodium carbonate anhydrous, sodium hydrogen carbonate, magnesium oxide light, acesulfame potassium, peppermint oil, levomenthol, acacia, titanium dioxide (E171), carnauba wax.

NICORETTE® FRESHMINT 4 mg: each piece contains 20 mg nicotine-resin complex 20 %, equivalent to 4 mg nicotine.

List of excipients: chewing gum base, xylitol, sodium carbonate anhydrous, magnesium oxide light, acesulfame potassium, peppermint oil, levomenthol, acacia, titanium dioxide (E171), quinoline yellow (E104), carnauba wax.

PHARMACOLOGICAL CLASSIFICATION

A 34. Other

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

When used as directed, the 2 mg strengths produce peak blood nicotine concentrations equivalent to ⅓, and the 4 mg strengths produce peak blood nicotine concentrations equivalent to ⅔ that of smoking a mild cigarette. Owing to the slower rate of absorption of nicotine through the buccal mucosa, it does not reproduce the pleasure of cigarette smoking.

Although one is still supplying the body with nicotine, the blood levels achieved after repeated administration of NICORETTE® are less than those achieved after smoking.

Pharmacokinetic properties:

Absorption:

Nicotine administered in chewing gums is readily absorbed from
the oral mucosa membrane. Demonstrable blood levels of nicotine are obtained within 5 – 7 minutes after starting chewing and reaches a maximum about 5 – 10 minutes after stopping chewing. The amount of nicotine absorbed depends on the proportion of the dose extracted from the gum and the proportion lost due to swallowing and subsequent first-pass elimination in the liver.

Distribution:

The volume of distribution, following intravenous administration of nicotine, is about 2 to 3 ℓ/kg and half-life is about 2 to 3 hours. **Plasma protein binding** of nicotine is less than 5 %. Therefore, changes in nicotine binding from use of concomitant medicines or alterations of plasma proteins by disease states
would not be expected to have significant effects on nicotine pharmacokinetics.

Biotransformation:

The major eliminating organ is the liver, although the lungs and brain also metabolise nicotine to a small extent. The enzyme primarily involved in biotransformation of nicotine is CYP2A6. The primary metabolite of nicotine in plasma, cotinine, has a terminal half-life of 15 to 20 hours and plasma concentrations that exceed nicotine by 10-fold. The primary urinary metabolites are cotinine (15 % of the dose) and trans-3-hydroxy-cotinine (45 % of the dose).

Elimination:

The major eliminating organ is the liver, and average plasma clearance is about 70 ℓ/hour. The kidneys and lungs also metabolise nicotine. About 10 % of nicotine is excreted unchanged in the urine. As much as 30 % of nicotine may be excreted unchanged in the urine with high flow rates and acidification of the urine below pH 5. Progressive severity of renal impairment is associated with decreased total clearance of nicotine. The pharmacokinetics of nicotine is unaffected in

cirrhotic patients with mild liver impairment (Child Pugh score 5) and decreased in cirrhotic patients with moderate liver impairment (Child Pugh score 7). Raised nicotine levels have been seen in smoking patients undergoing haemodialysis.

INDICATIONS

NICORETTE® is indicated as a temporary aid to the cigarette smoker seeking to give up his or her smoking habit while participating in a behavioural modification programme under professional supervision. The efficacy of NICORETTE® use without concomitant participation in a behavioural modification programme has not been established. The benefits of NICORETTE® use beyond three months have not been demonstrated.

CONTRAINDICATIONS

Safety and effectiveness in children and adolescents who smoke have not been evaluated. NICORETTE® should not be given to children.

NICORETTE® is contraindicated in patients during the immediate post-myocardial infarction period, in patients with life-threatening dysrhythmias, and patients with severe or worsening angina pectoris. NICORETTE® is also contraindicated in patients with active temporomandibular joint disease.

WARNINGS AND SPECIAL PRECAUTIONS

The risks of nicotine use in patients with certain cardiovascular and endocrine diseases should be carefully weighed against the benefits of including NICORETTE® in a smoking cessation programme in these patients. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac dysrhythmias or vasospastic diseases (Buerger's disease, Prinzmetal variant angina) should be carefully screened and evaluated before NICORETTE® is prescribed.

As the action of nicotine on the adrenal medulla (release of catecholamines) does not appear to be affected by tolerance, NICORETTE® should be used with caution in patients with hyperthyroidism, phaeochromocytoma or insulin-dependent diabetes.

Cigarette smoking is felt to play a perpetuating role in hypertension and peptic ulcer disease. Therefore, NICORETTE® should be used in patients with systemic hypertension or inactive peptic ulcer only when the benefits of including NICORETTE® in a smoking cessation programme outweigh the risks.

In females, tobacco smoking delays time to conception, decreases *in vitro* fertilisation success rates, and increases risk of infertility. In males, tobacco smoking reduces sperm production, increases oxidative stress and DNA damage. Spermatozoa from smokers have reduced fertilising capacity. The specific contribution of nicotine however, to these effects in humans, is unknown.

If the gum is chewed too fast, the patient may experience effects similar to those experienced when inhaling cigarette smoke for the first time, or when smoking too fast. These effects include light-headedness, nausea and vomiting, throat and mouth irritation, hiccups and stomach upset. Most of these effects are controlled by chewing more slowly. See instructions below.

Some other effects sometimes seen particularly during the first few days of using gum include mouth ulcers, jaw muscle ache, headache, heart palpitations and more than the usual amount of saliva in the mouth. There are other side effects which have been infrequently reported with the use of NICORETTE®. Patients should be encouraged to discuss any questions, and to report any disturbing side effects. Do not exceed the recommended dosage.

As the urge to smoke fades, gradually reduce the number of pieces of gum chewed each day. This may be possible within two or three months. Unless advised otherwise, no attempt to stop

using the gum should be made until the craving is satisfied with one or two pieces a day. The gum should not be used for more than 3 months.

Patients should remember to carry the gum with them at all times in case they feel the sudden urge to smoke again. THEY SHOULD NOT FORGET THAT ONE CIGARETTE IS ENOUGH TO START THE SMOKING HABIT AGAIN.

Children:

Not to be administered to children.

Some flavours of NICORETTE® chewing gum contains xylitol, which may cause diarrhoea and flatulence when taken orally in large amounts.
NICORETTE® 2 mg and 4 mg chewing gum contains sorbitol, and is therefore unsuitable for use in patients with hereditary fructose intolerance.

Effects on ability to drive and use machines:

NICORETTE® can cause dizziness. Patients should ensure that they know how NICORETTE® affects their ability to drive and use machines, before engaging in these activities.

INTERACTIONS

Smoking cessation, with or without nicotine substitutes, may alter response to concomitant medication in ex-smokers. Smoking is considered to increase metabolism and thus lower blood levels of medicines such as caffeine, theophylline, imipramine and pentazocine, through enzyme induction.
Cessation of smoking may result in increased levels of these medicines. Absorption of glutethimide may be decreased and the “first pass” metabolism of propoxyphene decreased by smoking cessation. Other reported effects of smoking, which do not involve enzyme induction, include reduced diuretic effects of furosemide and decreased cardiac output, and increased blood

pressure with propranolol, which may also relate to the hormonal effects of nicotine. Smoking cessation may reverse these actions.

Both smoking and nicotine can increase circulating cortisol and catecholamines. Therapy with adrenergic agonists or with adrenergic blockers may need to be adjusted according to changes in nicotine therapy or smoking status.

PREGNANCY AND LACTATION

Pregnancy:

NICORETTE® may cause foetal harm when administered to a pregnant woman. NICORETTE® is therefore contraindicated in women who are or may become pregnant, and female patients should be advised to take adequate precautions to avoid becoming pregnant. The doctor may wish to consider a pregnancy test before instituting therapy with NICORETTE®. If NICORETTE® is used during pregnancy, or if the patient becomes pregnant while taking NICORETTE®, the patient should be apprised of the potential hazard to the foetus. Nicotine passes to the foetus and affects its breathing movements and circulation. The effect on circulation is dose dependant. Maternal smoking in pregnancy is associated with low birth weight infants and increased risk of abortion, still birth and neonatal death.

Lactation:

Because of the potential for serious adverse reactions to nursing infants from nicotine, a decision should be made whether to discontinue NICORETTE®.

Nicotine passes freely into breast milk in quantities that may affect the infant, even at therapeutic doses, and therefore should not be used by mothers breastfeeding their infants. As nicotine is the major addictive substance in tobacco smoke, the possibility exists that dependence on the nicotine in NICORETTE® may occur.

DOSAGE AND DIRECTIONS FOR USE

Adults:

Use the gum for 3 months. Gradual weaning from the gum should then be initiated. Treatment should be stopped when the dose is reduced to 1 - 2 chewing gums per day.

1. The patient must give up smoking completely. The gradual cutting down of tobacco consumption will not work.
2. NICORETTE® has been prescribed as part of a programme to help the patient stop smoking.
3. Whenever the patient feels the need to smoke, one piece of gum should be placed in the mouth.
4. When the gum is chewed, nicotine is slowly released and is absorbed through the lining of the mouth.
5. The gum should be chewed very slowly until it is tasted or a slight tingling is felt in the mouth. Because of its nicotine content, the gum does not taste like an ordinary chewing gum.
6. As soon as the gum can be tasted, chewing must stop.
7. After the taste or tingling is almost gone (about one minute), the gum should be chewed slowly again until the taste is more pronounced. Then chewing should be stopped again.
8. The gum should be chewed slowly for 30 minutes to release most of the nicotine. The patient should not expect the gum to give the same quick satisfaction that smoking does.
9. Most people find that 10 to 12 pieces per day of NICORETTE® 2 mg or 4 mg are enough to control their urge to smoke. If this is not the case, consult your doctor or pharmacist. Do not use more than 15 pieces in 24 hours. Depending on the patient's needs, the rate of chewing and the time between pieces can be adjusted.

Children:

Not to be administered to children.

SIDE EFFECTS

Mechanical effects of gum chewing include traumatic injury to oral mucosa or teeth. Nicotine from NICORETTE® may sometimes cause irritation of the throat and mouth and may also cause

increased salivation and sometimes swelling of the tongue. Excessive swallowing of dissolved nicotine (in the saliva) may cause hiccups.

Excessive consumption of NICORETTE® could lead to nausea, faintness or headaches, diarrhoea, constipation, vomiting, hoarseness, dry mouth, flushing, sneezing, cough, euphoria, insomnia, dizziness, eructation, indigestion, anorexia, jaw muscle ache and atrial fibrillation.

Swallowed nicotine may exacerbate symptoms in patients suffering from gastritis or peptic ulcer. Smokers who wear dentures may experience difficulty in chewing NICORETTE®.
NICORETTE® should be used with caution in patients with oral or pharyngeal inflammation and in patients with a history of oesophagitis or peptic ulcer.

Frequent:

Nervous system disorders: Headache, dizziness

Gastrointestinal disorders: Gastrointestinal discomfort, hiccups, nausea, vomiting, diarrhoea

General disorders and administrative site conditions: Sore mouth or throat, jaw muscle ache

Less frequent:

Immune system disorders: Allergic reactions including angioedema

Cardiac disorders: Palpitations, reversible atrial fibrillation

Skin and subcutaneous tissue disorders: Erythema, urticaria.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage of NICORETTE® can only occur if many pieces are chewed simultaneously. The fatal dose of nicotine in man is about 60 mg.

Symptoms of overdosage include nausea, salivation, abdominal pain, vomiting, diarrhoea, cold sweat, headache, dizziness, disturbed hearing and vision, mental confusion and marked

weakness. Faintness and prostration may ensue and hypotension may occur, breathing is difficult, the pulse may be rapid, weak and irregular. Collapse may be followed by terminal convulsions. Death may result within a few minutes from respiratory failure caused by paralysis of the muscles of respiration. Nicotine is excreted four times more rapidly in acid than alkaline urine.

If the patient accidentally swallows a piece of gum, no adverse effects should be experienced. Overdose could occur if many pieces are chewed simultaneously or in rapid succession. IN CASE OF ACCIDENTAL OVERDOSAGE OR IF A CHILD CHEWS OR SWALLOWS ONE OR MORE PIECES OF THE GUM, A DOCTOR OR THE LOCAL POISON CONTROL CENTRE SHOULD BE CONTACTED IMMEDIATELY.

In the event of overdosage, vomiting should be induced with syrup of ipecacuanha. Artificial respiration with oxygen should be instituted if needed and continued for as long as necessary. Other therapy, including treatment of shock, is purely symptomatic.

IDENTIFICATION

NICORETTE® 2 mg: A beige, square piece.

NICORETTE® 4 mg: A yellow, square piece.

NICORETTE® MINT 2 mg: A square, light beige piece, with a characteristic minty taste and odour.

NICORETTE® MINT 4 mg: A square, light yellow piece, with a characteristic minty taste and odour.

NICORETTE® ICY WHITE 2 mg: A whitish coated, square piece of gum.

NICORETTE® ICY WHITE 4 mg: A cream coloured coated, square piece of gum.

NICORETTE® FRESHFRUIT 2 mg: A square, whitish coated piece, with a characteristic fruity taste and odour.

NICORETTE® FRESHFRUIT 4 mg: A square, coated and cream coloured piece, with a characteristic fruity taste and odour.

NICORETTE® FRESHMINT 2 mg: A square, whitish coated piece, with a characteristic minty taste and odour.

NICORETTE® FRESHMINT 4 mg: A square, coated and cream coloured piece, with a characteristic minty taste and odour.

PRESENTATION

NICORETTE® 2 mg & 4 mg, NICORETTE® MINT 2 mg & 4 mg, NICORETTE® ICY WHITE 2 mg & 4 mg, NICORETTE® FRESHFRUIT 2 mg & 4 mg, NICORETTE® FRESHMINT 2 mg & 4 mg: Cartons of 30 and 105 pieces, in the form of 2 and 7 press-through aluminium/PVC/PVDC blister packed strips, each containing 15 pieces.

STORAGE INSTRUCTIONS

Protect from light. Keep in a cool place (at or below 25 °C).

Keep any spare blisters in the box until immediately before use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

NICORETTE® 2 mg: P/34/187

NICORETTE® 4 mg: P/34/188

NICORETTE® MINT 2 mg: 30/34/0272

NICORETTE® MINT 4 mg: 30/34/0273

NICORETTE® ICY WHITE 2 mg: A46/34/0164

NICORETTE® ICY WHITE 4 mg: A46/34/0165

NICORETTE® FRESHFRUIT 2 mg: A40/34/0565

NICORETTE® FRESHFRUIT4 mg: A40/34/0566

NICORETTE® FRESHMINT 2 mg: A40/34/0520

NICORETTE® FRESHMINT 4 mg: A40/34/0523

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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SOUTH AFRICA

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