PRODUCT INFORMATION

QuitX® CHEWING GUM

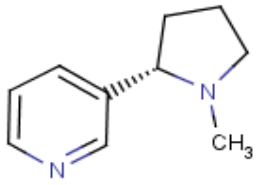
Freshmint and Classic Flavour

2 mg & 4 mg

NAME OF THE MEDICINE

QuitX Chewing Gum contains nicotine polacrilex.

The chemical name for nicotine is (S)-3-(1-methyl-2-pyrrolidinyl) pyridine. The chemical structure is;



CAS Registry No. 54-11-5

DESCRIPTION

The molecular formula of nicotine is $C_{10}H_{14}N_2$ with a molecular weight of 162.26.

In addition to the active ingredient, QuitX also contains the following ingredients

Freshmint Flavour:sodium carbonate, sodium bicarbonate, chewing gum base, xylitol, menthol, menthol flavour, natural toothpaste flavour, magnesium oxide light, acacia, hydroxypropylcellulose, acesulfame potassium, titanium dioxide, carnauba wax, and Sunset yellow (4mg strength only).

Classic Flavour: sodium carbonate, sodium bicarbonate, chewing gum base, sorbitol, menthol, acesulfame potassium, butylated hydroxytoluene, Mint fruit flavour, talc, carnauba wax, quinolone yellow (4mg strength only), and Brown lake blend colour (4mg strength only).

PHARMACOLOGY

Nicotine is a natural alkaloid which has ganglion stimulating properties and produces a wide range of pharmacological actions.

The use of nicotine is widespread in the form of tobacco products, chronic use of which is causally linked to a variety of serious diseases. Many smokers develop a dependence due to an interaction of pharmacological, social and psychological factors.

Pharmacodynamics.

QuitX Chewing Gum is a treatment aid in smoking cessation. Clinical studies have shown that nicotine replacement from nicotine containing products can help people give up smoking by relief of abstinence symptoms associated with smoking cessation.

Abrupt cessation of the use of tobacco containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability; frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving, which is recognised as a clinically relevant symptom, is also an important element in nicotine withdrawal.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking by relieving these withdrawal symptoms.

Pharmacokinetics.

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

Absorption
Nicotine administered in chewing gums is readily absorbed from the oral mucosa membranes. Demonstrable blood levels are obtained within five to seven minutes after starting chewing and reach a maximum about five to ten minutes after chewing is stopped. Blood levels are roughly proportional to the amount of nicotine released by chewing and are unlikely to exceed those obtained from smoking cigarettes. The amount of nicotine extracted from one chewing gum depends on how vigorously and for how long it is chewed. The amount of nicotine absorbed depends on the amount extracted and the loss from the oral cavity due to swallowing or expectoration.

The systemic availability of swallowed nicotine is lower due to first-pass hepatic metabolism. The high and rapidly rising nicotine concentration seen after smoking is rarely produced by treatment with the gum. Normally approximately 1.4 and 3.4 mg of nicotine will be extracted from the 2 and 4 mg gum, respectively. Steady state trough levels of 10 to 14 nanogram/mL for 2 mg and 24 to 29 nanogram/mL for 4 mg nicotine gum are achieved during standardised conditions, i.e. chewing every two seconds for 30 minutes. A twelve week study found that nicotine chewing gum 2 mg produced nicotine plasma levels of about 9 nanogram/mL, while 4 mg gum produced nicotine plasma levels of about 23 nanogram/mL. Afternoon peak plasma levels after cigarette smoking are about 35 nanogram/mL.

Distribution
The volume of distribution following intravenous (IV) administration of nicotine is about 2 to 3 L/kg and the half-life approximately two hours.

Metabolism
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 tenfold. The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxy-cotinine (45% of the dose).

Elimination
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.

Special populations
Plasma protein binding of nicotine is less than 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations 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.

Raised nicotine levels have been seen in smoking patients undergoing haemodialysis.

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).

CLINICAL TRIALS

Smoking reduction studies.

Placebo controlled double blind, randomised clinical studies in healthy smokers who did not intend to quit smoking but who were motivated to reduce their smoking have shown that nicotine chewing gum (4 studies) and nicotine inhaler (2 studies) is effective at helping smokers reduce the number of cigarettes smoked, and that reducing smoking leads to the increased likelihood of smoking cessation.

Pooled data from 4 nicotine gum smoking reduction studies showed that 12.8% of subjects using nicotine gum had achieved a sustained reduction (by at least 50%) in smoking at 4 months, compared to 5.7% of placebo treated subjects. Pooled data from the four nicotine gum studies and two similarly designed nicotine inhaler studies showed that a total if 193/1215 (15.9%) subjects in the nicotine treatment groups in the six studies managed to reduce their cigarette consumption by at least 50% from week 6 to month 4 compared to 81/1209 (6.7%) in the placebo treated groups. The point prevalence (PP) quit rates at month 12 for these individuals was 58/193 (30.1%) in the nicotine treatment groups compared to 15/81 (18.5%) in the placebo treated groups.

The corresponding figures for smokers who were unable to reduce their cigarette consumption by at least 50% from week 6 to month 4 with regards to PP abstinence at month 12 were 47/1022 (4.6%) in the nicotine treated groups and 39/1128 (3.5%) in the placebo treated groups.

Overall, at 1 year, 8.15% of subjects treated with nicotine gum or inhaler were abstinent, compared to 4.05% of placebo treated subjects, giving an odds ratio of 2.10 (95% confidence interval 1.48, 2.99). As regular smokers are generally adept at self regulating their nicotine intake within a narrow range it is unlikely that concomitant use of nicotine gum or inhaler and smoking will result in overdose or plasma nicotine levels higher than those achieved with smoking alone.

During the smoking reduction studies no clinically significant treatment related adverse events were observed during the concomitant use of gum or inhaler and cigarettes for up to 12 to 18 months. The adverse event profile did not differ markedly from that in smoking cessation studies.

In a 3 way open tolerability study in 19 healthy smokers investigating the concurrent use of 4 mg chewing gum and smoking during physical exercise subjects were administered each of the following treatments: placebo gum + smoking one cigarette; 4mg gum + one unlit cigarette; 4mg gum + smoking one cigarette. Each treatment was repeated 7 times during 7 consecutive hours on one day. During multiple submaximal exercise tests, no signs of myocardial ischemia with any of the 3 treatments or differences between the 3 treatments in the number of extra systoles, episodes of two or more systoles or other arrhythmias were observed. Changes in mean heart rate and systolic blood pressure during exercise, and diastolic blood pressure at rest, tended to be higher in the smoking + gum group; however, the differences between treatments were minor. Of 3,094 smokers with Chronic Obstructive Pulmonary Disease (COPD) participating in a 5 year lung health study, 25% of subjects were smoking and using gum, and 40% were abstinent and continued to use gum after 1 year. No increase in the incidence of cardiovascular events in the abstainers who used gum or in those who used gum and continued to smoke were observed.

INDICATIONS

Treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit.

In smokers currently unable or not ready to stop smoking abruptly, QuitX Chewing Gum may also be used as part of a smoking reduction strategy as a step towards stopping completely.

CONTRAINDICATIONS

QuitX Chewing Gum should not be administered to

- Non-smokers
- Patients with known hypersensitivity to nicotine or any of the excipients of the gum.

- Children under 12 years of age (see **DOSAGE AND ADMINISTRATION**, **Children**).

PRECAUTIONS

Any risks that may be associated with nicotine replacement therapy (NRT) are substantially outweighed by the well established dangers of continued smoking.

Denture warning
Smokers who wear dentures may experience difficulty in chewing nicotine chewing gum. The chewing gum may stick to, and may in rare cases, damage dentures.

Underlying cardiovascular disease.
In stable cardiovascular disease nicotine gum presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or cerebrovascular accident (CVA) and who are considered to be haemodynamically unstable should be encouraged to stop smoking with nonpharmacological interventions. If this fails, nicotine gum may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

Diabetes mellitus
Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism.

Gastrointestinal disease
Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastritis or peptic ulcers and oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

Nicotine chewing gum should be avoided if oral or pharyngeal inflammation is present.

Phaeochromocytoma and uncontrolled hyperthyroidism
Nicotine, from both NRT and smoking, causes the release of catecholamines from the adrenal medulla. Therefore, nicotine chewing gum should be used with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma.

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

Continued smoking while using nicotine replacement therapy
Nicotine chewing gum can safely be used while smoking. The adverse event profile (incidence and severity of events) of nicotine chewing gum in studies to reduce smoking did not differ markedly from that in smoking cessation studies. Intermittent use of nicotine

chewing gum and cigarettes does not appear to produce more side effects than use of NRT alone. Most regular smokers are adept at self titration of their nicotine intake in order to maintain their plasma nicotine levels within a narrow range.

Impaired renal function.
Nicotine chewing gum should be used with caution in patients with severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

Impaired hepatic function
Nicotine chewing gum should be used with caution in patients with moderate to severe hepatic impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

Use in the elderly
A minor reduction in total clearance of nicotine has been demonstrated in healthy elderly patients, however, not justifying an adjustment of dosage.

Carcinogenesis, mutagenesis, impairment of fertility.
Literature reports indicate that nicotine is neither an initiator nor a tumour promoter in mice. There is inconclusive evidence to suggest that cotinine, an oxidised metabolite of nicotine, may be carcinogenic in rats.

Neither nicotine nor cotinine was mutagenic in the Ames Salmonella test. Studies have shown a decrease of litter size in rats treated with nicotine during the time of fertilisation.

Use in pregnancy (Category D)

Category D
Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Nicotine is harmful to the foetus. The harmful effects of cigarette smoking on maternal and foetal health are clearly established. Short-term exposure during the first trimester is unlikely to cause a hazard to the foetus. NRT is not contraindicated in pregnancy.

The decision to use NRT should be made on a risk benefit assessment as early on in the pregnancy as possible with the aim of discontinuing use as soon as possible. Smoking during pregnancy is associated with risks such as intrauterine 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 passes to the foetus affecting breathing movements and has a dose dependent effect on placental/foetal circulation. 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. 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. If patches are used they
should be removed before going to bed.

Use in lactation
NRT is not contraindicated in lactation. Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to is relatively small and less hazardous than the second hand smoke they would otherwise be exposed to.

Using intermittent dose NRT preparations, such as nicotine chewing gum, may minimize the amount of nicotine in the breast milk as the time between administrations of NRT and feeding can be more easily prolonged. Women should breastfeed just before using the product.

Paediatric use
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. Nicotine gum should be disposed of with care.

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 (angina pectoris type chest pain) provoked by adenosine administration.

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 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, clozapine and ropinirole.

The plasma concentration of other drugs metabolised in part by CYP1A2, e.g. imipramine, olanzapine, clomipramine, fluvoxamine and caffeine may also increase on cessation of smoking, although data to support this are lacking and the possible clinical significance of this effect is unknown.

Limited data indicate that the metabolism of flecainide and pentazocine may also be induced by smoking.

ADVERSE EFFECTS

Nicotine chewing gum may cause adverse reactions similar to those associated with nicotine administered by other means and are mainly dose dependent.
Most of the undesirable effects reported by the patients occur during the first three to four weeks after start of treatment. The chewing gum may stick to and, in rare cases, may damage dentures.

The frequency of the more common reactions include the following.

Common (1/10 to 1/100)
Central nervous system: headache.
Gastrointestinal system: gastrointestinal discomfort, hiccups, nausea, vomiting.
Local: sore mouth or throat, jaw muscle ache.

Less common (1/100 to 1/1,000)
Circulation: palpitations.
Skin: erythema, urticaria.

Rare (1/1,000 to 1/10,000).
Cardiovascular system: reversible atrial fibrillation.
Other: allergic reactions such as angioedema.

Some symptoms, such as dizziness, headache and sleeplessness may be related to withdrawal symptoms associated with abstinence from smoking. Increased frequency of aphthous ulcer may occur after abstinence from smoking. The causality is unclear.

DOSAGE AND ADMINISTRATION

Smoking cessation
The initial dosage should be individualised on the basis of the patient's nicotine dependence. QuitX Chewing Gum should be used when the urge to smoke is felt. Most smokers require about 8 to 12 pieces of the 2 mg gum or four to six pieces of the 4 mg gum. Not more than 20 pieces of the 2 mg gum or ten pieces of the 4 mg gum (equivalent to a daily dose of 40 mg) should be chewed in one day.

Highly dependent smokers (smoke > 20 cigarettes/ day) or patients who have failed to stop smoking with the 2 mg gum should receive the 4 mg dosage initially. Other patients should begin treatment with the 2 mg dosage strength. Advice and support normally improve the success rate.

The following points should be observed.

Due to their nicotine content, QuitX Chewing Gum has an unusual taste. QuitX Chewing Gum should be chewed slowly until a strong taste or a slight tingling sensation is felt. When the tingling sensation occurs the smoker should stop chewing and the gum should be placed under the tongue or between the cheek and gums until the taste or tingling sensation has

disappeared. Chewing should then be resumed slowly and the procedure repeated. QuitX Chewing Gum should be chewed in this manner until the nicotine effect is no longer experienced (about 30 minutes).

The nicotine effects are not experienced until after a few minutes of chewing, the rapid satisfaction supplied by smoking is hence not to be expected. Rapid chewing may initially irritate the throat or cause hiccups or nausea. Adapting to the proper chewing technique takes a few days. Acidic beverages, e.g. coffee or soft drinks interfere with the buccal absorption of nicotine. Use of such beverages should therefore be avoided for 15 minutes before and during chewing.

Children
QuitX Chewing Gum should not be administered to children under 12 years of age.

Adults and elderly
QuitX Chewing Gum should be used for at least 3 months. Gradual weaning from the gum should then be initiated. Treatment should be stopped when the dose is reduced to 1 to 2 chewing gums per day. Any spare gum should be retained, as craving may suddenly occur.

Regular use of the gum beyond 12 months is generally not recommended. Some ex-smokers may need longer treatment with the gum to avoid returning to smoking.

Adolescents (12 to 18 years)
When deciding whether to recommend NRT an assessment should be made on the individual's nicotine dependence, motivation to quit and willingness to accept counselling. Counselling is considered to be vitally important in the effective treatment of tobacco dependence in this age group. Use for up to 8 weeks to break the habit of smoking, and then gradually reduce gum use over a 4 week period. When daily use is 1 to 2 gums, use should be stopped.

For those using 4 mg nicotine gum, the 2 mg nicotine gum will be helpful during withdrawal from treatment.

As data are limited in this age group, the recommended duration of treatment is 12 weeks. If longer treatment is required, advice should be sought from a healthcare professional.

Before a recommendation to extend treatment beyond 12 weeks is made the patient should be reassessed for commitment to quitting, expected benefit of continued treatment and maturity. Treatment should not be extended by more than a further 4 weeks.

Combination treatment
If smokers have previously relapsed with use of one form of nicotine replacement therapy (NRT), combination therapy could be beneficial. Smokers who experience breakthrough cravings or have difficulty controlling cravings using one form of NRT alone could combine the use of QuitX nicotine patch Step 1 (21mg/24 hours) with another form of NRT such as QuitX chewing gum 2 mg. QuitX chewing gum 4 mg should not be used with nicotine patches.

When using QuitX nicotine patch Step 1 (21mg/24hours) in addition to QuitX chewing gum 2 mg, it is recommended that 4 to 12 pieces are used each day. Most people will use 5 to 6 pieces. Do not exceed 12 pieces a day.

Combination therapy should be used for 12 weeks, after which one of the two following programs should be followed.

1. Stop use of QuitX nicotine patch and gradually reduce the number of gums used until they are no longer needed.

2. Continue with QuitX nicotine patch Step 2 (14mg/24 hours) for 3 to 4 weeks, then QuitX nicotine patch Step 3 (7mg/24 hours) for a further 3 to 4 weeks while maintaining the number of QuitX chewing gum 2 mg that is used each day. After use of patches is ceased, gradually reduce the number of gums used until they are no longer needed.

Smoking reduction (reducing to stop)
The smoker should use QuitX Chewing Gum between smoking episodes in order to prolong intervals between cigarettes, with the aim of reducing smoking as much as possible. Highly dependent smokers (smoke $\geq$ 20 cigarettes/day) or patients who have failed to stop smoking with the 2 mg gum should use the 4 mg dosage.

Other patients should begin treatment with the 2 mg dosage. Not more than 20 pieces of the 2 mg gum or 10 pieces of the 4 mg gum (equivalent to a daily dose of 40 mg) should be chewed in one day. If the smoker has not achieved a reduction in the number of cigarettes per day after 6 weeks, he or she should consult a healthcare professional. This six week time period is given to the smoker to allow them to familiarise themselves with nicotine chewing gum and to deal with craving symptoms while they attempt to reduce their smoking. Smokers who do reduce their smoking with nicotine chewing gum should make a cessation attempt as soon as they feel ready, but not later than 6 months after they start using nicotine chewing gum.

When making a cessation attempt, the smoking cessation instructions above, can be followed. If the smoker has not made a cessation attempt within 9 months of commencing treatment he or she should consult a healthcare professional.

OVERDOSAGE

Excessive use of nicotine from either NRT and/or smoking might cause symptoms of an overdose. The risk of poisoning as a result of swallowing the gum is very small, as absorption in the absence of chewing is slow and incomplete.

Symptoms
Symptoms of overdosage are those of acute nicotine poisoning and include nausea, salivation, vomiting, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and marked weakness. At high doses, these symptoms may be followed by hypotension, weak and irregular pulse, breathing difficulties, prostration, circulatory collapse and general convulsions.

Overdosage with nicotine can occur if the patient has a very low pretreatment nicotine intake or uses other forms of nicotine. The acute minimum lethal oral dose of nicotine in nonsmokers is believed to be 40 to 60 mg. Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal. The lethal dose of nicotine in a small child is approximately 10 to 15 mg.

Treatment
Contact the Poison Information Centre (13 1126) for advice on management of overdose.

If chewing gum is ingested, activated charcoal should be given as soon as possible.

The administration of nicotine should be stopped immediately and the patient should be treated symptomatically. Activated charcoal reduces gastrointestinal absorption of nicotine.

PRESENTATION AND STORAGE CONDITIONS

QuitX Freshmint Chewing Gum 2 mg (white square, biconvex coated gum): blister packs of 30's, and 100's.

QuitX Freshmint Chewing Gum 4 mg (light peach, square, biconvex coated gum): blister packs of 30's, and 100's.

QuitX Classic Chewing Gum 2 mg (off-white to tan, square, biconvex uncoated gum): blister packs of 30's, and 100's.

QuitX Classic Chewing Gum 4 mg (yellowish, square, biconvex uncoated gum): blister packs of 30's, and 100's.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Medis Pharma Pty Ltd
Level 3, 5 Essex St
The Rocks NSW 2000
Australia

POISON SCHEDULE OF THE MEDICINE

Not scheduled

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

Freshmint gums: 12 December 2011

Classic Gums: 17 July 2014

DATE OF MOST RECENT AMENDMENT

Not applicable