

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0329/010/002

Case No: 2060488

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pierre Fabre Medicament

45 Place Abel Gance, 92100 Boulogne, Cedex, France

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Nicopass Fresh Mint 1.5mg lozenge

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **05/07/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicopass Fresh Mint 1.5mg lozenge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 1.50 mg nicotine corresponding to 8.33 mg nicotine resinate.

Excipients: aspartame (E 951) (1.00 mg), soya oil, isomalt (E 953) (2.32 g)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lozenge

Beige, opaque, square lozenge.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Relief of nicotine withdrawal symptoms, in nicotine dependency as an aid to smoking cessation.

4.2 Posology and method of administration

Adults and elderly

Lozenges containing 1.5 mg of nicotine are recommended for smokers with low or moderate nicotine dependency e.g. smokers who smoke 20 cigarettes or less a day (score up to 6 in the Fagerström test).

Posology

The treatment of nicotine dependence usually proceeds in 2 phases.

1st phase:

Suck slowly a lozenge whenever there is an urge to smoke.

The number of 1.5 mg lozenges is generally 8 to 12 daily and must not on any account exceed 20 lozenges daily.

The duration of this phase is about 3 months, but may vary according to the individual response.

2nd phase:

When the urge to smoke is completely suppressed, gradually reduce the number of lozenges daily.

Treatment should be stopped when the dose is reduced to 1 to 2 lozenges daily.

It is recommended not to use lozenges for more than 6 months.

Children and adolescents (< 18 years)

Nicopass should not be used by people under 18 years of age without recommendation from a physician. There is no experience in treating adolescents under the age of 18 years with Nicopass.

Method of administration**OROMUCOSAL USE.**

The lozenge must be placed in the mouth where it will dissolve gradually. It must be regularly moved from one side of the mouth to the other and slowly sucked until it is completely dissolved. The matrix structure of the sucking lozenges has been designed to ensure they dissolve in about 30 minutes, allowing a gradual release of the nicotine and hence slow absorption in the oral mucosa.

They must therefore not be chewed or swallowed.

Refrain from drinking or eating when the lozenge is in the mouth. Acidic beverages (coffee or soda) should be avoided for 15 minutes prior to Nicopass.

4.3 Contraindications

- Non-smoker or occasional smoker.
- Hypersensitivity to nicotine or any of the excipients.
- Hypersensitivity to peanut or soya because of the content in soya oil.

4.4 Special warnings and precautions for use

The use of this medicinal product must be associated with total cessation of tobacco consumption.

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, Nicopass may be considered but as data on safety in this patient group are limited, initiation should only be under close medical supervision.

In the case the patient has any of the following medical conditions consultation of the physician is recommended:

- stable cardiovascular diseases,
- diabetes mellitus, hyperthyroidism or pheochromocytoma,
- severe hepatic and/or renal impairment.

Swallowed nicotine may exacerbate symptoms in subjects suffering from active oesophagitis, oral or pharyngeal inflammation, gastritis or peptic ulcer.

Nicopass contains aspartame, a source of phenylalanine that may be harmful for people with phenylketonuria.

Because Nicopass contains isomalt, patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Nicotine is a toxic substance.

Patient should be warned to keep lozenges out of the reach of children.

In fact, the therapeutic dose intended for adults might cause severe and even fatal intoxication in children (see section

4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Aromatic hydrocarbons in tobacco smoke induce cytochrome P450 (CYP) 1A2 activity. At cessation of smoking CYP1A2 activity decreases which can lead to increased blood concentrations of medicinal products metabolised via CYP1A2, such as caffeine, theophylline, flecainide, clozapine, olanzapine, ropinirole and pentazocine. The dose may need to be adjusted, and for medicinal products with a narrow therapeutic margin, such as theophylline, smoking cessation should be accompanied by close clinical and even laboratory monitoring and the patient should be informed about the risks of overdose.

Because of its specific cardiovascular, neurological and endocrine pharmacological properties, nicotine, like tobacco, can:

- cause an increase in cortisol and catecholamine concentrations,
- require a dosage adjustment of nifedipine, beta-blockers and insulin,
- reduce the effects of diuretics,
- delay the rate of healing of gastric ulcers by H2 antihistamines,
- increase the incidence of undesirable effects of oestrogen-progestagen combinations.

4.6 Pregnancy and lactation

Pregnancy

In pregnant women complete cessation of tobacco smoking should always be recommended without nicotine replacement therapy.

Nevertheless, in case of failure in highly dependent pregnant smokers, tobacco withdrawal via nicotine replacement therapy may be recommended. Indeed foetal risk is probably lower than that expected with tobacco smoking, due to

- lower maximal plasma nicotine concentration than with inhaled nicotine,
- no additional exposure to polycyclic hydrocarbons and carbon monoxide,
- improved chances of quitting smoking by the third trimester.

Smoking continued during the third trimester may lead to intra-uterine growth retardation or even premature birth or stillbirth, depending on the daily amount of tobacco.

Tobacco withdrawal with or without nicotine replacement therapy should not be undertaken alone but as part of a medically supervised smoking cessation program.

In the third trimester nicotine has haemodynamic effects (e.g. changes in foetal heart rate) which could affect the foetus close to delivery. Therefore, after the sixth month of pregnancy, the lozenge should only be used under medical supervision in pregnant smokers who have failed to stop smoking by the third trimester.

Lactation

Nicotine is excreted in breast milk in quantities that may affect the child even in therapeutic doses. The lozenge, like smoking itself, should therefore be avoided during breast feeding. Should smoking withdrawal not be achieved, use of the lozenge by breast feeding smokers should only be initiated after advice from a physician. Where nicotine

replacement therapy is used while breast feeding, the lozenge should be taken just after breast feeding and not during two hours before breast feeding.

4.7 Effects on ability to drive and use machines

Smoking cessation can cause behavioural changes. There is no evidence of any risks associated with driving or operating machinery when the lozenge is used following the recommended dose.

4.8 Undesirable effects

Nicopass in the recommended dose has not been found to cause any serious undesirable effects. Most of the undesirable effects which are reported by patients occur generally during the first 3-4 weeks after initiation of therapy.

At the start of treatment, nicotine lozenge may sometimes cause a slight irritation of the throat and may also increase salivation. Excessive swallowing of dissolved nicotine may, at first, cause hiccupping.

Sensitive patients may present at first slight signs of dyspepsia or heartburn.

Nicotine lozenges may cause undesirable effects similar to nicotine administered by other modes.

SYSTEM ORGAN CLASS (MedDRA classification)	COMMON (≥1/100, <1/10)	UNCOMMON (≥1/1,000, <1/100)	RARE (≥1/10,000, <1/1,000)
Immune system disorders	-	-	Allergic reactions such as angioneurotic oedema
Nervous system disorders	Dizziness Headache	-	-
Cardiac disorders	-	Palpitations	Atrial fibrillation reversible
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain Hiccup	-	-
Gastrointestinal disorders	Sore throat Mouth irritation (burning and tickle sensation) Dry mouth Nausea Vomiting Abdominal discomfort	-	-
Skin and subcutaneous tissue disorders	-	Erythema Urticaria	-

Excessive consumption of nicotine lozenges by patients who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches (as may be experienced by such a patient if tobacco is inhaled).

Some symptoms, such as dizziness, headache and sleep disturbances may be related to withdrawal symptoms. Increased frequency of aphthous ulcer may occur after abstinence from smoking.

4.9 Overdose

In overdose, symptoms corresponding to heavy smoking may be seen.

The acute lethal oral dose of nicotine is about 0.5 - 0.75 mg per kg body weight, corresponding in an adult to 40 - 60 mg. 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.

Overdose with Nicopass may only occur if many pieces are sucked simultaneously. Nicotine toxicity after ingestion will most likely be minimized as a result of early nausea and vomiting that occur following excessive nicotine exposure.

General symptoms of nicotine poisoning include: weakness, perspiration, salivation, throat burn, nausea, vomiting, diarrhoea, abdominal pain, hearing and visual disturbances, headache, tachycardia and cardiac arrhythmia, dyspnoea, prostration, circulatory collapse, coma and terminal convulsions.

Treatment of overdose:

Following overdose, symptoms may be rapid particularly in children. Emesis is usually spontaneous. Administration of oral activated charcoal and gastric lavage should be considered as soon as possible and within 1 hour of ingestion. It is advisable to monitor vital signs and treat symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: DRUGS USED IN NICOTINE DEPENDENCE

ATC code: N07BA01.

Abrupt cessation of smoking following a prolonged period of daily use results in a withdrawal syndrome that includes four or more of the following symptoms: dysphoria or depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness or impatience, decreased heart rate, increased appetite or weight gain. Nicotine craving is considered a separate clinical symptom of the withdrawal syndrome.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking or reduce their consumption of tobacco by decreasing the withdrawal symptoms.

The adverse reactions of continuing tobacco intoxication in coronary patients and/or patients with a previous history of stroke have been clearly demonstrated. Studies conducted in these patients have shown the absence of undesirable effects of nicotine substitutes.

5.2 Pharmacokinetic properties

Complete dissolution of the lozenges in the oral cavity is generally achieved within 30 minutes.

The nicotine in this medicinal product presented in the form of lozenges is combined with an ion exchange resin.

Nicotine is absorbed in the oral mucosa.

A maximum concentration of about 4.20 ng/ml is reached within about 50 minutes after a single dose.

Distribution

The volume of distribution after intravenous administration of nicotine is 2 - 3 l/kg and the half-life is approximately 2 hours.

Plasma protein binding is less than 5%. Therefore, changes in nicotine plasma protein binding as a result of medicinal product interactions or alterations of plasma proteins do not necessarily affect the kinetic parameters of nicotine.

Metabolism

Metabolism is predominantly hepatic.

More than 20 metabolites of nicotine have been identified and all are considered less active than nicotine. The principal plasma metabolite of nicotine, cotinine, has a half-life of 15 to 20 hours and its concentration attains levels 10 times greater than those of nicotine.

Nicotine is also metabolised in the kidneys and lungs.

Elimination

The mean plasma clearance is about 70 litres hourly.

The principal metabolites excreted in the urine are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). About 10% of nicotine is excreted in the urine in the unchanged form. This level may increase to 30% in the case of marked glomerular filtration or acidification of the urine (pH < 5).

5.3 Preclinical safety data

Nicotine was positive in some in vitro genotoxicity tests but there are also negative results with the same test systems. Nicotine was negative in standard 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.

The results of a local tolerance study on hamster cheek pouch showed a good tolerance of Nicopass.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Isomalt
 Hypromellose
 Aspartame (E951)
 Acesulfame potassium
 Peppermint flavour IFF 13 571-016 (natural peppermint flavour, pulegone)
 Long-lasting fresh mint flavour IFF 13-627-517 (natural peppermint flavour, carnauba wax, hypromellose, mono and diglycerides of fatty acids, ethyl cellulose, partially hydrogenated soya oil)
 Permaseal masking flavour GIVAUDAN 1 1031-31 (natural flavouring substances, maltodextrin, acacia, propylene glycol)
 Sodium hydrogen carbonate
 Anhydrous sodium carbonate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

12 lozenges in blisters (PVC/PE/PVDC/aluminium).

Pack sizes: Boxes with 12, 24, 36, 48, 60, 72, 84, 96 or 204 lozenges.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pierre Fabre Medicament
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92100 Boulogne
Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA 329/10/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 October 2005

Date of last renewal: 5 July 2009

10 DATE OF REVISION OF THE TEXT

March 2010