Nicabate Soft Gum
Product Information

NAME OF THE DRUG

Nicotine

DESCRIPTION

Nicotine is 3-[(2S)-1-methylpyrolidin-2-yl]-pyridine and is the major pharmacologically active alkaloid of tobacco. The free alkaloid is absorbed rapidly through the skin and respiratory tract.

2 mg - Off-white rectangular pillow-shaped soft gum.
4 mg - Yellow rectangular pillow-shaped soft gum.

List of Excipients

2 mg and 4 mg soft gum: Gum base, calcium carbonate, butylated hydroxytoluene, sorbitol, maltitol solution, glycerol, acesulfame potassium, mint flavour, mannitol, sodium carbonate anhydrous, sodium hydrogen carbonate, carnauba wax.
4 mg soft gum: Also contains Quinoline yellow, CI47005

PHARMACOLOGY

Pharmacodynamics

The pharmacological effects of nicotine are well documented. Those resulting from chewing Nicabate soft gum are comparatively small. The response at any one time represents a summation of stimulant and depressant actions from direct, reflex and chemical mediator influences on several organs.

The main pharmacological actions are central stimulation and/or depression, transient hyperpnoea, peripheral vasoconstriction (usually associated with a rise in systolic pressure), suppression of appetite and stimulation of peristalsis.

Withdrawal symptoms associated with the abrupt cessation of the use of nicotine include dysphoria, depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness or impatience, decreased heart rate, increased appetite or weight gain and nicotine craving. These symptoms have been shown in clinical studies to be relieved by nicotine replacement products such as Nicabate soft gum.

Pharmacokinetics

Nicotine administered in chewing gums is readily absorbed from the buccal mucous membranes. The mean T_{max} from studies was attained at approximately 35 - 40 minutes with a range of approximately 20 - 70 minutes based on a standardized chewing regime requiring chewing every four seconds for 30 minutes. Blood levels are

roughly proportional to the amount of nicotine chewed and have been shown never to exceed those obtained from smoking cigarettes.

Mean steady state trough levels of 9-10 ng/mL for the 2 mg and 19-20 ng/mL for the 4 mg Nicabate soft gum are achieved during standardised conditions ie, chewing every four seconds for 30 minutes.

The volume of distribution following IV administration of nicotine is about 2 to 3 L/kg and the half-life approximately 2 hours. The major eliminating organ is the liver and average plasma clearance is about 70 L/hour. The kidney and lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified all of which are believed to be less active than the parent compound. The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15 to 20 hours and 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). 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.

Plasma protein binding of nicotine is less than 5%. Therefore, changes in nicotine binding, from use of concomitant drugs or alternatives, of plasma proteins by disease states would not be expected to have significant effects on nicotine kinetics.

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

There are no differences in nicotine kinetics between men and women.

INDICATIONS

Nicabate soft gum are indicated for the relief of nicotine withdrawal symptoms including nicotine cravings associated with smoking cessation. Nicabate soft gum may also be used as part of a smoking reduction strategy by smokers who are unable or not ready to stop smoking abruptly as a step towards stopping completely. If possible, when stopping smoking, Nicabate soft gum should be used in conjunction with a behavioural support programme.

CONTRAINDICATIONS

Nicabate should not be used by:

- Non-smokers
- Children under 12 years of age
- Those with hypersensitivity to nicotine or any of the excipients

PRECAUTIONS

The risks associated with the use of NRT are substantially outweighed in virtually all circumstances by the well established dangers of continued smoking.
Patients hospitalised for myocardial infarction, severe dysrhythmia or CVA (cerebrovascular accident) who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, Nicabate soft gum may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. Use with caution in patients with recent or unstable cardiovascular disease. In patients with unstable cardiovascular disease, do not continue NRT if patient continues to smoke.

The combination NRT regimen should not be used in people with known cardiovascular disease without evaluation of the risk/benefit of a healthcare professional.

Diabetes mellitus: Patients with diabetes mellitus should be advised to monitor their sugar levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism and vasoconstriction may delay/reduce insulin absorption.

Allergic reactions: Susceptibility to angioedema and urticaria. NRT should be used with caution by patients who are susceptible to angioedema and/or urticaria.

A risk-benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

- *Renal and hepatic impairment*: Use with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

- *Phaeochromocytoma and uncontrolled hyperthyroidism:* Use with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma as nicotine causes release of catecholamines.

- *GI disease:* Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers. Oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

Danger in small children: Doses of nicotine tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal. Products containing nicotine should not be left where they may be misused, handled or ingested by children.

Transferred dependence: Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

Dental - Smokers who wear dentures or who have temporomandibular joint disease may experience difficulty in chewing Nicabate soft gum.

Oral - Use of Nicabate soft gum may exacerbate oral inflammation

Each piece of soft gum contains 230 mg (2 mg soft gum) / 218 mg (4 mg soft gum) sugar alcohols. Products containing mannitol, maltitol and sorbitol may have a laxative effect or cause diarrhoea.

Each piece of soft gum (1 dose) contains up to 156 mg sorbitol. Sorbitol is unsuitable for those with hereditary fructose intolerance.

Use in Pregnancy (Pregnancy category D)
Smoking during pregnancy is associated with risks such as intra-uterine growth retardation, premature birth or stillbirth. Stopping smoking is the single most effective intervention for improving the health of both pregnant smoker and her baby. The earlier abstinence is achieved the better.

Ideally smoking cessation during pregnancy should be achieved without NRT. However for women unable to quit on their own, NRT may be recommended to assist a quit attempt. Nicotine is harmful to the foetus. However, the risk of using NRT to the foetus is lower than that expected with tobacco smoking, due to lower maximal plasma nicotine concentration and no additional exposure to polycyclic hydrocarbons and carbon monoxide.

However, as nicotine passes to the foetus affecting breathing movements and has a dose dependent effect on placental/foetal circulation, the decision to use NRT should be made as early on in the pregnancy as possible. The aim should be to use NRT for only 2-3 months.

While no data exist to support one form of NRT over another, it may be prudent to use intermittent dosing products as these usually provide a lower daily dose of nicotine than patches. However patches may be preferred if the woman is suffering from nausea during pregnancy. If patches are used they should be removed before going to bed.

Use in Lactation
Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to from NRT is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to. Nicabate patches should not be used while breastfeeding. Intermittent dosing products such as Nicabate soft gums or lozenges, should be used while breastfeeding and women should breast feed just before they use the product to allow as long a time as possible between NRT use and feeding.

Carcinogenesis, Mutagenesis and Impairment of Fertility
Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumours in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumour initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Nicotine and cotinine were not mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears

to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Effects on Ability to Drive or Use Machines
Used as recommended there are minimal risks associated with the use of Nicabate soft gum in driving vehicles or operating machinery.

Drug Interactions
No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

Smoking cessation, with or without nicotine replacement, may alter the individual's response to concomitant medication and may require adjustment of dose.

Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolised by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs.

The following drugs may require adjustment in dose at cessation of smoking:
Caffeine, theophylline, imipramine, pentazocine, tacrine, clomipramine, insulin, clozapine, olanzapine and fluvoxamine. In particular, anticonvulsants may require special monitoring and/or dosage adjustment.

Other reported effects of smoking include reduced analgesic efficacy of dextropropoxyphene, reduced diuretic response to frusemide and altered pharmacological response to propranolol, as well as altered rates of ulcer healing with H_2 antagonists. Both smoking and nicotine can increase levels of circulating cortisol and catecholamines. Dosages of nifedipine, adrenergic agonists, or adrenergic blocking agents may need to be adjusted.
Insulin dependent diabetes – smoking cessation may lead to an increase in subcutaneous insulin absorption.

ADVERSE REACTIONS

Nicotine lozenges / gum / films can cause adverse reactions similar to those associated with nicotine from tobacco. Many of the observed adverse reactions are consistent with the pharmacological effects of nicotine, which are dose dependent.

The following undesirable effects detailed in Tables 1 and 2 are nicotine related adverse events for all oral dosage forms.

Table 1 shows events which were identified from a double-blind, randomised, placebo controlled lozenge clinical study involving 1818 patients. Adverse events reported in this study have been considered for inclusion, where the incidence in the 2 mg or 4 mg

nicotine arm was higher than the corresponding placebo arm. Frequencies are calculated from the study safety data.

Table 1

Gastrointestinal Disorders	
Very common ≥1/10	nausea
Common ≥1/100; <1/10	vomiting, dyspepsia†, abdominal pain upper, diarrhoea, dry mouth, constipation, hiccups, stomatitis, flatulence,oral discomfort
Nervous System Disorders	
Common ≥1/100; <1/10	headache*, dizziness*
Psychiatric Disorders	
Common ≥1/100; <1/10	insomnia*
Respiratory, Thoracic and Mediastinal Disorders	
Common ≥1/100; <1/10	pharyngitis, cough*, pharyngolaryngeal pain

* These events may also be due to withdrawal symptoms following smoking cessation

† Individuals with a tendency to experience indigestion may suffer initially from minor degrees of indigestion or heartburn if the 4 mg dose is used - slower chewing in the case of gum or the use of the 2 mg dose (if necessary more frequently) will usually overcome this problem

Additional events which have been noted in studies with Nicorette Gum are weakness and palpitations.

Post Marketing Data

Table 2 shows events which were identified from post-marketing experience of oral nicotine products. Frequencies for these events cannot be estimated for oral nicotine dosage forms from the available data.

Table 2

Cardiac Disorders
palpitations, tachycardia, reversible atrial fibrilation
Gastrointestinal Disorders
dysphagia, eructation, salivary hypersecretion
General Disorders and Administration Site Conditions
asthenia*, fatigue*, malaise*, influenza type illness*
Immune System Disorders
Hypersensitivity, angioedema, erythema, urticaria, ulcerative stomatitis, and very rare anaphylactic reactions
Nervous System Disorders
Tremor
Psychiatric Disorders
nervousness*
Respiratory, Thoracic and Mediastinal Disorders
Dyspnoea

* These events may also be due to withdrawal symptoms following smoking cessation

DOSAGE AND ADMINISTRATION

Adults (18 years and over including the elderly)
Nicabate soft gum 2 mg is suitable for smokers who smoke fewer than 20 cigarettes a day.

Nicabate soft gum 4 mg is suitable for smokers who smoke more than 20 cigarettes a day.

Users should make every effort to stop smoking completely during treatment with Nicabate soft gum.

Behavioural therapy, advice and support will normally improve the success rate.

Users should follow the schedule of treatment below:

STEP 1	STEP 2	STEP 3	
Initial treatment period. 12 weeks	Step down treatment period. 2 weeks	Step off treatment period 2 weeks	
Chew 1 piece whenever there is an urge to smoke. Use 8 – 12 pieces/day of the 2 mg strength or 8-10 pieces/day of the 4 mg strength.	Gradually reduce soft gum use to 4 - 6 pieces/day.	Use 1 – 3 pieces of soft gum/day. Reduce to zero over 2 weeks.	To help you stay smoke free, take 1 piece of soft gum when you are strongly tempted to smoke.

The user dose and duration of treatment is individual and dependent on how much nicotine you need to reduce the withdrawal symptoms. Clinical experience has shown that the treatment should last for at least 3 months.

Users should not use more than one piece of soft gum at a time and should not exceed 20 pieces/day of the 2 mg strength or 10 pieces/day of the 4 mg strength. Absorption of nicotine is through the buccal mucosa and any nicotine that is swallowed is destroyed by the liver.

Directions for Use
Patients should be directed to chew each piece of soft gum slowly until the taste becomes strong (about 1 minute) then stop and rest the soft gum against the cheek. Once the taste fades, the soft gum should be chewed a few times until the taste gets strong then rested again against the cheek. This sequence should be repeated for about 30 minutes until the soft gum has lost its strength.

Acidic beverages eg coffee or soft drink interfere with the buccal absorption of nicotine.

Those who use the soft gum beyond 9 months are recommended to seek additional help and advice from a healthcare professional who may consider alternate quit strategies such as combination therapy.

Children and adolescents
Data are limited in relation to the value of NRT use in young people where the demand for cessation products and the motivation to quit is low. Nevertheless NRT is safe in this group. NRT should only be used by adolescents in conjunction with a counselling programme. Counselling is needed in this age group because NRT is likely to be ineffective in the absence of counselling.

Adolescents (12-17 years) should follow the schedule of treatment for adults in the table above for steps 1, 2 and 3 but, as data are limited, duration of NRT in this age group is restricted to 10 weeks. If longer treatment is required, advice from a

healthcare professional should be sought who can then reassess the patient for their commitment to quitting and the benefits of continued treatment. If treatment is continued, it should not be extended for more than another four weeks. Adolescents should not quit with a Combination NRT Regimen.

Nicabate soft gum is not recommended for use in children under 12 years of age.

Combination therapy
In some instances, it may be beneficial to utilize more than one form of NRT concurrently. For example, combination therapy could be used by smokers who have relapsed with NRT monotherapy in the past, who experience breakthrough cravings or have difficulty controlling cravings for cigarettes using single therapy. This would allow users to identify the combination most appropriate for their individual quit attempt. If required, Nicabate soft gum 2 mg or Nicabate lozenges 2 mg may be combined with Nicabate 21 mg patches. Nicabate 4 mg lozenges and/or 4 mg soft gums should not be used with Nicabate patches.

When using Nicabate 21 mg patches in addition to Nicabate 2 mg soft gums or 2 mg lozenges, it is recommended that a minimum of 4 pieces of soft gum/4 lozenges are used daily. Most people will use 4-5 pieces. The maximum number of soft gums or lozenges used in conjunction with the patch is 12 pieces per day.

Combination treatment should be used for 12 weeks after which weaning may be initiated.
If required, weaning may be done by either:

1 Using Nicabate 14 mg patch for 2 weeks and then Nicabate 7 mg patch for 2 weeks while maintaining the number of pieces of 2 mg soft gum/lozenges that have been routinely used. Then, when a patch is no longer used, the number of pieces of soft gum/lozenges can be gradually reduced. OR

2 Stopping use of Nicabate 21 mg patch and then gradually reducing the number of pieces of 2 mg soft gum/lozenges that are being used.

Harm Reduction

Gradual cessation of smoking

Reduce to quit

For smokers who are unwilling or unable to quit abruptly. Use a piece of soft gum whenever there is a strong urge to smoke in order to reduce the number of cigarettes smoked as far as possible and to refrain from smoking as long as possible. The number of pieces of soft gum a day is variable and depends on the patient's needs. Nonetheless it should not exceed 20 pieces per day of the 2 mg strength or 10 pieces per day of the 4 mg strength.

If a reduction in cigarette consumption has not been achieved after 6 weeks of treatment, a healthcare professional should be consulted. Reduced tobacco consumption may help to lead to complete cessation of smoking. This should be attempted as soon as possible. When the number of cigarettes has been

reduced to a level from which the user feels able to quit completely, then start on the schedule for “abrupt cessation’ as given above.

If an attempt to stop smoking completely has not been started within 6 months after the beginning of treatment, it is recommended to consult a healthcare professional.

OVERDOSAGE

Overdosage can occur if many soft gums are taken simultaneously or in rapid succession. The consequences of an overdose are most likely to be minimised by the early nausea and vomiting known to occur with excessive nicotine intake. Nicotine is also subject to a significant first-pass metabolism.

Even small quantities of nicotine may be dangerous in children. If poisoning is suspected in a child, a doctor must be consulted immediately.

The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Symptoms of acute nicotine poisoning include nausea, salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and marked weakness. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse and terminal convulsions.

Treatment of overdose

In the event of overdose or poisoning, the Poisons Information Centre should be contacted on 13 11 26.

All nicotine intake should cease immediately and the patient should be treated symptomatically.

PRESENTATION

Nicabate soft gum is available in two strengths: 2 mg and 4 mg in packs of 12, 24, 48 and 96 soft gums.

Not all pack sizes may be marketed.

All presentations contain information on Nicabate soft gum and how to use it.

Store below 25°C.

POISON SCHEDULE **Unscheduled**

GlaxoSmithKline
Consumer Healthcare
82 Hughes Avenue
Ermington NSW 2115

Approved by TGA: – 8th December 2011