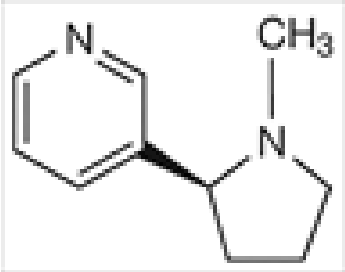
Nicabate Extra Fresh Mint Gum
Product Information

NAME OF THE MEDICINE

Nicotine

Chemical structure:



CAS No: 54-11-5
Molecular formula: $C_{10}H_{14}N_2$
Chemical Name: (S)-3-(1-Methylpyrrolidin-2-yl)pyridine

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 and 4 mg - Off-white rectangular pillow-shaped extra fresh mint gum and is approximately 20 x 12 mm.

List of Excipients

2 mg and 4 mg extra fresh mint gum: Gum Base 25048 (incl. 0.09 %w/w Butylated hydroxytoluene (E321), calcium carbonate (E170), sorbitol (E420), glycerol (E422), acesulfame potassium (E950), eucamenthol flavour, mannitol, sodium carbonate anhydrous (E500), carnauba wax (E903), xylitol (E967), levomenthol flavour, optacool flavour, sucralose (E955), talc-purified, titanium dioxide (E171), acacia (E414).

PHARMACOLOGY

Pharmacodynamics

The pharmacological effects of nicotine are well documented. Those resulting from chewing Nicabate extra fresh mint 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 extra fresh mint gum.

Pharmacokinetics

Absorption
Nicotine administered in chewing gums is readily absorbed from the buccal mucous membranes. Demonstrable blood levels are obtained within 5 - 7 minutes and reach a maximum about 30 minutes after the start of chewing. Blood levels are roughly proportional to the amount of nicotine chewed and have been shown never to exceed those obtained from smoking cigarettes.

Distribution
As the plasma protein binding of nicotine is low (4.9% - 20%), the volume of distribution of nicotine is large (2.5 l/kg). The distribution of nicotine to tissue is pH dependent, with the highest concentrations of nicotine found in the brain, stomach, kidney and liver. Nicotine crosses the blood-brain barrier, the placenta and is detectable in breast milk.
Mean steady state trough levels of 9-10 ng/mL 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.

Metabolism
The metabolism of nicotine primarily occurs in the liver, but also in the lung and kidney. More than 20 metabolites of nicotine have been identified all of which are believed to be less active than the parent compound. Nicotine is metabolized primarily to cotinine but is also metabolized to nicotine N'-oxide. Cotinine has a half-life of 15 to 20 hours and its blood levels are 10 times higher than nicotine. Cotinine is further oxidized to trans-3'-hydroxycotinine, which is the most abundant metabolite of nicotine in the urine. Both nicotine and cotinine undergo glucuronidation.

Elimination
The elimination half-life of nicotine is approximately 2 hours (range 1 – 4 hours). Total clearance for nicotine ranges from approximately 62 to 89 l/hr. Non-renal clearance for nicotine is estimated to be about 75% of total clearance. Nicotine and its metabolites are excreted almost exclusively in the urine. The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxy-cotinine (45% of the dose). The renal excretion of unchanged nicotine is highly dependent on urinary pH with greater excretion occurring at acidic pH. About 10% of nicotine is excreted unchanged in the urine. As much as 30% of nicotine may be excreted unchanged 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 extra fresh mint gum is indicated for the relief of nicotine withdrawal symptoms including nicotine cravings associated with smoking cessation. Nicabate extra fresh mint 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 extra fresh mint gum should be used in conjunction with a behavioural support programme as this normally improves the success rate.

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 extra fresh mint gum may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. Once patients are discharged from hospital, they can use NRT on medical advice. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the gum should be reduced or discontinued.

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.

Seizures: Potential risks and benefits of nicotine should be carefully evaluated before use in subjects taking anti-convulsant therapy or with a history of epilepsy as cases of convulsions have been reported in association with nicotine.

Diabetes mellitus: Blood glucode levels may be more variable when stopping smoking, with or without NRT, so it is important for patients with diabetes mellitus to monitor their blood glucose 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 active oesophagitis, oral or pharyngeal inflammation, gastritis and 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.

Stopping smoking: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolised by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops smoking, this may result in a slower metabolism and a consequent rise in blood levels of such drugs. This is of potential clinical importance for products with a narrow therapeutic window, e.g. theophylline, tacrine, clozapine and ropinirole. The plasma concentration of other medicinal products metabolised in part by CYP1A2 e.g. imipramine, olanzapine, clomipramine and fluvoxamine may also increase on cessation of smoking, although data to support this are lacking and the possible clinical significance of this effect for these drugs is unknown. Limited data indicate that the metabolism of flecainide and pentazocine may also be induced by smoking.

Sorbitol (E420): Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Butylated hydroxytoluene (E321): May cause irritation of mucous membranes.

Sodium: Nicabate Extra Fresh Mint Gum contains 10.5 mg (2 mg gum) or 14.0 mg (4 mg gum) of sodium per piece of gum. To be taken into consideration by patients on a controlled sodium diet.

During a quit attempt, users should not interchange nicotine gums with nicotine lozenges since pharmacokinetic data indicate a higher availability of nicotine from some nicotine lozenges in comparison to the gum.

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

Nicotine gum may loosen fillings or dental implants.

Oral - Use of Nicabate extra fresh mint gum may exacerbate oral inflammation.

Effects on Fertility
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.

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 should only be used on the advice of a healthcare professional. 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.

Intermittent dosing products may be preferable 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

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.

Ideally smoking cessation during lactation should be achieved without NRT. However for women unable to quit on their own, NRT may be recommended to assist a quit attempt.

Using intermittent dose NRT preparations, compared with patches, may minimize the amount of nicotine in the breast milk as the time between administrations of NRT and feeding can be made as long as possible. Women should try to breastfeed just before they take the product.

Paediatric Use
Do not use in children under 12 years of age.

Genotoxicity
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.

Carcinogenesis
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.

Studies in male rats have shown that nicotine can decrease testis weight, cause a reversible decrease in Sertoli cell numbers with impairment of spermatogenesis, and result in a variety of changes in the epididymis and vas deferens. However, similar effects have not been reported to occur in humans.

Effects on Ability to Drive or Use Machines
Nicabate Extra Fresh Mint Gums have no or negligible influence on the ability to drive and use machines. However, users of nicotine replacement products should be aware that smoking cessation can cause behavioural changes.

INTERACTIONS WITH OTHER MEDICINES

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 (i.e. increase in blood pressure and heart rate and also increase pain response (anginapectoris type chest pain) provoked by adenosine administration, (see 'PRECAUTIONS').

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 EFFECTS

Nicotine lozenges / gum / patches 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.

At recommended doses Nicabate extra fresh mint gum has not been found to cause any serious adverse effects. Excessive consumption of Nicabate extra fresh gum by those who have not been in the habit of inhaling tobacco smoke, could possibly lead to nausea, faintness or headaches.

Certain symptoms that have been reported such as depression, irritability, anxiety, increased appetite and insomnia may be related to withdrawal symptoms associated with smoking cessation. Subjects quitting smoking by any means could expect to suffer from headache, dizziness, sleep disturbance, increased coughing or a cold.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥1/10), common (≥1/100 to 1/<10, uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class and Frequency	Adverse Reaction/Events
Psychiatric disorders	
Common	Insomnia, irritability
Central and peripheral nervous system disorders	
Common	Dizziness, headache
Uncommon	Lightheadedness, tremor
Gastrointestinal system disorders	
Common	Nausea, gastrointestinal discomfort, sore mouth, vomiting, indigestion, mouth irritation, mouth ulceration, dyspepsia, abdominal pain upper, diarrhoea, dry mouth, constipation, hiccups, flatulence, oral discomfort
Uncommon	Stomatitis
Respiratory, thoracic and mediastinal disorders	
Common	Hiccups, sore throat, pharyngitism cough, pharyngolaryngeal pain
Uncommon	Dyspnoea
Musculoskeletal and connective tissue disorders	
Common	Jaw pain
Cardiac disorders	
Uncommon	Palpitation, tachycardia
Rare	Atrial fibrillation
Skin and subcutaneous tissue disorders	
Uncommon	Erythema, urticaria, increased sweating
Immune system disorders	
Rare	Allergic reactions such as angio-oedema
Very rare	Anaphylactic reactions
Special senses other, disorders	
Uncommon	Parageusia, metallic taste, taste perversion
General disorders and administration site conditions	
Uncommon	Chest pain, arthralgia, myalgia, malaise

Paediatric population (12-17 years inclusive)
There are no specific adverse event data for this population. However, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults, based upon the pharmacokinetic study demonstrating a similar pharmacokinetic profile in the adolescent age group to adults.

DOSAGE AND ADMINISTRATION

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

Nicabate extra fresh mint 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 extra fresh mint gum.

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

Nicabate extra fresh mint gums should be chewed as directed whenever there is an urge to smoke, to maintain complete abstinence from smoking.

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 extra fresh mint gum use to 4 - 6 pieces/day.	Use 1 – 3 pieces of extra fresh mint gum/day. Reduce to zero over 2 weeks.	To help you stay smoke free, take 1 piece of extra fresh mint 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. When daily use is 1-2 gums, use should be stopped. Any spare gums should be retained as cravings may suddenly return.

Users should not use more than one piece of extra fresh mint 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 extra fresh mint gum slowly until the taste becomes strong (about 1 minute) then stop and rest the gum against the cheek. Once the taste fades, the 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 gum has lost its strength.

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

The user should not eat or drink while using the chewing-gum. Drinks that lower the pH in the mouth, e.g. coffee, fruit juice or sodas, may reduce the absorption of nicotine from the oral cavity. To achieve the maximum absorption of nicotine, these drinks should be avoided up to 15 minutes prior to using the chewing gum.

Those who use the 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 extra fresh mint 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 gum 2 mg or Nicabate lozenges 2 mg may be combined with Nicabate 21 mg patches. Nicabate 4 mg lozenges and/or 4 mg gums should not be used with Nicabate patches.

When using Nicabate 21 mg patches in addition to Nicabate 2 mg gums or 2 mg lozenges, it is recommended that a minimum of 4 pieces of gum/4 lozenges are used daily. Most people will use 4-5 pieces. The maximum number of 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 gum/lozenges that have been routinely used. Then, when a patch is no longer used, the number of pieces of 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 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 extra fresh mint 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 extra fresh mint 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 extra fresh mint 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 and may prove fatal. 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. Signs and symptoms of an overdose from nicotine gum would be expected to be the same as those of acute nicotine poisoning including pallor, nausea, vomiting, salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and vision, tremor, mental confusion and marked weakness. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, respiratory failure, 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. Artificial respiration with oxygen should be instituted if necessary. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

PRESENTATION AND STORAGE CONDITIONS

Nicabate extra fresh mint gum is available in two strengths: 2 mg and 4 mg in blister packs of 24 gums.

Not all pack sizes may be marketed.

All presentations contain information on Nicabate extra fresh mint gum and how to use it.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline
Consumer Healthcare
82 Hughes Avenue
Ermington NSW 2115

POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

28 August 2015

DATE OF MOST RECENT AMENDMENT

2 October 2015