1. NAME OF THE MEDICINAL PRODUCT

Nicotinell Gum 2 mg (Fruit); Nicotinell Gum 2 mg (Mint);
Nicotinell Gum 4 mg (Fruit); Nicotinell Gum 4 mg (Mint)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicotinell Gum 2 mg (Fruit) / Nicotinell Gum 2 mg (Mint):
One piece of medicated chewing gum contains 2 mg nicotine .

Nicotinell Gum 4 mg (Fruit) / Nicotinell Gum 4 mg (Mint):
One piece of medicated chewing gum contains 4 mg nicotine .

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medicated Chewing gum
Each piece of coated chewing gum is offwhite in colour and rectangular in shape

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As an aid to smoking cessation and for the relief of nicotine withdrawal symptoms.
In smokers currently unable or not ready to stop smoking abruptly the gum may also be used as part of a program to reduce smoking prior to stopping completely

4.2 Posology and method of administration

Adults and elderly

2 mg strength:
One piece of Nicotinell gum to be chewed when the user feels the urge to smoke. Normally, 8-12 pieces per day can be used, up to a maximum of 25 pieces per day.
The 2 mg chewing gum is recommended in smokers with a low to moderate nicotine dependency.
The 2 mg chewing gum may not be well suited to smokers with a strong or very strong nicotine dependency.

4 mg strength:
One piece of Nicotinell gum to be chewed when the user feels the urge to smoke. Normally, 8-12 pieces per day can be used, up to a maximum of 15 pieces per day.
The 4 mg chewing gum is intended to be used by smokers with a strong or very strong nicotine dependency and those who have previously failed to stop smoking with the aid of nicotine replacement therapy.

The optimal dosage form is selected according to the following table:

Low to moderate dependency	Moderate to strong dependency	Strong to very strong dependency
Less than 20 cigarettes / day	From 20 to 30 cigarettes / day	Over 30 cigarettes / day
Low dose forms are preferable (2 mg gum)	Low (2 mg gum) or high (4 mg gum) dose forms are acceptable depending on patient characteristics and preference.	High dose forms are preferable (4 mg gum)

If an adverse event is noted when high dose forms are initiated, this should be replaced by the lower dosage form.
The characteristics of chewing-gum as a pharmaceutical form are such that individually different nicotine levels can result in the blood. Therefore, dosage frequency should be adjusted according to individual requirements within the stated maximum limit.

Directions for use:

1. One piece of gum should be chewed until the taste becomes strong.
2. The chewing gum should be rested between the gum and cheek.
3. When the taste fades, chewing should commence again.
4. The chewing routine should be repeated for 30 minutes.

The treatment time is individual. Normally, treatment should continue for at least 3 months.
After three months, the user should gradually cut down the number of pieces chewed each day until they have stopped using the product.
Treatment should be discontinued when the dose has been reduced to 1-2 pieces of gum per day.

4.3 Contraindications

Hypersensitivity to nicotine or any components of the gum.
Nicotinell gum should not be used by non-smokers.

4.4 Special warnings and precautions for use

Any risks that may be associated with nicotine replacement therapy are substantially outweighed by the well established dangers of continued smoking.
Precautions: Users should be informed that if they continue to smoke while using the gums they may experience increased adverse effects due to the hazards of smoking, including cardiovascular effects.

Cardiovascular disease
In stable cardiovascular disease Nicotinell gum presents a lesser hazard than continuing to smoke. However dependant smokers currently hospitalised as a result of a recent myocardial infarction, unstable or worsening angina pectoris including Prinzmetal's angina, severe cardiac arrhythmias, uncontrolled hypertension, or recent cerebrovascular accident who are considered to be haemodynamically unstable should be encouraged to stop smoking with nonpharmacological interventions (such as counselling). If this fails, Nicotinell 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 nicotine replacement therapy is initiated as catecholamines released by nicotine can affect carbohydrate metabolism.

Allergic reactions
Angioedema and urticaria have been reported.

Gastro-intestinal disease
Swallowed nicotine may exacerbate symptoms in patients suffering from active oesophagitis, oral or pharyngeal inflammation, gastritis, or peptic ulcers and oral nicotine replacement therapy preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

Renal and or hepatic impairment
Should be used 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.

Danger in small children
Doses of nicotine tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal (please see section 4.9). Products containing nicotine should not be left where they may be misused, handled or ingested by children. Nicotinell gum should be disposed of with care.

Pheochromocytoma and uncontrolled hyperthyroidism
Nicotinell gum should be used with caution in patients with uncontrolled hyperthyroidism or pheochromocytoma as nicotine causes the release of catecholamines.

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 catalysed by CYP 1A2 (and possibly CYP 1A1). When a smoker stops, this may result in slower metabolism and a consequential rise in blood levels of drugs such as theophylline, tacrine, olanzaprine and clozaprine.

Other warnings
People having problems with the joint of the jawbone and denture wearers may experience difficulty in chewing the gum.
In this case, it is recommended that they use a different pharmaceutical form of nicotine replacement therapy.

Special warnings about excipients
Because Nicotinell gum contains sorbitol: Patients with rare hereditary conditions of fructose intolerance should not take this medicine.

Nicotinell 2mg Gum (Fruit) contains sweeteners including Sorbitol (powder) 208.0 mg per gum.
Nicotinell 2mg Gum (Mint) contains sweeteners including Sorbitol (powder) 207.9 mg per gum.

Nicotinell 2 mg Gum contains sodium 11.50 mg per piece of gum.
The gum base contains butylated hydroxyl toluene which may cause local irritation to mucous membranes.

Nicotinell 4mg Gum (Fruit) contains sweeteners including Sorbitol (powder) 192.1 mg per gum.

Nicotinell 4mg Gum (Mint) contains sweeteners including Sorbitol (powder) 192.0 mg per gum.

Nicotinell 4 mg Gum contains sodium 11.52 mg per piece of gum.
The gum base contains butylated hydroxy toluene which may cause local irritation to mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

No information is available on interactions between Nicotinell gum and other drugs. No clinically relevant interactions between nicotine replacement therapy and other drugs has definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

4.6 Fertility, pregnancy and lactation

Pregnancy
Stopping smoking is the single most effective intervention for improving the health of both the pregnant smoker and her baby, and the earlier abstinence is achieved the better. However, if the mother cannot (or is considered unlikely to) quit without pharmacological support, NRT may be used as the risk to the foetus is lower than that expected with smoking tobacco. Stopping completely is by far the best option but Nicotinell gums may be used in pregnancy as a safer alternative to smoking. Because of the potential for nicotinefree periods, intermittent dose forms are preferable, but patches may be necessary if there is significant nausea and/or vomiting. If patches are used they should, if possible, be removed at night when the foetus would not normally be exposed to nicotine.

Lactation
The relatively small amounts of nicotine found in breast milk during NRT use are less hazardous to the infant than second-hand smoke. Intermittent dose forms would minimize the amount of nicotine in breast milk and permit feeding when levels were at their lowest.

4.7 Effects on ability drive and use machines

There is no evidence of any risks associated with driving or operating machinery when Nicotinell gum is used following the recommended dose.

4.8 Undesirable effects

Certain symptoms such as dizziness, headache and sleep disturbances may be related to withdrawal symptoms in connection with smoking cessation and may be due to insufficient administration of nicotine. Cold sores may develop in connection with smoking cessation, but any relation with the nicotine treatment is unclear.
Nicotinell gums can cause adverse reactions similar to those associated with nicotine administered by other means (including smoking). These can be attributed to the pharmacological effects of nicotine, which are dose dependant. Non dose-dependent adverse reactions are as follows:

Jaw muscle ache, erythema, urticaria, hypersensitivity, angioneurotic oedema and anaphylactic reactions.
At recommended doses Nicotinell gum has not been found to cause any serious adverse effects. Excessive consumption of Nicotinell gum by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Increased frequency of aphthous ulcer may occur after abstinence from smoking.

Most of the side effects which are reported by patients occur generally during the first 3-4 weeks after initiation of therapy.

Nicotine from gums may sometimes cause a slight irritation of the throat and increase salivation at the start of the treatment.

Excessive swallowing of nicotine which is released in the saliva may, at first, cause hiccups. Those who are prone to indigestion may suffer initially from minor degrees of dyspepsia or heartburn; slower chewing will usually overcome this problem.

The gum may stick to and in rare cases damage dentures and dental appliances.

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) or *very rare* (<1/10,000),

Nervous system disorders:	Common: Headache, dizziness
Gastrointestinal disorders:	Common: Salivary hypersecretion, stomatitis, oral pain, pharyngolaryngeal pain, hiccups, nausea, vomiting, dyspepsia and flatulence.
Musculoskeletal, connective and bone disorders:	Common: Jaw muscle ache
Cardiac disorders:	Uncommon: palpitations Rare: Atrial arrhythmia
Skin and subcutaneous tissue disorders:	Uncommon: Erythema, urticaria.
Immune system disorders:	Rare: Hypersensitivity, angioneurotic oedema and anaphylactic reactions.

The patient may still experience nicotine dependence after smoking cessation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form.
https://sideeffects.health.gov.il/

4.9 Overdose

In overdose, symptoms corresponding to heavy smoking may be seen, however the toxicity of nicotine cannot be directly compared with that of smoking, because tobacco smoke contains additional toxic substances (eg. Carbon monoxide and tar).

Overdose with Nicotinell gum may only occur if many pieces are chewed simultaneously. Nicotine toxicity after ingestion will most likely be minimized as a result of early nausea and vomiting that occur following excessive nicotine exposure. Risk of poisoning by swallowing the gum is small. Since the release of nicotine from the gum is slow, very little nicotine is absorbed from the stomach and intestine, and if any is, it will be inactivated in the liver.

Chronic smokers can tolerate doses of nicotine that, in a non-smoker, would be more toxic, because of the development of tolerance.

The acute lethal dose of nicotine in a non-tolerant man has been estimated to be 0.5 - 0.75 mg per kg bodyweight, corresponding in an adult to 40-60mg.

Even small quantities of nicotine are dangerous in children, and may result in severe symptoms of poisoning which may prove fatal. If poisoning is suspected in a child, a doctor must be consulted immediately.

Symptoms

Symptoms of acute nicotine poisoning include nausea, vomiting, salivation, throat burn, abdominal pain, diarrhoea, perspiration, headache, dizziness, hearing and visual disturbances and marked weakness. In extreme cases, these symptoms may be followed by hypotension, tachycardia, cardiac arrhythmia, dyspnoea, prostration, circulatory collapse, coma and terminal convulsions.

Treatment of overdose

Treatment of overdose should be immediate as symptoms may develop rapidly (particularly in children). All nicotine intake should stop immediately. Emesis is usually spontaneous. Artificial respiration with oxygen should be instituted if necessary. Consider activated charcoal, provided airway can be protected in those presenting within 1 hour of ingestion of more than 0.2mg/kg of nicotine. Monitor vital signs and treat symptomatically.

Toxicity

Nicotine is highly toxic by ingestion, inhalation and skin contact. The fatal dose has been estimated to be as little as 40 mg of nicotine in an adult and just a few milligrams of nicotine have caused severe symptoms. It can be very rapidly absorbed with CNS, neuromuscular and autonomic features. The half-life of nicotine ranges from 24 minutes to 2 hours but symptoms may persist for up to 72 hours in severe cases of poisoning.

• All patients who have taken a deliberate overdose should be referred for assessment.
• Children and adults who have ingested 0.2 mg/kg or more nicotine, or those who are symptomatic, should be referred for medical assessment.
•Children or adults who have accidentally ingested less than 0.2 mg/kg nicotine and who have no new symptoms since the time of ingestion do not need to be referred for medical assessment. Patients should be advised to seek medical attention if symptoms develop.
• All symptomatic children and adults following accidental transdermal patch application should be referred for medical assessment.

Features

• Early features of ingestion include burning in the mouth and throat, nausea, vomiting, confusion, dizziness, weakness, hypersalivation, sweating and increased bronchial secretions. There may be sympathetic features including tachycardia, tachypnoea, hypertension and agitation followed by bradycardia, systemic hypotension and respiratory depression.
• More severe poisoning leads to arrhythmias including atrial fibrillation, coma, convulsions and respiratory and cardiac arrest. Recovery is likely if survival exceeds 2-3 hours.
• Skin contact may lead to irritation followed by variable absorption depending on the length of exposure and concentration. Systemic features may follow.
• Eye contact with liquid may lead to irritation and lacrimation.

Management

General measures

• Maintain a clear airway/ensure adequate ventilation. Monitor pulse and BP. Perform 12 lead ECG and measure QRS duration and QT interval and repeat especially if the patient is symptomatic or has taken slow release preparations.
• Good neurological outcome after cardiac arrest (due to nicotine poisoning) may occur after prolonged resuscitation. Cardiac arrest in hospital or witnessed out of hospital, with bystander CPR, should be continued for at least 1 hour (discuss with local poisons centre).

• The benefits of gastric decontamination are uncertain. Consider activated charcoal (50g adults: 1g/kg children) provided airway can be protected in those presenting within 1 hour of ingestion of more than 0.2mg/kg of nicotine.
• Asymptomatic patients who have ingested more than 0.2mg/kg of nicotine should be observed for at least 4 hours. However, if other cardiac/cardiotoxic agents have been taken monitor for the longest period recommended for these.
• In symptomatic patients check U&Es, creatinine kinase and arterial blood gases.
• Contact the local poisons information centre for specific advice.

Bradycardia
• If symptomatic give IV atropine
• If associated with hypotension, dobutamine or isoprenaline may be considered
• Temporary pacemaker or external pacing may be required

Agitation
• Agitated adults can be sedated (IV diazepam: if ineffective oral or parenteral haloperidol)
• Agitated children are better managed without sedation. Exclude other causes (eg hypoxia: infection: hypoglycaemia: raised ICP). Seek expert paediatric advice.

Hypertension
• Adults: in agitated patient hypertension may settle with sedation. If hypertension persists give IV nitrates until blood pressure controlled. Calcium antagonists are an alternative as second line therapy. Phentolamine or sodium nitroprusside are options if there is hypertension without evidence of cardiac ischaemia (but may cause a rapid fall in blood pressure) or alternatively IV labetalol.
• Children (under 5 years): Seek expert paediatric advice.

Convulsions
• Give oxygen, check blood sugar, U&Es and arterial blood gases. Correct acidbase balance and metabolic disturbances as necessary.
• A single brief convulsion does not require treatment. Otherwise control with IV diazepam or lorazepam. If unresponsive seek advice from NPIS/NPIC or appropriate specialist.

Other points to note
• A high percentage of urine screens will be positive for nicotine in both smokers and non-smokers.
• Quantitative blood concentrations are not readily available. Appropriate history and recognition of clinical finding are important.
• Other treatments/measures indicated by patient's clinical condition.
• On discharge patients should be advised to seek medical attention if symptoms develop.

Skin exposure
• Remove soiled clothes, nicotine patches or contaminating fluid.
• Wash skin with soap and water.
• Treat symptoms of systemic toxicity as above.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N07B A01

Pharmacotherapeutic group: Drugs used in nicotine dependence

Nicotine, the primary alkaloid in tobacco products and a naturally occurring autonomous substance, is a nicotine receptor agonist in the peripheral and central nervous systems and has pronounced CNS and cardiovascular effects. On consumption of tobacco products, nicotine has proven to be addictive, resulting in craving and other withdrawal symptoms when administration is stopped. This craving and these withdrawal symptoms include a strong urge to smoke, dysphoria, insomnia, irritability, frustration or anger, anxiety, concentration difficulties agitation and increased appetite or weight gain. The gum replaces part of the nicotine that would have been administrated via tobacco and reduces the intensity of the withdrawal symptoms and smoking urge.

5.2 Pharmacokinetic properties

When the gum is chewed, nicotine is steadily released into the mouth and is rapidly absorbed through the buccal mucosa. A proportion, by the swallowing of nicotine containing saliva, reaches the stomach and intestine where it is inactivated.

The nicotine peak plasma mean concentration after a single dose of the 2 mg coated gum is approximately 6.4 nanograms per ml (after 45 minutes) (average plasma concentration of nicotine when smoking a cigarette is 15-30 nanograms per ml).

The nicotine peak plasma mean concentration after a single dose of the 4 mg coated gum is approximately 9.3 nanograms per ml (after approximately 60 minutes) (average plasma concentration of nicotine when smoking a cigarette is 15-30 nanograms per ml).

Nicotine is eliminated mainly via hepatic metabolism; small amounts of nicotine are eliminated in unchanged form via the kidneys. The plasma halflife is approximately three hours. Nicotine crosses the blood-brain barrier, the placenta and is detectable in breast milk.

5.3 Preclinical safety data

No definite conclusion can be drawn on the genotoxic activity of nicotine *in vitro*. Nicotine was negative in *in-vivo* tests. Animal experiments have shown that nicotine induces post-implantation loss and reduces the growth of foetuses. The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nicotinell Gum 2 mg (Fruit) ; Nicotinell Gum 4 mg (Fruit):

Center: Gum Base*, Calcium Carbonate, Sorbitol (powder), Sodium Carbonate Anhydrous, Sodium Hydrogen Carbonate, Amberlite, Glycerol, Purified Water, L-Menthol, Tutti, Saccharin, Sodium Saccharin, Acesulfame K, Carnauba Wax, Talcum Powder.
Coat: Xylitol, Mannitol, Gelatine, Titanium dioxide, L-Menthol, Tutti, Carnauba Wax, Talc.

Nicotinell Gum 2 mg (Mint) ; Nicotinell Gum 4 mg (Mint):

Center: Gum Base*, Calcium Carbonate, Sorbitol (powder), Sodium Carbonate Anhydrous, Sodium Hydrogen Carbonate, Amberlite, Glycerol, Purified Water, L-Menthol, Peppermint Oil**, Eucalyptus Oil, Saccharin, Sodium Saccharin, Acesulfame K.
Coat: Xylitol, Mannitol, Gelatine, Titanium dioxide, L-Menthol, Carnauba Wax, Talc.

*Containing butylated hydroxy toluene

**Mint falvouring system composed of L-Menthol (Ph-Eur), Peppirmint oil (Ph-Eur) and Mint Oil (Ph-Eur)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25ºC

6.5 Nature and contents of container

The chewing gum is packed in PVC/PVdC/aluminium blisters. The blisters are packed in boxes containing 12, 24, 48, 96 and 204 pieces of gum.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER

Dr. Reddy's Laboratories SA, Basel, Switzerland

8. MARKETING AUTHORISATION HOLDER

Professional Pharma Ltd., 16 Shenkar Arie st., Herzliya 4672516, Israel

9. MARKETING AUTHORISATION NUMBER(S)

Nicotinell Gum 2 mg (Fruit):
115-78-29638-21; 115-78-29638-22

Nicotinell Gum 2 mg (Mint):
115-78-29638-23; 115-78-29638-24

Nicotinell Gum 4 mg (Fruit):
115-79-29639-21; 115-79-29639-22

Nicotinell Gum 4 mg (Mint):
115-79-29639-23; 115-79-29639-24

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