IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0329/010/003
Case No: 2067398

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 Liquorice Mint 2.5mg 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 **23/04/2010** until **22/04/2015**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicopass Liquorice Mint 2.5mg Lozenge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 2.50 mg nicotine corresponding to 13.88 mg nicotine resinate.

Excipient : aspartame (1.00 mg), isomalt (2.30 g).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lozenge.

Brown, opaque, square lozenge.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Adults and elderly

Lozenges containing 2.5 mg of nicotine are suitable for smokers with strong or very strong nicotine dependency who smoke more than 20 cigarettes a day (score of 7 to 10 in the Fagerström test).

Children and adolescents: (< 18 years)

Nicopass Liquorice Mint 2.5mg Lozenge 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 Liquorice Mint 2.5mg Lozenge.

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 lozenge 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 Liquorice Mint 2.5mg Lozenge.

Posology

The treatment of nicotine dependence usually proceeds in 2 phases.

First phase:

Initially, a lozenge can be taken whenever there is an urge to smoke.

The number of 2.5 mg lozenges is generally 8 to 12 daily and should not exceed 15 lozenges daily.

The duration of this phase is about 3 months, but may vary between individuals.

Second phase:

When the urge to smoke has stopped, a gradual weaning from the lozenges should be initiated.

Treatment should be discontinued when the dose is reduced to 1 to 2 lozenges per day.

Treatment with the lozenges for more than 6 months is generally not recommended. If there are no significant results after 9 months of treatment with the lozenges, another treatment strategy should be considered.

4.3 Contraindications

• Non-smoker or occasional smoker.
• Hypersensitivity to nicotine or to any of the excipients

4.4 Special warnings and precautions for use

Special warnings

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 hypertensions or recent cerebrovascular accident should be encouraged to stop smoking with non-pharmacological interventions. 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 (hypertension, stable angina pectoris, cerebrovascular disease, occlusive

peripheral arterial disease, heart failure),

- 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.

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).

Special warnings about excipients

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

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

This medicine contains low dose of dry extract of deglycyrrhizinated liquorice root as a flavour. Therefore the possible mineralocorticoid effects (pseudoaldosteronism) due to liquorice have to be taken into consideration in liquorice susceptible patients with cardiovascular diseases and hypertension.

For these populations where use of nicotine replacement therapy is recommended, the use of other flavoured nicotine medicated lozenge may be considered.

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, tacrine and clozapine, 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.

Increased subcutaneous absorption of insulin which occurs upon smoking cessation may necessitate a reduction in insulin dose.

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.

There is no adequate data from the use of preparations containing glycyrrhizin in pregnant and lactating women.

Nicopass liquorice mint lozenge should therefore not be used during pregnancy and lactation. Where use of nicotine replacement therapy is recommended the use of other flavoured nicotine medicated lozenge may be considered.

4.7 Effects on ability to drive and use machines

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

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	-	-	Hypersensitivity reactions such as angioneurotic oedema and anaphylactic reaction

Nervous system disorders	Dizziness Headache	-	-
Cardiac disorders	-	Palpitations	Atrial fibrilation 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 Oesophagitis Stomatitis Flatulence	-	-
Skin and subcutaneous tissue disorders	-	Erythema Urticaria	-

As with other nicotine replacement products, gastritis may occur. 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:

The doses of nicotine tolerated by adults smokers during treatment can cause acute intoxication which may be fatal in young 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.

The administration of nicotine must be discontinued immediately. Assisted ventilation and oxygen therapy should be administered where necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

DRUGS USED IN NICOTINE DEPENDENCE

ATC code: N07BA01.

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.

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.

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.

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).

Renal impairment

Progressive severity of renal impairment is associated with decreased total clearance of nicotine. Nicotine clearance was decreased by on average 50% in subjects with severe renal impairment. Raised nicotine levels have been seen in smoking patients undergoing hemodialysis.

Hepatic impairment

The clearance of nicotine is unaffected in cirrhotic patients with mild liver impairment (Child-Pugh score 5) and decreased by 40-50% in cirrhotic patients with moderate liver impairment (Child-Pugh score 7). There is no information available in subjects with a Child-Pugh score > 7.

Elderly

A small reduction in total nicotine clearance has been observed in healthy, elderly users. An adjustment of the dose is however not necessary.

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 (E953)

Hypromellose

Aspartame (E951)

Acesulfame potassium

Peppermint flavour

Permaseal masking flavour (natural flavouring substances, maltodextrin, acacia, propylene glycol)

Dry extract of deglycyrrhizinated liquorice root

Anhydrous sodium carbonate

Sodium hydrogen 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).

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
France

8 MARKETING AUTHORISATION NUMBER

PA 329/10/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd April 2010

10 DATE OF REVISION OF THE TEXT