

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Niqero Fruit 2 mg medicated chewing gum

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewing-gum contains 2 mg nicotine as nicotine resinate.

Butylated hydroxytoluene up to 0.5 mg

Maltitol 188 mg

Sorbitol 223 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Medicated chewing-gum

White to yellowish chewing-gum, slightly convex, rectangular with an approximate size of 18×12×5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nicotine is indicated for the treatment of tobacco dependence by relieving nicotine withdrawal symptoms including cravings (see section 5.1), thereby facilitating smoking cessation or temporary smoking reduction in smokers motivated to quit smoking. Permanent cessation of tobacco use is the eventual objective.

Niqero Fruit is indicated in adults.

Advice and support normally improve the success rate

4.2 Posology and method of administration

Posology

The strength of the chewing-gum should be selected based on the user's dependence on nicotine. For low nicotine dependence a 2 mg chewing-gum is indicated. For high nicotine dependence (FTND \geq 6 or smoking of 20 cigarettes or more per day) or previous failure with 2 mg, a 4 mg chewing-gum is indicated.

Initially one piece of gum can be taken every 1-2 hours. In most cases 8-12 chewing-gums a day will be sufficient. For smoking cessation the maximum daily dose is 24 chewing-gums. For smoking reduction when used in between periods of smoking the maximum daily dose is 24 chewing-gums of 2 mg or 12 chewing-gums of 4 mg.

Paediatric population

Niqero Fruit chewing-gum should not be used in children below 18 years of age unless prescribed by the physician.

The safety and efficacy of Niqero Fruit chewing-gum in children below 18 years of age has not been established.

Method of administration

Adults and elderly

Each Niqero Fruit chewing-gum should be chewed slowly with breaks for approximately 30 minutes.

Niqero Fruit should be chewed until a strong taste or a light tingling sensation is felt. Stop chewing and let the chewing-gum rest between cheek and gum until the taste and the tingling sensation have faded. Chew slowly again and repeat chewing routine.

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.

Smoking cessation

The duration of treatment is individual. Normally, treatment should continue for at least 3 months. After that the number of chewing-gums used should be gradually reduced. Treatment should be discontinued when the dose is reduced to 1-2 gums per day. Regular use of Niqero Fruit chewing-gum for more than 6 months is generally not recommended. In some cases a longer treatment period may be necessary in order to avoid relapse. Any spare chewing-gums should be retained, as craving may suddenly occur. If cessation has not been achieved after 6 months, professional advice should be sought.

Counselling and support can improve the chance of success.

Smoking reduction

Niqero Fruit chewing-gum is used between periods of smoking to prolong the smoke-free intervals and to reduce smoking as much as possible. The number of cigarettes should be gradually replaced by Niqero Fruit chewing-gums. If a reduction of at least 50 % in number of cigarettes per day has not been achieved after 6 weeks, professional advice should be sought.

An attempt to quit smoking should be made as soon as the smoker is motivated, however, no later than 4 months after treatment start. After that the number of chewing-gums should be gradually reduced, for example by quitting one chewing-gum every 2-5 days.

Professional help should be consulted if a serious attempt to quit smoking within 4 months has not been possible. Regular use of Niqero Fruit chewing-gum for more than 6 months is generally not recommended.

Some ex-smokers may require a longer treatment period in order to avoid relapse. Any spare chewing-gums should be retained, as craving may suddenly occur.

Counselling and support can improve the chance of success

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Niqero Fruit chewing-gum should not be used by non-smokers.

4.4 Special warnings and precautions for use

Chewing-gum may stick to, and may in rare cases, damage dentures and dental bridges.

Dependent smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal's angina, severe cardiac arrhythmias, uncontrolled hypertension or recent cerebrovascular accident should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Niqero Fruit chewing-gum may be considered but as data on safety in this patient group are limited, initiation should only be under close medical supervision.

Diabetes Mellitus. Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when smoking is stopped and NRT is initiated as reduction in nicotine induced catecholamine release can affect carbohydrate metabolism.

Allergic reactions: Susceptibility to angioedema and 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.
- *Gastrointestinal Disease:* Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers and oral NRT preparations should be used with caution in these conditions.

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, see section 4.9.

Transferred dependence: Transferred dependence can occur but 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 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.

Excipients:

The gum contains maltitol and sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

The gum contains butylated hydroxytoluene which may cause local skin reactions (e.g. contact dermatitis) and local irritation to mucous membranes in the mouth.

4.5 Interaction with other medicinal products and other forms of interaction

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, (see section 4.4, Stopping smoking).

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Nicotine passes to the foetus and affects its breathing movements and circulation. The effect on the circulation is dose-dependent.

Therefore, the pregnant smoker should always be advised to stop smoking completely without the use of nicotine replacement therapy. The risk of continued smoking may pose greater hazard to the foetus compared to the use of nicotine replacement products in a supervised smoking cessation programme. Use of Niqero Fruit by the pregnant highly dependent smoker should only be initiated after advice from a physician.

Breastfeeding

Nicotine passes freely into breast milk in quantities that may affect the child even with therapeutic doses. Niqero Fruit should therefore be avoided during breast-feeding. Should smoking cessation not be achieved, use of Niqero Fruit by breast feeding smokers should only be initiated after advice from a healthcare professional. Women should take the product just after having breastfed.

4.7 Effects on ability to drive and use machines

Niqero Fruit has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Niqero Fruit may cause adverse reactions similar to those associated with nicotine administered by other means. Most undesirable effects reported by patients usually occur during the first 3-4 weeks after treatment start. The undesirable effects of nicotine chewing-gum are mainly due to incorrect chewing technique or due to the pharmacological effects of nicotine, which are dose dependent.

In the below table all undesirable effects are classified according to system organ class and frequency.

Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1\ 000$, $< 1/100$); rare ($\geq 1/10\ 000$, $< 1/1\ 000$); very rare ($< 1/10\ 000$), not known (cannot be estimated from the available data).

Organ system class	Undesirable effects
Nervous system disorders	
Common	Dizziness, headache
Cardiac disorders	
Uncommon	Palpitations
Rare	Atrial fibrillation
Gastrointestinal disorders	
Common	Gastrointestinal discomfort, hiccups, nausea, vomiting.
Skin and subcutaneous tissue disorders	
Uncommon	Erythema, urticaria
General disorders and administration site conditions	
Common	Jaw muscle ache, irritation of the mouth or throat
Rare	Allergic reactions such as angioedema

Some symptoms such as dizziness, headache and sleep disturbances 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.

Chewing gum may stick to, or may in rare cases, damage dentures and dental bridges.

4.9 Overdose

Symptoms of overdose with nicotine may occur in patients with low pre-treatment nicotine intake or if other sources of nicotine are used concomitantly.

Symptoms of overdose are those of acute nicotine poisoning and include nausea, salivation, 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.

Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal.

Management of overdose: Nicotine intake must be stopped immediately and the patient should be treated symptomatically. Activated charcoal reduces the gastrointestinal absorption of nicotine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug used in nicotine dependence.
ATC code: N07BA01

Nicotine, the main alkaloid in tobacco products, is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects.

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use may result in a characteristic withdrawal syndrome that includes four or more of the following symptoms: dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; concentration difficulties; restlessness or impatience; decreased heart rate; increased appetite or weight gain. Smoking craving, which is recognised as a clinically relevant symptom, is also an important part of the abstinence symptoms in connection with smoking cessation.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking.

5.2 Pharmacokinetic properties

Absorption

The amount of released nicotine absorbed from a nicotine chewing gum depends on the amount of nicotine released in the oral cavity and the amount that is swallowed. The main part of nicotine released is absorbed through the buccal mucosa. The systemic bioavailability of swallowed nicotine is lower due to first- passage elimination. The high and rapidly rising nicotine concentrations observed after smoking are rarely produced by treatment with the chewing-gum.

In normal case approximately 1.4 mg of nicotine is released from a 2 mg chewing-gum and approximately 3.4 mg of nicotine from a 4 mg chewing-gum. Maximal blood concentration is achieved after 30 minutes of chewing and is then comparable to the concentration, appearing 20-30 minutes after smoking a cigarette of medium strength.

Distribution

The volume of distribution following IV administration of nicotine is about (2-) 3l/kg. Plasma protein binding of nicotine is less than 5 %. Other diseases or concomitant use of other drugs which influence levels of plasma proteins are not expected to have any significant effect on the kinetics of nicotine.

Metabolism

Nicotine is metabolised mainly in the liver and plasma clearance is in average about 70 l/ hour. Nicotine is also metabolised in the kidneys and lungs. More than 20 metabolites are identified whereof all are believed to be less active than nicotine. The primary metabolite of nicotine is cotinine which has a half-life of 15-20 hours and which gives plasma concentrations approximately 10-fold higher than nicotine.

Elimination

The major metabolites in urine are cotinine (15 % of the dose) and trans-3-hydroxycotinine (45% of the dose). About 10% of the nicotine is excreted unchanged in the urine. Up to 30% of nicotine may be excreted in the urine at increased diuresis and acidification of the urine below pH 5. The half-life of nicotine is about 2 hours.

Special populations

Severely impaired renal function is assumed to have an influence on the total clearance of nicotine. The pharmacokinetics of nicotine is unaffected in cirrhotic patients with mild liver impairment (Child score 5) and decreased in liver cirrhosis patients with moderate liver impairment (Child score 7). Increased nicotine levels have been observed in smoking haemodialysis patients.

A minor reduction of total clearance of nicotine has been demonstrated in healthy, elderly users; however, an adjustment of the dose is not necessary.

No differences in nicotine kinetics have been observed between males and females.

5.3 Preclinical safety data

In vitro genotoxicity testing of nicotine has yielded predominantly negative results. There are some equivocal results when testing at high nicotine concentrations.

In vivo tests of genotoxicity have been negative.

Animal experiments have shown that nicotine exposure results in decreased birth-weight, decreased litter size and decreased survival of offspring.

Results of carcinogenicity assays do not provide any clear evidence of a tumorigenic effect of nicotine.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients***Core:*

Gum base (containing butylated hydroxytoluene (E321))

Calcium carbonate

Sorbitol (E420)

Sodium carbonate anhydrous

Sodium hydrogen carbonate

Saccharin (E954)

Acesulfame potassium (E950)

Levomenthol

Lemon liquid flavour no. 2

Mango liquid flavour

Lemon powder flavour

Talc

Coating:

Maltitol (E965)

Acacia

Titanium dioxide (E171)

Acesulfame potassium (E950)

Levomenthol

Lemon liquid flavour no. 2

Mango liquid flavour

Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container

Blisters of PVC/PVdC/Aluminium in cardboard boxes:

Pack sizes:

2, 10, 12, 20, 24, 30, 36, 40, 48, 50, 60, 70, 72, 80, 84, 90, 96, 100, 108, 110, 120, 150, 192, 200, 204, 210

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Stasisport Pharma
Square Marie Curie 50
1070 Anderlecht
Belgium

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PA1750/001/001

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