เอกสารกำกับยาสำหรับแพทย์

1. NAME OF THE MEDICINAL PRODUCT

NICORETTE INVISIPATCH 10 MG
NICORETTE INVISIPATCH 15 MG
NICORETTE INVISIPATCH 25 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 Nicorette Invisipatch 10 mg of 9 cm^2 adsorption area contains:
15.8 mg nicotine (1.75 mg/cm^2). Average release of active substance: 10 mg/16 hours.
1 Nicorette Invisipatch 15 mg of 13.5 cm^2 adsorption area contains:
23.6 mg nicotine (1.75 mg/cm^2). Average release of active substance: 15 mg/16 hours.
1 Nicorette Invisipatch 25 mg of 22.5 cm^2 adsorption area contains:
39.4 mg nicotine (1.75 mg/cm^2). Average release of active substance: 25 mg/16 hours.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch, matrix patch; 16-hour patch

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For treatment of tobacco dependence by alleviating nicotine craving and withdrawal symptoms and thus assisting smoking cessation in smokers who are motivated to quit or to alleviate smoking reduction in smokers who are unable or unwilling to quit smoking.

Nicorette Invisipatch should preferably be used in conjunction with a smoking cessation program.

4.2 Posology and Method of Administration

Nicorette Invisipatch can be used as a single treatment or in combination with Nicorette 2 mg chewing gum/lozenge/sublingual tablet or Nicorette Inhalator 10 mg or Nicorette oromucosal spray 1 mg/spray.

Children and Adolescents

Do not administer to persons under 18 years of age without recommendation from a health care professional. There is insufficient clinical data from controlled trials to recommend routine use in adolescents under the age of 18.

Adults and the elderly

Treatment with patches for single use
Nicorette Invisipatch can be used both when you stop smoking abruptly, and to prolong smoke-free intervals with intention to reduce smoking as much as possible before an attempt to stop smoking is made.

Persons with **high** nicotine dependence (more than 20 cigarettes per day) are recommended to start with one 25 mg/16 hour transdermal patch daily. The period of treatment is individual.
Normally treatment should continue for 2 months. The dose is then reduced gradually by using 15 mg/16 hour transdermal patches for 2 weeks followed by 10 mg/16 hour patches for an additional 2 weeks.

Persons with **low** nicotine dependence (maximum 20 cigarettes per day) are recommended to start with one 15 mg/16 hour transdermal patch daily. The period of treatment is individual. Normally treatment should continue for 2 months. The dose is then reduced gradually by using 10 mg/16 hour transdermal patches for the following 4 weeks.

Dosage given in tabular format:

Dosage at high nicotine dependence (more than 20 cigarettes/day)		**Dosage at low nicotine dependence (maximum 20 cigarettes/day)**	
Patch	*Duration*	*Patch*	*Duration*
25 mg/16 hours	Week 1-8		
15 mg/16 hours	Week 9-10	15 mg/16 hours	Week 1-8
10 mg/16 hours	Week 11-12	10 mg/16 hours	Week 9-12

Treatment for longer than 6 months is not recommended. Certain former smokers may however need treatment for longer in order not to return to smoking.

Nicorette Invisipatch is applied in the morning and taken off when going to bed.

The patch is applied on a clean, dry, hairless and uninjured area of skin on the trunk, arms or hips. To reduce the risk of local irritation the Nicorette Invisipatch should be applied alternately at different sites.

The hands should be washed carefully after applying the transdermal patch to avoid irritation of the eyes with nicotine from the fingers.

Administration of nicotine should be stopped temporarily if any symptoms of nicotine excess occur. Nicotine intake should be decreased by either lowering dosing frequency or strength if nicotine excess symptoms persist.

Treatment with Nicorette Invisipatch in combination with either Nicorette chewing gum, lozenge, sublingual tablet, inhaler or oromucosal spray.
Highly dependent smokers, those who experience cravings despite use of nicotine medicine or those who have failed with single treatment with nicotine medicine, can use Nicorette Invisipatch in combination with another nicotine medicine for fast relief of cravings.

Initial combination treatment
Nicorette Invisipatch 25 mg/16 h patch should be applied to in the morning and removed at bedtime. Nicorette 2 mg chewing gum, lozenge or sublingual tablet can be used as required for fast relief of cravings (usually 5-6 chewing gums/tablets per day). Alternatively, Nicorette Inhalator 10 mg (usually 4-5 cartridges per day) or Nicorette oromucosal spray 1 mg/spray (usually 13 sprays per day) can be used when cravings occur.

The dosing schedule for use of the oral pharmaceutical form in combination with the patch is flexible and the users are dosing based on their requirements.

The maximum recommended daily dose varies between dosage forms (2 mg chewing gums: 24 pieces, 2 mg lozenge: 15 pieces, sublingual tablet: 24 pieces, inhaler: 12 nicotine plugs, oromucosal spray: 32 sprays).

Smokers should stop completely during the course of the combination treatment. Normally, the treatment continues for 8 weeks.

Weaning from nicotine medicine:
After the initial 8 weeks, gradual weaning from nicotine medicine is started by either

- using a patch with a lower strength, i.e. 15 mg/16 hour during 2 weeks followed by 10 mg/16 hours for additional 2 weeks in combination with the initial dose of Nicorette chewing gum/lozenge/sublingual tablet/inhaler or oromucosal spray. Thereafter gradually reduce the number of chewing gums/lozenges/sublingual tablets/cartridges or sprays, up to 12 months.

Or

- stop using the patch and gradually reduce the number of chewing gums/lozenges/sublingual tablets, cartridges or sprays, up to 12 months.

Recommended dosage:

Initial treatment			
Time period	**Patch**	**Flexible dosage form (one of the following products can be used)**	**Dose per day in combination with patch**
Week 1-8	1 patch 25mg/ 16 hours per	2 mg chewing gum,	As needed. Usual dose is 5-6 chewing gums (max 24)
		2 mg lozenge	As needed. Usual dose is 5-6 lozenges (max 15)
		2 mg sublingual tablet	As needed. Usual dose is 5-6 sublingual tablets (max 24)
		inhaler	As needed. Usual dose is 4-5 cartridges (max 12)
		oromucosal spray	As needed. Usual dose is 13 sprays per day (max 32 sprays/day)

Weaning from nicotine medicine - alternative 1		
Time period	**Patch**	**Flexible dosage form**
Week 9-10	1 patch 15 mg/16 hours per day	Continue to use chewing gums/lozenges/ sublingual tablets/inhaler/oromucosal spray as needed
Week 11-12	1 patch 10 mg/16 hours per day	Continue to use chewing gums/lozenges/ sublingual tablets/inhaler/oromucosal spray as needed
Up to 12 months	---	Reduce the number of chewing gums/ lozenges/sublingual tablets/cartridges/sprays gradually
Weaning from nicotine medicine – alternative 2		
Up to 12 months	---	Continue to reduce the number of chewing gums/lozenges/sublingual tablets/cartridges/ sprays gradually

4.3. Contraindications

• Hypersensitivity to nicotine or to any of the ingredients listed in section 6.1.
• Children under the age of 12 years.
• Non-smokers.

4.4. Special Warnings and Special Precautions for Use

The benefits of quitting smoking outweigh any risks associated with correctly administered nicotine replacement therapy (NRT).

A risk-benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

- *Cardiovascular disease. Dependent smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal's angina, severe cardiac arrhythmias, recent cerebrovascular accident, and/or who suffer with uncontrolled hypertension should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Nicorette Invisipatch 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 reductions in nicotine-induced catecholamine release can affect carbohydrate metabolism.*
- *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: Nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers and NRT preparations should be used with caution in these conditions.*
- *Epilepsy and seizures: Caution should be exercised in patients with a history of epilepsy or seizures during introduction of nicotine replacement therapy. Tobacco smoke contains substances – including nicotine – which act on brain receptors, and the changes in intake of these when switching from smoked tobacco to nicotine replacement therapy during quitting may affect seizure threshold.*

Danger in children: Doses of nicotine tolerated by smokers can produce severe toxicity in children that may be fatal. Products containing nicotine should not be left where they may be handled or ingested by children.

Transferred dependence: Transferred dependence can occur but is unusual 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 metabolised by CYP1A2. 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.

If symptoms persist or get worse, or if new symptoms occur, stop use and consult a physician.

Nicorette Invisipatch *should be removed prior to undergoing any Magnetic Resonance Imaging (MRI) procedures to prevent the risk of burns.*

4.5. Interactions 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 increased pain response (angina-pectoris type chest pain) provoked by adenosine administration. (see Section 4.4)

4.6. Pregnancy and Lactation

Women of childbearing potential / Contraception in males and females.

In contrast to the well-known adverse effects of tobacco smoking on human conception and pregnancy, the effects of therapeutic nicotine treatment are unknown. Thus, whilst to date no specific advice regarding the need for female contraception has been found to be necessary, the most prudent state for women intending to become pregnant to be in is to be both non-smoking, and not using NRT.

Whilst smoking may have adverse effects on male fertility, no evidence exists that particular contraceptive measures are required during NRT treatment by males.

Fertility

In females, tobacco smoking delays time to conception, decreases in-vitro fertilization success rates, and significantly increases the risk of infertility. In males, tobacco smoking reduces sperm production, increases oxidative stress, and DNA damage. Spermatozoa from smokers have reduced fertilizing capacity. The specific contribution of nicotine to these effects in humans is unknown.

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 the 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 use of nicotine replacement therapy. The risk of continued smoking may pose greater hazard to the foetus as compared with the use of nicotine replacement products in a supervised smoking cessation programme. Use of Nicorette Invisipatch by the pregnant smoker should only be initiated after advice from a health care professional.

Breastfeeding
Nicotine passes freely into breast milk in quantities that may affect the child even with therapeutic doses. Nicotine should therefore be avoided during breast-feeding. Should smoking cessation not be achieved, use of the Nicorette Invisipatch by breast feeding smokers should only be initiated after advice from a health care professional.

4.7. Effects on Ability to Drive or Use Machines
Nicorette Invisipatch has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable Effects
Effects of smoking cessation
Regardless of the means used, a variety of symptoms are known to be associated with quitting habitual tobacco use. These include emotional or cognitive effects such as dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, and restlessness or impatience. There may also be physical effects such as decreased heart rate; increased appetite or weight gain, dizziness or presyncopal symptoms, cough, constipation, gingival bleeding or aphthous ulceration, or nasopharyngitis. In addition, and of clinical significance, nicotine cravings may result in profound urges to smoke.

Adverse Drug Reactions
Most of the undesirable effects reported by the subjects occur during the early phase of treatment and are mainly dose dependent. Allergic reactions (including symptoms of anaphylaxis) occur rarely during use of nicotine products.

About 20% of users experienced mild local skin reactions during the first weeks of treatment.

As would be expected, the types of adverse reactions seen for nicotine in clinical trials are similar to those associated with nicotine administered by other means.

Clinical Trial Data
The safety of nicotine from clinical trial data is based on data on a meta-analysis of randomized clinical trials (RCTs) for the treatment of smoking cessation.

ADRs Reported with a Frequency ≥1% Identified from Meta-analysis of Clinical Trial Data with Nicotine Patch Formulations

System Organ Class	Active	Placebo
Preferred Term	N = 3917 (%)	N = 1366 (%)
Gastrointestinal Disorders		
Nausea[a#]	4.7	6.1
Vomiting[a]	1.5	0.1

System Organ Class	Active	Placebo
Preferred Term	N = 3917 (%)	N = 1366 (%)
General Disorders and Administration Site Conditions		
Fatigue[a*#]	0.4	1.0
Immune System Disorders		
Hypersensitivity[a*]	0.4	0.2
Nervous System Disorders		
Headache[a#]	5.2	6.1
Paraesthesia[a*]	0.4	0.3
Skin and Subcutaneous Tissue Disorders		
Pruritus	18.0	10.7

[a]:Systemic effects
[*]Although the frequency is <1% the PT occurred at a frequency ≥1% in any other formulation in which the PT was identified as a systemic ADR.
[#] Although the frequency in the active group is less than that of the placebo group, the frequency in the
specific formulation in which the PT was identified as a systemic ADR was greater in the active group than the placebo group.

Post Marketing Data
Adverse drug reactions (ADRs) first identified during post-marketing experience with Nicotine Patch Formulations are presented in Table below. Frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

ADRs Identified During Post-Marketing Experience with Nicotine Patch Formulations with Frequency Category Estimated from Spontaneous Reporting Rates

System Organ Class	
Frequency category	**Preferred Term**
Cardiac Disorders	
Very rare	*Palpitations***
Very rare	*Tachycardia***
Gastrointestinal Disorders	
Very rare	*Gastrointestinal discomfort**
General Disorders and Administration site Conditions	
Very rare	*Application site reactions*

Very rare	*Asthenia***
Very rare	*Chest discomfort and pain***
Very rare	*Malaise***
Immune System Disorders	
Very rare	*Anaphylactic reaction***
Musculoskeletal and Connective Tissue Disorders	
Very rare	*Myalgia**
Very rare	*Pain in extremity*
Nervous System Disorder	
Not known	*Seizure***
Psychiatric Disorders	
Very rare	*Abnormal dream**,****
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	*Dyspnoea***
Skin and Subcutaneous Tissue Disorders	
Very rare	*Angioedema***
Very rare	*Erythema***
Very rare	*Hyperhidrosis***
Very rare	*Rash***
Very rare	*Urticaria***
Vascular Disorders	
Very rare	*Flushing***
Very rare	*Hypertension***

*In vicinity/region of patch
**systemic effects
***systemic effect, identified only for formulations administered during night

4.9. Overdose

Symptoms of overdose with nicotine from Nicorette Invisipatch may occur in smokers who have previously had a low nicotine intake from cigarettes or if other sources of nicotine are used concomitantly with Nicorette Invisipatch.
Acute or chronic toxicity of nicotine in man is highly dependent on mode and route of administration. Adaptation to nicotine (e.g. in smokers) is known to significantly increase tolerability compared with non-smokers. The acute minimum lethal oral dose of nicotine is believed to be 40 to 60 mg in children (oral intake of tobacco from cigarettes) or 0.8 to 1.0 mg/kg in adult nonsmokers.

Symptoms of overdose are those of acute nicotine poisoning and include nausea, vomiting, increased 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 children and may prove fatal. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

Management of overdose: *Administration of nicotine must be stopped immediately and the patient should be treated symptomatically.*

Remove patch and rinse application site with water.

Keep out of reach of children. In the event of overdose, get medical help right away.

5. PHARMACOLOGICAL PROPERTIES

Chemical Name:
Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)- 3-[(2S) 1-methylpyrrolidin-2-yl]pyridine (IUPAC)

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Drug used in nicotine dependence. ATC code: N07B A01

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. Abrupt cessation of the established, regular use of tobacco-containing products results in the characteristic syndrome, with withdrawal symptoms including cravings (urges to smoke) as described in Section 4.8. Clinical studies have shown that nicotine replacement products can help smokers abstain from or reduce their smoking by relieving these withdrawal symptoms.
The majority of smokers will gain weight on stopping smoking. In clinical trials, nicotine replacement therapy has been shown to attenuate post-cessation weight gain.

Patch treatment mimics the fluctuations of nicotine over the day in smokers, with no nicotine administration during sleep. Daytime nicotine patch treatment does not give the nicotine induced sleep disturbances seen with nicotine administration during sleep.

Clinical efficacy
A total of 479 smokers motivated to quit were enrolled in a multicenter, randomized, double blind, placebo-controlled, 52-week smoking cessation study. Subjects received full treatment for the first 6 weeks, subsequently reducing use over the next 6 weeks. Occasional use of the product was allowed up to week 24. The primary objective of the study was to evaluate the efficacy of Nicotine versus placebo in achieving continuous abstinence from the week 2 visit until and including the week 6, week 24, and week 52 visits,
respectively. Nicotine was 2.5 (RR 2.48) times more effective at helping smokers quit at 52 weeks (P= 0.007) compared to placebo. See table below for smoking cessation rates.

CO-verified continuous abstinence rates from Week 2. Data from one phase III study in 479 subjects.

Time point	Active spray (n=318)	Placebo spray (n=161)	P value	Odds ratio [95 % CI]	Risk ratio [95% CI]
Week 6	26.1 % (n=83)	16.1 % (n=26)	0.014	1.83 [1.12, 3.00]	1.62 [1.09,2.41]
Week 24	15.7 % (n=50)	6.8 % (n=11)	0.006	2.54 [1.28, 5.04]	2.30 [1.23, 4.30]
Week 52	13.8 % (n=44)	5.6 % (n=9)	0.007	2.71 [1.29, 5.71]	2.48 [1.24, 4.94]

5.2. Pharmacokinetic Properties

Nicotine is dibasic with a pKa1 of approximately 3 and a pKa2 around 8. Thus, nicotine is a weak base and its movement across cell membrane is pH dependent. It is easily soluble in both water and lipids depending on the degree of ionization. There are two stereoisomers of nicotine, (S)- and (R)- form, but it is only (S)-nicotine that is biologically active.

The pharmacokinetic studies of nicotine products have been performed in adult smokers.

5.2.1 ABSORPTION

Nicotine is released from the patch and absorbed through the skin. Vasodilatation caused by high ambient temperature and physical exercise increases absorption, whereas vasoconstriction caused by vasoconstrictor drugs decreases absorption.

Representative mean values of PK parameters for the patches are presented in the tables below.

Product	PK parameter	Mean	SD	n
Semi-transparent patch 10 mg/16 h	C_{max}	11.0 ng/mL	4.0	14
	T_{max}	10 h**	N/A	
	AUC_{∞}	140 ng/mL×h	51	
Semi-transparent patch 15 mg/16 h	C_{max}	15.4 ng/mL*	N/A	N/A
	AUC_{∞}	188 ng/mL×h*	N/A	
Semi-transparent patch 25 mg/16 h	C_{max}	24.2 ng/mL	5.4	28
	T_{max}	8 h**	N/A	
	AUC_{∞}	310.7 ng/mL×h	70.5	

* Calculated value based on linear equations established in a dose proportionality study.
** Median

During multiple dosing (i.e. one reference patch worn for 16 hours every 24 hours) there is no accumulation of nicotine in the body as a 16-hour application allows the nicotine plasma concentration to return to baseline prior to the next dosing interval.

When applied for 24 hours, additional nicotine was delivered (on average 3 mg for an original patch 15 mg). Bioavailability of absorbed nicotine is close to 100%.

5.2.2 DISTRIBUTION

The volume of distribution following intravenous administration of nicotine, has been investigated in numerous studies. In six studies, mean values ranges between 2.2 and 3.3 L/kg.

Plasma protein binding of nicotine is considered to be low, about 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 the nicotine pharmacokinetics.

5.2.3 METABOLISM

Results of pharmacokinetic studies suggest that nicotine metabolism and elimination are independent of the choice of nicotine formulation, and thus results from studies with intravenous administration of nicotine are used to describe distribution, biotransformation, metabolism and excretion.

The major eliminating organ is the liver, although the lungs and brain also metabolize nicotine to a small extent. The enzyme primarily involved in biotransformation of nicotine is CYP2A6. Seventeen 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 terminal half-life of 14 to 20 hours; the plasma concentrations of cotinine exceed those of nicotine 10-fold.

5.2.4 ELIMINATION

Mean values of total clearance of nicotine between 66.6 and 90.0 L/h have been reported and the

elimination half-life averages about 2-3 hours.

The primary urinary metabolites of nicotine are cotinine and trans-3-hydroxycotinine. On average 10-12% of the absorbed nicotine dose is excreted as cotinine and 28-37% of the dose is excreted as trans-3-hydroxycotinine. About 10-15% of nicotine is excreted unchanged in the urine. However, with low urine pH (below 5), as much as 23% of the nicotine dose was excreted unchanged.

There is a linear relationship between delivered amount of nicotine and C_{max}, AUC_t and AUC_∞.

5.2.4.1 Renal impairment

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

5.2.4.2 Hepatic Impairment

In smokers with liver cirrhosis but only mild impairment of hepatic function (Child-Pugh score 5), the pharmacokinetics of nicotine is unaffected. However, in smokers with moderately impaired liver function (Child-Pugh score 7), total clearance has been reported to be reduced on average by 40-50%. There is no data about pharmacokinetics of nicotine in smokers with a Child-Pugh score exceeding 7.

5.2.4.3 Geriatric

Total clearance of nicotine is reduced in healthy elderly subjects, but deviations are variable and not considered sufficiently important to justify general age-dependent dose adjustments.

5.3 Pre-clinical Safety data

Summary:

In vitro and in vivo genotoxicity testing of nicotine has yielded predominantly non- genotoxic results. Some positive findings from in vitro and in vivo genotoxicity tests have been reported but investigations using regulatory accepted assays and protocols have shown no evidence of genotoxic activity at therapeutic doses.

Analysis of the results from long-term carcinogenicity assays data with nicotine or cotinine, major nicotine metabolite, predominately indicate nicotine does not have any significant or relevant carcinogenic activity.

5.3.1. GENERAL TOXICOLOGY

Nicotine has oral and dermal LD_{50} in the range of 70 mg/kg. The general toxicity of repeated administration of nicotine is well known. Observations in chronic 2 years dosed feeding study in rats (5 mg/kg/day) showed no evidence of toxicity or overt behavior and health including any tumor responses.

5.3.2. GENETIC TOXICOLOGY

Nicotine showed negative results in in vitro tests but few in vitro and in vivo genotoxicity studies examining strand-breaking activity assessed by the comet assay, chromosome aberration or micronucleus formation gave positive results. However, the tested range is beyond the systemic nicotine levels achieved in humans by using nicotine products

5.3.3. CARCINOGENICITY

Long term animal studies with nicotine suggest that nicotine does not have any significant or relevant carcinogenic activity

5.3.4. TERATOGENICITY

In animal experiments nicotine induced maternal toxicity, fetal toxicity including post-implantation loss and growth retardation.

5.3.5. FERTILITY

In animal experiments, nicotine adversely affected spermatogenesis. To which extent female fertility is affected is not known.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Triglycerides, medium-chain
Basic butylated methacrylate copolymer
Polyethylenterephthalate (PET) film

Acrylate Matrix
Acrylic adhesive solution
Potassium hydroxide
Croscarmellose sodium
Aluminium acetylacetonate

Release Liner
Polyethylenterphthalate (PET) film single side aluminised, both sides siliconized

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

Refer to outer packaging

6.4. Special Precautions for Storage

Do not store above 30 ºC.

6.5. Nature and Contents of Container

Pack sizes:

Nicorette Invisipatch 10 mg: 7, 14 patches
Nicorette Invisipatch 15 mg: 7, 14, 21, 28 patches
Nicorette Invisipatch 25 mg: 7, 14, 21, 28 patches

Each patch is packed in a sealed laminate pouch consisting of paper, PET-film, aluminium and acrylnitrilcopolymer or cyclo olefine copolymer coextrudate.

All pack sizes may not be marketed.

6.6. Instructions for Use and Handling and Disposal

After removal, used patches should be disposed of carefully. The patches should be folded after use with the sticky side inwards, put back in an empty pouch and disposed of where children cannot reach it.

DO NOT DISPOSE OF UNUSED MEDICINES BY EMPTYING THEM INTO YOUR SINK, TOILET OR STORM DRAIN.

7. MARKETING AUTHORIZATION HOLDER

Johnson & Johnson (Thailand) Ltd.
Bangkok, Thailand.
Tel.: 1800-333-666 (Toll free except mobile phone)

Manufactured by:
LTS Lohmann Therapie-Systeme AG
Lohmannstr. 2, 56626 Andernach, Germany

8. MARKETING AUTHORISATION NUMBER/DATE OF FIRST AUTHORIZATION

PRODUCT	MARKETING AUTHORISATION NUMBER	DATE OF FIRST AUTHORISATION
Nicorette Invisipatch 10 mg	1C 15027/63(N)	05 - February-2020
Nicorette Invisipatch 15 mg	1C 15028/63(N)	05 - February-2020
Nicorette Invisipatch 25 mg	1C 15029/63(N)	05 - February-2020

9. DATE OF REVISION OF THE TEXT

November 2022 (Based on CCDS V3.0 19 April 2022)

10. WARNING ACCORDING TO ANNOUNCEMENT OF MINISTRY OF PUBLIC HEALTH

1. This medicine is use for smoking cessation purpose only.
2. Ask physician or pharmacist prior use this medicine.
3. This medicine will not effective in improper usage or unmotivated smoker.
4. Ask physician before use in pregnancy, breastfeeding women, and cardiovascular disease patients. If usage is necessary.