PRODUCT INFORMATION
NICABATE, NICABATE CLEAR, NICABATE PRE-QUIT and Nicabate P
Rate controlled nicotine transdermal patches

Nicotine is S-3-(1-methyl-2-pyrrolidinyl)-pyridine and is the major pharmacologically active alkaloid of tobacco. The free alkaloid is absorbed rapidly through the skin and respiratory tract.

DESCRIPTION

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 and 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.

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<table>
<thead>
<tr>
<th>Occlusive Backing</th>
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<tbody>
<tr>
<td>Drug Reservoir</td>
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<tr>
<td>Rate-controlling Membrane</td>
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<tr>
<td>Contact Adhesive</td>
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<tr>
<td>Protective Liner</td>
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(not to scale)

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

The rate of delivery of nicotine to the patient from each system (40 mcg/cm²•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.
The Nicabate Pre-Quit patch has the same formulation as the Nicabate Clear 21 mg/24 hour patch.

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

PHARMACOLOGY

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.

Pharmacodynamics
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.

**Pharmacokinetics**

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.

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. The major eliminating organ is the liver and average plasma clearance is about 1.2 L/min; the kidney and lung also metabolise nicotine. 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.

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.

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 \textit{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 nonsmoking patients will have nondetectable nicotine concentrations in 10 to 12 hours.

<table>
<thead>
<tr>
<th>Dose Absorbed (mg/day)</th>
<th>21</th>
<th>14</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}}) (ng/mL)</td>
<td>23</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>(C_{\text{avg}}) (ng/mL)</td>
<td>17</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>(C_{\text{min}}) (ng/mL)</td>
<td>11</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>(T_{\text{max}}) (h)</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

\(C_{\text{max}}\): maximum observed plasma concentration  
\(C_{\text{avg}}\): average plasma concentration  
\(C_{\text{min}}\): minimum observed plasma concentration  
\(T_{\text{max}}\): 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.

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

INDICATIONS

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

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

CONTRAINDICATIONS

Nicabate 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 Pre-Quit patches should not be used by:

- Those who smoke less than 15 cigarettes per day
- Those with cardiovascular disease
- Those who weigh less than 45 kg

Nicabate P patches should not be used by:

- Those who smoke less than 10 cigarettes per day
- Those who weigh less than 45 kg

PRECAUTIONS

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 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 lozenges or soft gums 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 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.

Allergic reactions:
The user should stop use and consult a healthcare professional if he/she gets skin rashes, 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 severe or persistent local reactions at the site of application (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 patches and contact their physicians.

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

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

- 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.

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.

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

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.

Carcinogenesis, Mutagenesis, Impairment Of Fertility
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.

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. 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 (Category D)
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 may be recommended to assist a quit attempt. 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. Intermittent dosing products such as Nicabate soft gums or lozenges, should be used while breastfeeding and women should breast feed just before they use the product to allow as long a time as possible between NRT use and feeding.

**Effects On Ability To Drive Or Use Machines**
Used as recommended there are minimal risks associated with the use of Nicabate in driving vehicles or operating machinery.

**Drug 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

<table>
<thead>
<tr>
<th>Substance</th>
<th>Possible Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol, caffeine, oestrogens, imipramine, lignocaine, oxazepam, pentazocine, theophylline, warfarin</td>
<td>Reversal of hepatic enzyme induction on smoking cessation.</td>
</tr>
<tr>
<td>Insulin</td>
<td>Increase in subcutaneous insulin absorption with smoking cessation.</td>
</tr>
<tr>
<td>Adrenergic antagonists (eg, prazosin, labetalol)</td>
<td>Decrease in circulating catecholamines with smoking cessation.</td>
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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.

ADVERSE REACTIONS

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 or spontaneously post-marketing (very common ≥1/10: common ≥1/100; <1/10: uncommon ≥1/1000; <1/100 and very rare <1/10000)

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 > 1/1000; < 1/100: tachycardia

**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 < 1/10,000: 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: 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. 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.
DOSAGE AND 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.

Treatment should be initiated with Nicabate 21 mg/day* or 14 mg/day – 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; 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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Nicabate 21 mg/day</td>
<td>First 6 Weeks</td>
</tr>
<tr>
<td>Nicabate 14 mg/day</td>
<td>Next 2 Weeks</td>
</tr>
<tr>
<td>Nicabate 7 mg/day</td>
<td>Last 2-4 Weeks</td>
</tr>
</tbody>
</table>

*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 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. 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.

Intermittent dosing products (eg Nicabate lozenges or soft 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 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): 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. Nevertheless NRT is safe in this group. 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 12 weeks. 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. 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 soft gum 2 mg or Nicabate lozenges 2 mg may be combined with Nicabate 21 mg patches. Nicabate 4 mg lozenges and/or 4 mg soft gums should not be used with Nicabate patches.

When using Nicabate 21 mg patches in addition to Nicabate 2 mg soft gums or 2 mg lozenges, it is recommended that a minimum of 4 pieces of soft gum/4 lozenges are used daily. Most people will use 4-5 pieces. The maximum number of soft gums or lozenges 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 soft gum/lozenges that have been routinely used. Then, when a patch is no longer used, the number of pieces of soft gum/lozenges can be gradually reduced. OR

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

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

**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.

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).

**OVERDOSAGE**

The effects of applying several Nicabate patches simultaneously, or swallowing Nicabate patches are unknown (see Precautions).

The oral LD$_{50}$ for nicotine in rodents varies with species but is in excess of 24 mg/kg; death is due to respiratory paralysis. The oral minimum lethal dose of nicotine in dogs is greater than 5 mg/kg. The oral minimum acute lethal dose for nicotine in human adults is reported to be 40 to 60 mg (< 1 mg/kg).

Three dogs, each weighing 11 kg, were fed two damaged Nicabate 14 mg/day systems. Nicotine plasma concentrations of 32 to 79 ng/mL were observed.
No ill effects were apparent.

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.

**Overdose From Topical Exposure**

Nicabate should be removed immediately 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**

Persons ingesting Nicabate should be referred to a health care facility for management. 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 reduces the gastrointestinal absorption of nicotine.

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.

**PRESENTATION**

7 mg/day containing 36 mg nicotine with a 7 cm$^2$ release area:
- Nicabate: packs of 3, 7
- Nicabate Clear: packs of 3, 7

14 mg/day containing 78 mg nicotine with a 15 cm$^2$ release area:
- Nicabate: packs of 3, 7
- Nicabate Clear: packs of 3, 7

21 mg/day containing 114 mg nicotine with a 22 cm$^2$ release area:
- Nicabate: packs of 3, 7 & 14
Nicabate Clear: packs of 3, 7 & 14
Nicabate Pre-Quit: packs of 3, 14
Nicabate P: pack 14 & 28 patches

All presentations contain information on Nicabate and how to use it.

Nicabate P transdermal 21mg nicotine patches are only available on the PBS.

Safety Note

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 and placed in the protective pouch that contained the new system. The used system should be immediately disposed of in such a way to prevent its access by children or pets. Because Nicabate contains residual nicotine after use, it must therefore be kept out of 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.

POISON SCHEDULE

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