AUSTRALIAN PRODUCT INFORMATION
NICABATE CLEAR PATCH and NICABATE P
Rate controlled nicotine transdermal patches

1 NAME OF THE MEDICINE

Nicotine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: Nicotine is S-3-(1-methyl-2-pyrrolidinyl)-pyridine and is the major pharmacologically active alkaloid of tobacco.

Nicabate transdermal patch is a delivery system for transdermal use available in sizes of 22, 15 and 7 cm^2, each containing 5.1 mg/cm^2 of nicotine, releasing 21 mg, 14 mg and 7 mg respectively over 24 hours.

Nicotine is the active ingredient; other components of the system are pharmacologically inactive.

*Nicabate P transdermal nicotine patch is only available in 21mg patches.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

The free alkaloid is absorbed rapidly through the skin and respiratory tract.

The rate of delivery of nicotine to the patient from each system (40 mcg/cm^2- h) is proportional to the surface area. About 73% of the total amount of nicotine remains in the system 24 hours after application. Nicabate* is labelled by the dose actually absorbed by the patient (i.e. 7 mg/d, 14 mg/d or 21 mg/d). The dose of nicotine absorbed from Nicabate represents 68% of the amount released in 24 hours. The other 32% evaporates from the edge of the system.

Nicabate is a multilayered rectangular film containing nicotine as the active agent. For the three doses the composition per unit area is identical. Proceeding from the visible surface toward the surface attached to the skin are: (1) an occlusive backing consisting of polyethylene / aluminium / polyethylene terephthalate/ ethylene-vinyl acetate copolymer; for Nicabate P and polyethylene terephthalate / ethylene-vinyl acetate copolymer for Nicabate Clear Patch; (2) a drug reservoir containing nicotine (in an ethylene-vinyl acetate copolymer matrix containing ethylene dioleamide as slip agent): (3) a rate-controlling membrane (polyethylene); (4) a polyisobutylene adhesive; and (5) a protective liner that covers the adhesive layer and must be removed before application to the skin.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Nicabate Clear Patches and Nicabate P Patches: For the treatment of nicotine dependence as an aid to smoking cessation.

Nicabate P Patches: Treatment with Nicabate is indicated as an aid to smoking cessation. Nicabate P Patches may be used by people who smoke 15 or more cigarettes per day for two weeks prior to quitting smoking.

4.2 DOSE AND METHOD OF ADMINISTRATION

Prior to initiation of therapy users should be committed to stopping smoking. During an abrupt quit attempt every effort should be made to stop smoking during treatment with Nicabate patches. The patient should read the patient instruction booklet on Nicabate therapy and be encouraged to ask any questions.

Generally , treatment should be initiated with Nicabate 21 mg/day* or 14 mg/day.

In patients who smoke less than 10 cigarettes/day, have cardiovascular disease or weigh less than 45 kg should start with the Nicabate 14 mg/day patches.

All other patients should start with the Nicabate 21 mg/day patches.

*Nicabate P transdermal nicotine patch (21 mg/day) is available on the PBS and can be used for a total of twelve weeks. The product may be used in an abrupt quit setting or it may be used for two weeks prior to quit date while continuing to smoke and then for 10 weeks from the quit date.

NICABATE Pre-Quit Patch Therapy

Nicabate Pre-Quit patches can be used for the first 2 weeks of a quit attempt by smokers of 15 or more cigarettes a day who choose to smoke while preparing to quit. This should then be followed by the use of 21 mg, 14 mg and 7 mg patches in the established dosage regimen (see **Nicabate Pre-Quit patch therapy**).

NICABATE Abrupt Quit Patch Therapy

Adults (18 years and over)
Once the appropriate dosage is selected, the patient should begin 6 weeks of therapy at that dosage.

Users should make every effort to stop smoking completely during an abrupt quit attempt with Nicabate patches.

Behavioural therapy, advice and support will normally improve the success rate.

Recommended Dosing Schedule for Healthy Patients[a]

Dose	Duration
Nicabate 21 mg/Day	First 6 Weeks
Nicabate 14 mg/Day	Next 2 Weeks
Nicabate 7 mg/Day	Last 2-4 Weeks

[a] Start with Nicabate 14 mg/day for 6 weeks for patients who smoke less than 10 cigarettes/day, have cardiovascular disease or weigh less than 45 kg.

Nicabate should be applied promptly upon its removal from the protective pouch to prevent evaporative loss of nicotine from the system. Nicabate should be used only when the pouch is intact to assure that the product has not been tampered with. The user should wash hands thoroughly with water after handling the patch and avoid contact with eyes and nose.

Nicabate should be applied only once a day to a non-hairy, clean, dry skin site on the upper body or upper outer arm. After 24 hours, the used Nicabate patch should be removed and a new patch applied to an alternate skin site.

Skin sites should not be reused for at least a week. Areas where the skin creases should be avoided. It should not be applied to skin that is red, broken or irritated. It should be pressed firmly on the skin with the palm of the hand for 10 seconds. Water will not harm the nicotine transdermal patch, if it has been applied properly. The user can bathe, swim or shower for short periods while wearing the patch. Patients should be cautioned not to continue to use the same patch for more than 24 hours. The patch is recommended to be worn for 24 hours to minimise the chance of morning cravings. However, if the user experiences any vivid dreams or other disruptions of sleep while wearing the patch for 24 hours, the patch may be removed at bed time (after 16 hours) and a new one put on upon waking the next day.

The patches should not be used for longer than 4 months.

Intermittent dosing products (eg Nicabate lozenges or gums) could be used beyond 12 weeks if they are needed to stay cigarette free, however those who use NRT beyond 9 months are recommended to seek additional help and advice from a healthcare professional who may consider alternate quit strategies such as combination therapy.

Further courses may be used at a later time for Nicabate patch users who continue or resume smoking.

Children and adolescents

Children: Safety and efficacy in children who smoke have not been evaluated. Nicabate patches are not recommended for use in children under 12 years of age.

Adolescents (12 to 17 years): Medical advice should be obtained before use of Nicabate patches. The use of NRT in adolescents should only be used when the benefits of abstinence outweigh the risks of continued smoking. Data are limited in relation to the value of NRT use in young people where the demand for cessation products and the motivation to quit is low. NRT should only be used by adolescents in conjunction with a counselling programme. Counselling is needed in this age group because NRT is likely to be ineffective in the absence of counselling.

Adolescents (12 to 17 years) should follow the schedule of treatment for an abrupt quit attempt in adults presented above but as data are limited, duration of NRT in this age group is restricted to 10 weeks after obtaining medical advice. If longer treatment is required advice from a healthcare professional should be sought who can then reassess the patient for their commitment to quitting and the benefits of continued treatment. If treatment is continued, it should not be extended for more than another four weeks.

Adolescents should not quit with Pre-Quit or Combination Therapy.

Nicabate Pre-Quit Patch Therapy

For smokers of 15 or more cigarettes a day who chose to smoke while preparing to quit, Nicabate Pre-Quit patches should be applied once daily for the first 2 weeks of the quit attempt.

After the 2-week Pre-Quit course is completed, the patient should stop smoking completely then continue their quit attempt with the regular Nicabate or Nicabate Clear 21 mg, 14 mg and 7 mg patches. Every effort should be made to remain abstinent from smoking. Nicabate 21 mg patches should be used for 6 weeks, followed by use of the 14 mg patches for the next 2 weeks and use of the 7 mg patches for 2-4 weeks. Combination therapy may also be used once smoking has ceased (see **Combination therapy**).

The Nicabate Pre-Quit Patches, and Nicabate and Nicabate Clear Patches, should be applied as indicated under Nicabate Patch Therapy -**Adults (18 years and over)**.

Combination Therapy

In some instances, it may be beneficial to utilize more than one form of NRT concurrently. For example, combination therapy could be used by smokers who have relapsed with NRT monotherapy in the past, who experience breakthrough cravings or have difficulty controlling cravings for cigarettes using single therapy. This would allow users to identify the combination most appropriate for their individual quit attempt. If required, Nicabate gum 2 mg or Nicabate Minis 2 mg may be combined with Nicabate 21 mg patches. Nicabate 4 mg gums and/or Nicabate 4 mg Minis should not be used with Nicabate patches.

Patients should stop smoking completely during combination therapy treatment. When using Nicabate 21 mg patches in addition to Nicabate 2 mg gums, or 2 mg Minis, it is recommended that a minimum of 4 pieces of gum/4 Minis are used daily. Most people will use 4-5 pieces. The maximum number of gums or Minis used in conjunction with the patch is 12 pieces per day.

Combination treatment should be used for 12 weeks after which weaning may be initiated.
If required, weaning may be done by either:

1 Using Nicabate 14 mg patch for 2 weeks and then Nicabate 7 mg patch for 2 weeks while maintaining the number of pieces of 2 mg gum or 2 mg Minis that have been routinely used. Then, when a patch is no longer used, the number of pieces of gum/ Minis can be gradually reduced. OR

2 Stopping use of Nicabate 21 mg patch and then gradually reducing the number of pieces of 2 mg gum or 2 mg Minis that are being used.

Reduce to Quit

For smokers who are unwilling or unable to quit abruptly, Nicabate gum or Minis should be used as the number of cigarettes is gradually reduced over a number of weeks.

Drug Abuse and Dependence

To minimise the risk of dependence, patients should be encouraged to withdraw gradually from Nicabate after 4 to 8 weeks of use. Recommended dose reduction is to progressively decrease the dose every 2 to 4 weeks (see Dosage and Administration).

4.3 CONTRAINDICATIONS

Nicabate Clear patches should not be used by:

- Non-smokers
- Children under 12 years of age
- Those with hypersensitivity to nicotine or any of the excipients
- Those with diseases of the skin that may complicate patch therapy

Nicabate P patches should not be used by:

- Those who smoke less than 10 cigarettes per day
- Those who weigh less than 45 kg
- Those with hypersensitivity to nicotine or any of the excipients

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The risks associated with the use of NRT are substantially outweighed in virtually all circumstances by the well-established dangers of continued smoking.

Patients hospitalised for, or with a recent myocardial infarction, severe dysrhythmia or CVA (cerebrovascular accident) who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions.

If this fails, Nicabate patches may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. Once patients are discharged from hospital they can use NRT on medical advice. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the nicotine patch dose should be reduced or Nicabate Patch use discontinued.

The precessation or combination NRT regimens should not be used in people with known cardiovascular disease without evaluation of the risk/benefit by a healthcare professional.

Diabetes mellitus: Patients with diabetes mellitus should be advised to monitor their sugar levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism and vasoconstriction may delay/reduce insulin absorption. Blood glucose levels may be more variable when stopping smoking, with or without NRT, so it is important for diabetics to continue monitoring their blood sugar levels while using this product.

Seizures: Potential risks and benefits of nicotine should be carefully evaluated before use in subjects taking anti-convulsant therapy or with a history of epilepsy as cases of convulsions have been reported in association with nicotine.

Allergic reactions: The user should stop use and consult a healthcare professional if he/she gets skin redness, swelling or rash that does not go away after 4 days, or if a generalised skin reaction occurs. This may be more likely if there is a history of dermatitis.

Susceptibility to angioedema and urticaria: NRT should be used with caution by patients who are susceptible to angioedema and/or urticaria.

Atopic or eczematous dermatitis (due to localised patch sensitivity): In the case of local reactions at the site of application (eg erythema, pruritus or oedema) or a generalised skin reaction (eg urticaria, hives or generalised skin rashes), users should be instructed to discontinue use of Nicabate patches and contact their physicians. These effects may be more likely if there is a history of dermatitis.

Contact sensitisation: Patients with contact sensitisation should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking.

Paediatric use

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. The patches should be folded in half with the adhesive side innermost and disposed of with care.

Safety on handling: Nicabate patches are potentially a dermal irritant and can cause contact sensitisation. Care should be taken during handling and in particular contact with the eyes and nose avoided. After handling, wash hands with water alone as soap may increase nicotine absorption. Nicabate patches should be removed prior to undergoing MRI procedures.

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

Use in hepatic impairment

Use with caution in patients with moderate to severe hepatic impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

Use in renal impairment

Use with caution in patients with moderate to severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

Use in the elderly

'No data Available'

• *Phaeochromocytoma and uncontrolled hyperthyroidism:* Use with caution in patients with uncontrolled hyperthyroidism or Phaeochromocytoma as nicotine causes release of catecholamines.

GI disease: Nicotine replacement therapy may exacerbate symptoms in persons suffering from active oesophagitis, oral and pharyngeal inflammation, gastritis, gastric ulcer or peptic ulcer.

Patients who initiate quitting with pre-cessation NRT and experience exaggerated effects as listed in the "OVERDOSE" section, should discontinue smoking and remove the patch.

Transferred dependence: Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

Effects on laboratory tests

'No data Available'

Drug Abuse and Dependence

Nicabate therapy is likely to have a low abuse potential based on differences between it and cigarettes in four characteristics commonly considered important in contributing to abuse: much slower absorption; much smaller fluctuations in blood levels, lower blood levels of nicotine, and less frequent use (i.e. once daily).

Dependence on nicotine polacrilex chewing gum replacement therapy has been reported. Such dependence might also occur from transference to Nicabate of tobacco-based nicotine dependence.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically relevant interactions between nicotine replacement therapy and other drugs have been established however, nicotine may possibly enhance the haemodynamic effects of adenosine. Healthcare professionals are reminded that smoking itself may require the adjustment of some drug therapy.

Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolised by CYP 1A2 (and possibly CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs.

Smoking cessation, with or without nicotine replacement, may alter the individual's response to concomitant medication and may require adjustment of dose. In particular, anticonvulsants may require special monitoring and/or dosage adjustment.

May Require a Decrease in Dose at Cessation of Smoking	**Possible Mechanism**
Paracetamol, caffeine, oestrogens, imipramine, lignocaine, oxazepam, pentazocine, theophylline, warfarin	Reversal of hepatic enzyme induction on smoking cessation.
Insulin	Increase in subcutaneous insulin absorption with smoking cessation.
Adrenergic antagonists (eg, prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation.

May Require an Increase in Dose at Cessation of Smoking	Possible Mechanism
Adrenergic agonists (eg, isoprenaline, phenylephrine)	Decrease in circulating catecholamines with smoking cessation.

Other reported effects of smoking include reduced analgesic efficacy of propoxyphene, reduced diuretic response to frusemide and altered pharmacological response to propranolol, as well as altered rates of ulcer healing with H2 antagonists. Both smoking and nicotine can increase levels of circulating cortisol and catecholamines. Dosages of nifedipine, adrenergic agonists, or adrenergic blocking agents may need to be adjusted.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In rats and rabbits, implantation can be delayed or inhibited by a reduction DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Use in pregnancy – Pregnancy Category D

Adverse reproductive and developmental effects have been reported following exposure to tobacco and nicotine during 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.

Ideally smoking cessation during pregnancy should be achieved without NRT. However for women unable to quit on their own, NRT (transdermal patches) should only be used on the advice of a healthcare professional and if the expected benefits to the mother outweigh the potential risks to the foetus. Nicotine is harmful to the foetus. However, the risk of using NRT to the foetus is lower than that expected with tobacco smoking, due to lower maximal plasma nicotine concentration and no additional exposure to polycyclic hydrocarbons and carbon monoxide.

However, as nicotine passes to the foetus affecting breathing movements and has a dose dependent effect on placental/foetal circulation, the decision to use NRT should be made as early on in the pregnancy as possible. The aim should be to use NRT for only 2-3 months.

While no data exist to support one form of NRT over another, intermittent dosing products (ie Nicabate lozenges and soft gums) should preferably be used while pregnant as these usually provide a lower daily dose of nicotine than patches. However patches may be preferred if the woman is suffering from nausea during pregnancy. If patches are used they should be removed before going to bed.

Use in lactation.

Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to from NRT is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to. Nicabate Patches should not be used while breastfeeding. Should smoking

cessation not be achieved, intermittent dosing products such as Nicabate soft gums or mini lozenges, should be used while breastfeeding. However the use of any form of NRT in breast feeding women should be initiated only if the expected benefits to the nursing mother outweigh the potential risks to the infant. Women should breast feed just before they use the product to allow as long a time as possible between NRT use and feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Used as recommended there are minimal risks associated with the use of Nicabate in driving vehicles or operating machinery. However, one should take into consideration that smoking cessation can cause behavioural changes.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

NRT may cause adverse reactions similar to those associated with nicotine administered by other means, including smoking. These may be attributable to the pharmacological effects of nicotine, some of which are dose dependent. At recommended doses, Nicabate patches have not been found to cause any serious adverse effects. Excessive use of Nicabate patches by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Certain symptoms which have been reported such as depression, irritability, nervousness, restlessness, mood lability, anxiety, drowsiness, impaired concentration, insomnia and sleep disturbances may be related to withdrawal symptoms associated with smoking cessation. Subjects quitting smoking by any means could expect to suffer from asthenia, headache, dizziness, sleep disturbance, coughing or influenza-like illness.

The following undesirable effects have been reported in clinical trials and/or spontaneously post-marketing reports (very common ≥1/10: common ≥1/100, <1/10: uncommon ≥1/1000, <1/100: rare ≥1/10000, <1/1000 and very rare <1/10000)

Organ system	Adverse event
Immune system disorders	*Uncommon:* hypersensitivity * *Very rare*: anaphylactic reaction
Psychiatric disorders	*Very common*: sleep disorders including abnormal dreams and insomnia *Common:* nervousness
Nervous system disorders	*Very common*: headache, dizziness *Common*: tremor

Cardiac disorders	*Common:* palpitations *Uncommon*: Tachycardia *Rare:* Arrhythmia
Respiratory, thoracic and mediastinal disorders	*Common*: dyspnoea, pharyngitis, cough
Gastrointestinal disorders	*Very common*: nausea, vomiting *Common:* dyspepsia, abdominal pain upper, diarrhoea, dry mouth, constipation
Skin and subcutaneous tissue disorders	*Common*: sweating increased *Very rare:* dermatitis allergic*, dermatitis contact*, photosensitivity
Musculoskeletal and connective tissue disorders	*Common*: arthralgia, myalgia
General disorders and administration site conditions	*Very common*: application site reactions* *Common*: Application site pain, chest pain*, pain in limb*, pain, asthenia, fatigue *Uncommon*: malaise, influenza-like illness

*Application site reactions, including transient rash, itching, burning, tingling, numbness, swelling, pain and urticaria are the most frequent undesirable effects of Nicabate patches. The majority of these topical reactions are minor and resolve quickly following removal of the patch, though in severe cases some reactions could last between 1 to 3 weeks. Pain or sensation of heaviness in the limb or area around which the patch is applied (eg chest) may be reported.

Hypersensitivity reactions, including contact dermatitis and allergic dermatitis have also been reported. In the case of severe or persistent local reactions at the application site (eg severe erythema, pruritus or oedema) or a generalised skin reaction (eg urticaria, hives or generalised skin rashes) users should be instructed to discontinue use of Nicabate and contact their physician.

If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the Nicabate dose should be reduced or discontinued.

4.9 OVERDOSE

The effects of applying several Nicabate patches simultaneously, or swallowing Nicabate patches are unknown (see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Symptoms of acute nicotine poisoning include nausea, salivation, abdominal pain, diarrhoea, sweating,

headache, dizziness, disturbed hearing and marked weakness. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse and terminal convulsions.

Symptoms and Signs
Even small quantities of nicotine are dangerous in children, and may result in severe symptoms of poisoning which may prove fatal. Signs and symptoms of an overdose from a nicotine patch would be expected to be the same as those of acute nicotine poisoning, including pallor, cold sweat, excessive sweating, salivation, vomiting, abdominal pain, diarrhoea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion and weakness. Prostration, hypotension, circulatory collapse, respiratory failure and convulsions may ensue with large overdoses.

Overdose From Topical Exposure
Nicabate should be removed immediately in the event of an overdose or if the patient shows signs of overdosage and the patient should seek immediate medical care. The skin surface may be flushed with water and dried. **No soap should be used, since it may increase nicotine absorption**. Nicotine will continue to be delivered into the bloodstream for several hours (see Pharmacokinetics) after removal of the system because of a depot of nicotine in the skin.

Overdose From Ingestion
All nicotine intake should stop immediately. The patient should seek medical attention immediately and be treated symptomatically and all vital signs monitored. Due to the possibility of nicotine-induced seizures, activated charcoal should be administered. In unconscious patients with a secure airway, instil activated charcoal via a nasogastric tube. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the system. Repeated doses of activated charcoal should be administered as long as the patch remains in the gastrointestinal tract since it will continue to release nicotine for many hours.

Management of Nicotine Poisoning
All nicotine intake should stop immediately and the patient should be treated symptomatically. Artificial respiration with oxygen should be instituted if necessary. Activated charcoal may reduce the absorption of nicotine if given within one or two hours after ingestion. In patients who are not fully conscious or have an impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected,

Other supportive measures include diazepam for seizures, atropine for excessive bronchial secretions or diarrhoea, respiratory support for respiratory failure and vigorous fluid support for hypotension and cardiovascular collapse.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological action

Nicotine, the chief alkaloid in tobacco products, binds stereoselectively to acetylcholine receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect, exerted mainly in the cortex via the locus ceruleus, produces increased alertness and cognitive performance. A "reward" effect via the "pleasure system" in the brain is exerted in the limbic system. At low doses the stimulant effects predominate, while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, noradrenaline, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone and ACTH.

Pharmacodynamic Effects

The actions of nicotine in man are complex, depending on dose, rate of delivery, prevalent autonomic tone, individual variation and prior exposure (tolerance).

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than 1 hour), but at distinct rates for different physiological effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms, such as cigarette craving, can be reduced in some individuals by plasma nicotine levels lower than those for smoking.

Withdrawal from nicotine in addicted individuals is characterised by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue) and weight gain. Nicotine toxicity is characterised by nausea, abdominal pain, vomiting, diarrhoea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respiration and hypotension.

The cardiovascular effects of Nicabate 21 mg/day used continuously for 24 hours were compared with smoking every 30 minutes during waking hours for 5 days. Both regimens elevated heart rate (about 10 beats/min) and blood pressure (about 5 mm Hg) compared with an abstinence period and these increases were similar between treatments throughout the 24 hour period, including during sleep.

The circadian pattern and release of plasma cortisol following 5 days of treatment with Nicabate 21 mg/day did not differ from that following 5 days of nicotine abstinence. Urinary excretion of noradrenaline, adrenaline and dopamine was also similar for Nicabate 21 mg/day and abstinence.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following application of Nicabate to the upper body or upper outer arm, approximately 68% of the nicotine released from the system enters the systemic circulation (eg. 21 mg/day for the highest dose patch). The remainder of the nicotine released from the system is lost via evaporation from the edge. All Nicabate systems are labelled with the actual amount of nicotine absorbed by the patient.

Distribution

The volume of distribution following IV administration of nicotine is approximately 2 to 3 L/kg and the half-life of nicotine ranges from 1 to 2 hours. Plasma protein binding of nicotine is less than 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 consequences.

Metabolism

The metabolism of nicotine primarily occurs in the liver but also in the lung and kidney. There is no significant skin metabolism of nicotine. More than 20 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 half-life of 15 to 20 hours and concentrations that exceed nicotine by 10 fold.

Elimination

The major eliminating organ is the liver and average plasma clearance is about 1.2 L/min.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3- hydroxycotinine (45% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% may be excreted in the urine with high urine flow rates and urine acidification below pH 5.

After Nicabate application, plasma concentrations rise rapidly, plateau within 2 to 4 hours, and then slowly decline until the patch is removed; after which they decline more rapidly.

The pharmacokinetic model that best fits the plasma nicotine concentrations from Nicabate systems is an open, two-compartment disposition model with a skin depot through which nicotine enters the central circulation compartment. Nicotine in the adhesive layer is absorbed into and then through the skin, causing the initial rapid rise in plasma concentrations. The nicotine from the reservoir is released slowly through the membrane with a release rate constant approximately 20 times smaller than the skin absorption rate constant, as demonstrated in vitro in cadaver skin flux studies and verified by pharmacokinetic trials. Therefore, the slow decline of plasma nicotine concentrations from 4 to 24 hours is determined primarily by the release of nicotine from the system.

Following the second daily Nicabate application, steady-state plasma nicotine concentrations are achieved and are on average 30% higher compared with single dose applications. Plasma nicotine concentrations are proportional to dose (ie. linear kinetics are observed) for the three strengths of Nicabate patches. Nicotine kinetics are similar for all sites of application on the upper body and upper outer arm. Plasma nicotine concentrations from Nicabate 21 mg/day are the same as those from simultaneous use of Nicabate 14 mg/day and 7 mg/day.
Following removal of the Nicabate system, plasma nicotine concentrations decline in an exponential fashion with an apparent mean half-life of 3 to 4 hours compared with 1 to 2 hours for IV administration, due to continued absorption from the skin depot. Most non-smoking patients will have nondetectable nicotine concentrations in 10 to 12 hours.

Steady-State Nicotine Pharmacokinetic Parameters
for Nicabate transdermal patches (Mean, SD and Range)

	Dose Absorbed (mg/day)								
	21			14			7		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
C_{max} ng/mL	23	5	13-32	17	3	10-24	8	2	5-12
C_{avg} ng/mL	17	4	10-26	12	3	8-17	6	1	4-10

C_{min} ng/mL	11	3	6-17	7	2	4-11	4	1	3-6
T_{max} h	4	3	1-10	4	3	1-10	4	4	1-18

Cmax: maximum observed plasma concentration
Cavg: average plasma concentration
Cmin: minimum observed plasma concentration
Tmax: time of maximum plasma concentration

Half-hourly smoking of cigarettes produces average plasma nicotine concentrations of approximately 44 ng/mL. In comparison, average plasma nicotine concentrations from Nicabate 21 mg/day are about 17 ng/mL.

Special Patient Populations

There are no differences in nicotine kinetics between men and women using Nicabate systems. Linear regression of both AUC and Cmax vs total body weight shows the expected inverse relationship. Obese men using Nicabate had significantly lower AUC and Cmax values than normal weight men. Men and women having low body weight are expected to have higher AUC and Cmax values

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Nicotine and cotinine were not mutagenic in the Ames Salmonella test. Nicotine induced repairable DNA damage in an E.coli test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells.

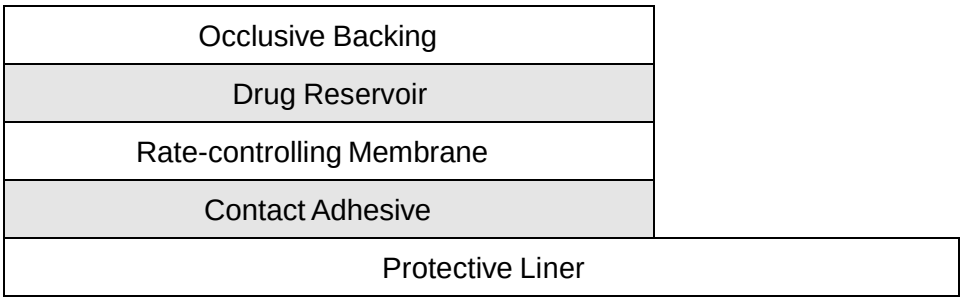
Carcinogenicity

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumours in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumour initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients: Nicabate is a multilayered rectangular film containing nicotine as the active agent. For the three doses the composition per unit area is identical. Proceeding from the visible surface toward the surface attached to the skin are: (1) an occlusive backing consisting of polyethylene / aluminium / polyethylene terephthalate/ ethylene-vinyl acetate copolymer; for Nicabate P and polyethylene terephthalate / ethylene-vinyl acetate copolymer for Nicabate Clear; (2) a drug reservoir containing nicotine (in an ethylene-vinyl acetate copolymer matrix containing ethylene dioleamide as slip agent): (3) a rate-controlling membrane (polyethylene); (4) a polyisobutylene adhesive; and (5) a protective liner that covers the adhesive layer and must be removed before application to the skin.



(not to scale)

6.2 INCOMPATIBILITIES

Not Applicable

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

7 mg/day containing 36 mg nicotine with a 7 cm^2 release area:
Nicabate Clear: packs of 7

14 mg/day containing 78 mg nicotine with a 15 cm^2 release area:
Nicabate Clear: packs of 7

21 mg/day containing 114 mg nicotine with a 22 cm^2 release area:
Nicabate Clear: packs of 7 & 14
Nicabate P: packs of 28

Not all packs may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

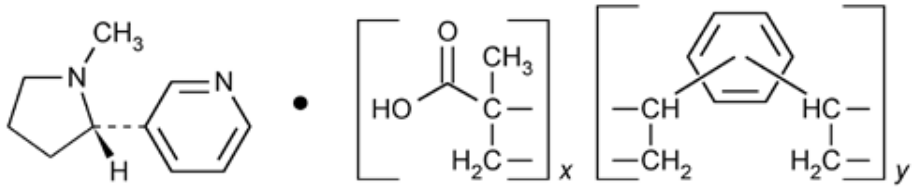
Nicabate can be a dermal irritant and can cause contact sensitisation. Although exposure of health care workers to nicotine from Nicabate systems should be minimal, care should be taken to avoid unnecessary contact with active systems. When the used patch is removed from the skin, it should be folded over with sticky side inward and placed in the protective pouch that contained the new system. The used system should be immediately disposed of carefully in such a way to prevent its access by children or pets. Because Nicabate contains residual nicotine after use and can be harmful to children, it must therefore be kept out of the sight and reach of children at all times. As with other nicotine containing transdermal patches, accidental application by small children could produce severe symptoms of poisoning and may prove fatal.

In Australia any unused medicine or waste material should be disposed of by taking to your local pharmacy or in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Nicotine is S-3-(1-methyl-2-pyrrolidinyl)-pyridine.



CAS number

54-11-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

UNSCHEDULED

8 SPONSOR

Haleon
Sydney, NSW, Australia

Telephone: 1800 028 533
Website: www.haleon.com

9 DATE OF FIRST APPROVAL

Nicabate Clear	7.12.2001
Nicabate P	12.5.2010

10 DATE OF REVISION

27TH SEPTEMBER 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Updates to multiple sections and statements, change to sponsor and contact details, removal of discontinued products