

AUSTRALIAN PRODUCT INFORMATION- NICOTINELL (NICOTINE) 21 MG/24 HOURS, 14 MG/24 HOURS, 7 MG/24 HOURS TRANSDERMAL PATCH

1 NAME OF THE MEDICINE

Nicotine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of Nicotinell 21 mg/24 Hours, 14 mg/24 Hours, 7 mg/24 Hours Patch is Nicotine.

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.

Nicotinell Patch is a round, multi-layered matrix patch. It consists of an external layer which protects the patch during storage, an adhesive layer, which is necessary for the contact between the transdermal patch and the skin during application, several matrix layers, a pad with the active ingredient solution and a backing foil for protection of the patch during wearing. Each patch is packaged in a heat sealed multilaminar sachet. Nicotine is the active ingredient; other components of the system are pharmacologically inactive. Nicotine penetrates the skin by diffusion and thus becomes directly bioavailable to the systemic circulation.

The following 3 systems are available as shown in the table below:

| | Nicotinell Step 1 | Nicotinell Step 2 | Nicotinell Step 3 |
|---------------------------------|--------------------------|--------------------------|--------------------------|
| Content of nicotine (mg) | 52.5 | 35.0 | 17.5 |
| Patch size (cm ²) | 30 | 20 | 10 |
| Printed codes (on backing film) | CG EME | CG FEF | CG CWC |
| Nominal release rate (mg/24 h) | 21 | 14 | 7 |

To sustain the concentration gradients for diffusion, more nicotine is contained in the Nicotinell Patch than is actually delivered over 24 hours. Nicotinell Patch releases approximately 0.7 mg/cm²/24 hours of nicotine. Therefore, the average daily dose administered is determined largely by the size of the contact area of the system.

List of excipients

Fractionated coconut oil, Durotak 280-2516 and Methacrylic acid copolymer.

3 PHARMACEUTICAL FORM

Transdermal patch.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of nicotine dependence, as an aid to smoking cessation. The Nicotinell Step 1 Patch may also be used by people who smoke 20 or more cigarettes per day for two weeks prior to quitting smoking.

4.2 DOSE AND METHOD OF ADMINISTRATION

Nicotinell should be applied as soon as it has been removed from the child-resistant pouch. The sachet has a pre-cut edge to facilitate removal of the Nicotinell Patch contents. Following removal of the metallic backing, the Nicotinell Patch should be immediately applied to a clean non-hairy, dry area of intact skin on the trunk or upper arm. The patch should be held in position for 10–20 seconds with the palm of the hand. A different site of application should be chosen each day. Several days should be allowed to elapse before using the same area again.

A new patch should be applied to a different place on skin that is dry, clean and hairless. It should be pressed firmly on the skin with the palm of hand for 10 seconds. The same skin site should not be used for at least 7 days. Areas where the skin creases should be avoided. It should not be applied to skin that is red, broken or irritated.

The patch should be kept sealed in its protective pouch until ready to use. The user should wash hands with water after handling the patch, and avoid contact with eyes and nose.

Water will not harm the nicotine transdermal patch, if it has been applied properly. The user can bath, swim or shower for short periods while wearing the nicotine transdermal patch.

Adults (18 years and over)

Nicotinell Abrupt Quit patch therapy

During an abrupt quit attempt, the patient should be advised to stop smoking completely when starting treatment with Nicotinell Patch.

For those smoking 20 or more cigarettes a day it is recommended that treatment be started with Nicotinell Patch Step 1. Those smoking less than 20 cigarettes a day should start with Nicotinell Patch Step 2.

Patients starting on Nicotinell Patch Step 1 should use this strength for 3–4 weeks, before moving onto Step 2 for 3–4 weeks, and finally Step 3 for 3–4 weeks.

Patients starting on Nicotinell Patch Step 2 may switch to Step 3 after 3–4 weeks, or continue to use Step 2 for 6–8 weeks before moving onto Step 3 for 3–4 weeks.

How quickly the patient moves through the program will vary depending on individual response, and maintaining or increasing the dose may be necessary if abstinence is not maintained or if withdrawal symptoms are experienced.

The treatment duration is about 3 months but may vary as a function of individual response. Intermittent dosing products (such as Nicotinell Gum) may be used beyond 3 months if

necessary, but those using NRT for more than 9 months should seek advice from a healthcare professional.

Nicotinell Pre-Quit patch therapy

For smokers of 20 or more cigarettes a day who choose to smoke while preparing to quit, Nicotinell Patch Step 1 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 and continue their quit attempt using Nicotinell Patch Step 1, 2, then 3 (see directions for Abrupt Quit patch therapy).

Combination therapy may also be used once smoking has ceased (see Combination Therapy).

Combination Therapy

If smokers have previously relapsed with use of one form of NRT, Combination Therapy could be beneficial. Smokers who experience breakthrough cravings or have difficulty controlling cravings using a single form of NRT may combine the use of Nicotinell Patch Step 1 with another form of NRT such as Nicotinell Gum 2 mg. Nicotinell Gum 4 mg should not be used with Nicotinell Patch.

When using Nicotinell Patch Step 1 in addition of Nicotinell Gum 2 mg, it is recommended that 4–12 pieces of the gum are used each day. Most people will use 5–6 pieces. Do not exceed 12 pieces a day.

Combination Therapy should be used for 12 weeks, after which one of the two following programs should be followed:

1. Stop use of Nicotinell Patch and gradually reduce the number of gums used until they are no longer needed.
2. Continue with Nicotinell Patch Step 2 for 3–4 weeks, then Nicotinell Patch Step 3 for a further 3–4 weeks while maintaining the number of Nicotinell Gum 2 mg that is used each day. After use of patches is ceased, gradually reduce the number of gums used until they are no longer needed.

Use in adolescents (12–17 years)

Adolescents aged 12–17 years should only use Nicotinell Patch under the advice of a healthcare professional. Treatment should not exceed 12 weeks without consultation with a healthcare professional, who can reassess the patient for their commitment to quit and the benefits of continued treatment. If treatment is continued, it should not be extended for more than another 4 weeks.

Adolescents aged 12–17 years should not use Combination or Pre-Quit therapy.

Use in children

Do not use in children under 12 years.

4.3 CONTRAINDICATIONS

Nicotinell Patch should not be used by non-smokers, occasional smokers, children under 12 years or those with generalised diseases of the skin which may complicate patch therapy (e.g. psoriasis or chronic dermatitis), or with hypersensitivity to nicotine or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Nicotine is a toxic and addictive drug and milligram doses are potentially fatal if rapidly absorbed. For any smoker, with or without concomitant disease or pregnancy, the risk of NRT in a smoking cessation program should be weighed against the hazard of continued smoking while using Nicotinell and the likelihood of achieving cessation of smoking without NRT.

Any risks that may be associated with NRT are substantially outweighed by the well-established dangers of smoking.

Treatment with Nicotinell Patch should be discontinued if symptoms of nicotine appear. Mild intoxication produces nausea, vomiting, abdominal pain, diarrhoea, headache, sweating, and weakness (see "Section 4.9 Ovedose").

Occasional smokers are not expected to benefit from the use of Nicotinell.

Dependent smokers with a recent myocardial infarction, unstable or worsening angina pectoris including Prinzmetal's angina, severe cardiac arrhythmias, uncontrolled hypertension or recent cerebrovascular accident should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Nicotinell may be considered but as data on safety in these patient groups are limited, initiation should only be under close medical supervision.

Nicotinell should be used with caution in patients with:

- severe hypertension, stable angina pectoris, cerebrovascular disease, occlusive peripheral arterial disease, heart failure,
- diabetes mellitus, hyperthyroidism or pheochromocytoma,
- moderate to severe hepatic and/or severe renal impairment.

Smokers with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when NRT is initiated because catecholamine release can affect carbohydrate metabolism and vasoconstriction may delay or reduce insulin absorption.

Nicotinell Patch should be used with caution in patients who are susceptible to angioedema and/or urticaria. Patients with generalised dermatological disorders such as psoriasis or chronic dermatitis should not use the patch (See Section 4.3 Contraindications).

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

In the event of a severe or persistent skin reaction, discontinue treatment and use another pharmaceutical form.

The Nicotinell Patch contains aluminium. The patch should therefore be removed prior to undergoing any MRI (Magnetic Resonance Imaging) procedures.

Nicotine transferred dependence can occur.

Use in the elderly

Experience in the use of Nicotinell Patch in smokers over the age of 65 years is limited.

Paediatric use

Data on the use of NRT in adolescents under the age of 18 years are limited.

NRT should only be used in adolescents 12–17 years after consultation with a healthcare professional and use should be restricted to 12 weeks. If treatment is required for longer than 12 weeks, this should be discussed with a healthcare professional. Do not use in children under 12 years.

Effects on laboratory tests

No data available.

Danger in small children

Nicotine is a toxic substance. Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal. Even used nicotine patches contain enough residual nicotine to be harmful to children. Nicotinell must be kept out of the reach and sight of children. As soon as a patch is removed from the skin, it should be folded firmly in half, with sticky sides together, and disposed of with care.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically-relevant interactions between NRT and other drugs have definitely been established. However, nicotine may enhance the haemodynamic effects of adenosine.

Cessation of smoking, with or without NRT, 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.

Smoking, but not nicotine, is associated with increased CYP1A2, and possibly CYP1A1, activity. After cessation of smoking there may be reduced clearance of substrates for these enzymes and increased plasma levels of some medicinal products. This is of potential clinical importance in products with a narrow therapeutic window e.g. theophylline, ropinirole, clozapine and olanzapine.

Smoking may lead to reduced analgesic effects of opioids (e.g. dextropropoxyphene, pentazocine), reduced diuretic response to furosemide, reduced effect of beta-adrenergic blockers (e.g. propranolol) on blood pressure and heart rate decrease and reduced responder rates in ulcer healing with H₂-antagonists.

Both smoking and nicotine may raise the blood levels of cortisol and catecholamines, i.e. may lead to a reduced effect of nifedipine or adrenergic antagonist, and to an increased effect of adrenergic agonists.

The increased subcutaneous absorption of insulin that occurs upon smoking cessation may necessitate a reduction in insulin dose.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in pregnancy – Pregnancy Category D

Ideally, complete smoking cessation during pregnancy should be achieved without NRT. However, for women unable to quit without pharmacological treatment, NRT may be recommended to assist a quit attempt. Nicotine is harmful to the fetus. However, the risk to the fetus with NRT is probably less than that expected with continued smoking due to:

- Lower maximal plasma concentrations compared with inhaled nicotine, resulting in a nicotine exposure less or not more than that associated with smoking.
- No exposure to polycyclic hydrocarbons and carbon monoxide.

As nicotine does pass to the fetus, the decision to use NRT should be made as early on in pregnancy as possible with the aim of discontinuing after use for 2–3 months.

If NRT is used during pregnancy, intermittent dosing products (Nicotinell Gum) should preferably be used as they usually provide a lower daily dose of nicotine than patches. However, if the woman suffers from nausea and/or vomiting, the patch may be preferred but should be removed before going to bed.

Due to an absence of specific studies, combination therapy with patches and oral forms is not recommended during pregnancy unless the healthcare professional considers it necessary to ensure abstinence.

Use in lactation.

Even at therapeutic doses, nicotine is excreted in breast milk in quantities that may affect the child. Like smoking, NRT should be avoided during breastfeeding. Nicotinell Patch should not be used while breastfeeding. Intermittent NRT products such as Nicotinell Gum may be used. Women should breastfeed just before using the product to allow the time between NRT use and feeding to be as long as possible.

Due to an absence of specific studies, combination therapy with patches and oral forms is not recommended during lactation unless the healthcare professional considers it necessary to ensure abstinence.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

When Nicotinell is used as recommended there are minimal risks for driving vehicles or operating machinery. Nevertheless, one should take into consideration that smoking cessation can cause behavioural changes.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In principle, Nicotinell can cause adverse reactions similar to those associated with nicotine administered by smoking. Since the maximum plasma concentrations of nicotine that are

produced by Nicotinell are lower than those produced by smoking and fluctuate less, nicotine-related adverse reactions occurring during treatment with Nicotinell can be expected to be less marked than during smoking.

Clinical trial experience has shown that skin reactions at the application sites are the most frequent adverse reactions. This led to premature discontinuation of Nicotinell in about 6% of clinical trial participants. These reactions include application site burning, oedema, erythema, irritation, pruritus, rash, urticaria and vesicles. Most of the skin reactions resolved within 48 hours, but in more severe cases the erythema and infiltration lasted from 1–3 weeks. The onset of significant skin reactions occurred between 3 and 8 weeks from the start of therapy.

Upper respiratory tract infection and cough reported as adverse reactions may be linked to a chronic bronchitis induced by long term smoking in the past.

Aphthous stomatitis may develop in connection with smoking cessation, but any relation with the nicotine treatment is unclear.

Adverse reactions (from both clinical and post-marketing experience) are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), or not known (can not to be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| SYSTEM ORGAN CLASS | VERY COMMON (≥1/10) | COMMON (≥1/100 to <1/10) | UNCOMMON (≥1/1,000 to <1/100) | RARE (≥1/10,000 to <1/1,000) | NOT KNOWN (cannot be estimated from available data) |
|--|-------------------------------|--|--|--|---|
| Immune system disorders | | | | | Allergic reactions such as urticaria, rash and pruritus; angioedema, anaphylactoid reaction |
| Psychiatric disorders* | | Agitation, anxiety, nervousness, insomnia, abnormal dreams | Disturbance in attention, somnolence, effect lability, irritability, depressed mood, confusional state | | |
| Nervous system disorders* | | Headache, dizziness, motor dysfunction | Paraesthesia, dysgeusia, blurred vision | Tremor | |
| Cardiac disorders | | | Palpitations | Chest pain, dyspnea, arrhythmia | |
| Vascular disorders | | | Hypertension, hot flush | | |
| Respiratory, thoracic and mediastinal disorders | | Cough | Upper respiratory tract infection | | |
| Gastrointestinal disorders* | | Nausea, abdominal pain, dyspepsia | Vomiting, constipation, diarrhoea, flatulence, dry mouth | | |
| Skin and subcutaneous tissue disorders | | | Hyperhidrosis | Skin discoloration, cutaneous vasculitis | |
| Musculoskeletal, connective tissue and bone disorders | | Myalgia, arthritis | Arthralgia, muscle cramp, back pain | | |
| General disorders and administration site conditions | Application site reactions | | Asthenic conditions, pain, discomfort | | |

*Symptoms may also be ascribed to withdrawal symptoms in connection with smoking cessation and may be due to insufficient replacement of nicotine.

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.

4.9 OVERDOSE

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

The acute lethal oral dose of nicotine in a non-smoker is about 0.5–0.75 mg per kg body weight, corresponding in an adult to 40–60 mg. Even small quantities of nicotine are dangerous in children, and may result in severe symptoms of poisoning which may prove fatal. If poisoning is suspected in a child, a doctor must be consulted immediately.

Overdose with Nicotinell Patch may occur when many patches are applied simultaneously on the skin.

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

Treatment

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or 0800 764 766 (New Zealand). Treatment of overdose should be immediate as symptoms may develop rapidly. Immediately discontinue nicotine administration and institute symptomatic treatment. Monitor vital signs.

Overdose from topical exposure

In the case of an overdose from topical exposure, the patch should be removed immediately. 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 blood stream for several hours after removal of the patch from a depot of nicotine in the skin.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Nicotine acts primarily on cholinergic receptors of the nicotine type in the peripheral and in the central nervous system. Nicotine, the chief alkaloid in tobacco products, bind 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.

Nicotine, the primary alkaloid in tobacco products and a naturally occurring autonomous substance, is a nicotine receptor agonist in the peripheral and central nervous systems. On consumption of tobacco products, nicotine has proven to be addictive.

Quitting smoking abruptly after prolonged, daily consumption induces a withdrawal syndrome consisting of at least four of the following symptoms: dysphoria or depressive mood, insomnia, irritability, feelings of frustration or anger, anxiety, difficulty concentrating, agitation or impatience, slowed cardiac rhythm, increased appetite and weight gain. The craving for nicotine is considered as a recognized clinical symptom of the withdrawal syndrome.

Clinical trials have shown that nicotine replacement therapy (NRT) may help smokers refrain from smoking or reduce their smoking habits by decreasing the withdrawal symptoms.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Nicotine is readily absorbed through the skin into the systemic circulation.

The absorption profile after single application of Nicotinell Patch to healthy abstinent smokers (patients undergoing a course of smoking cessation therapy with the patch) shows an initial 1-2 hours delay followed by a progressive rise in plasma concentrations, plateaus being attained at about 8-10 hours after application.

After the patch is removed, plasma concentrations decline more slowly than would be predicted by the 2-hour elimination half-life for this agent after an intravenous infusion.

About 10% of the total amount of nicotine that reaches the circulation is delivered from the skin after Nicotinell Patch is removed. This is likely due to the existence of a cutaneous deposit of nicotine. The absolute bioavailability of the patch, compared to intravenous nicotine perfusion, is about 77%.

The area under the plasma concentration curve (0-24h) increases in proportion to the dose of nicotine delivered by the patches: Nicotinell Patch 7 mg, 14 mg and 21 mg per 24 h. With repeated application of the patches 14 mg/24 h and 21 mg/24 h, the mean plasma concentration at steady state ranges from 7.1–12.0 ng/mL and 10.3–17.7 ng/mL, respectively.

Distribution

Nicotine is distributed widely in the body with a volume of distribution of approximately 2–3 L/kg following intravenous (IV) administration. It crosses the blood-brain barrier and the placenta. Plasma protein binding of nicotine is negligible, less than 5%. Therefore changes in nicotine binding from use of concomitant drugs or alternations of plasma proteins by disease states would not be expected to have significant consequences.

Metabolism

Nicotine is metabolised mainly in the liver to cotinine and nicotine-N-oxide. 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 15–20 hours and concentrations that exceed nicotine by tenfold. The kidneys and lungs also metabolise nicotine.

Excretion

Nicotine and its metabolites are excreted in the urine. 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. Renal excretion of unchanged nicotine is pH-dependent and minimal under alkaline conditions.

Nicotine is excreted in breast milk.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Animal experiments have shown that nicotine induces post-implantation loss and may reduce the growth of fetuses.

Studies have shown a decrease in litter size in female rats treated with nicotine during gestation. Nicotine reduced fertility in male rats.

Carcinogenicity

The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

Nicotinell Step 1 contain 52.5 mg nicotine with a 30cm² release area; release rate 21 mg/24 h (approx); branding EME.

Nicotinell Step 2 contain 35 mg nicotine with a 20cm² release area; release rate 14 mg/24 h (approx); branding FEF.

Nicotinell Step 3 contain 17.5 mg nicotine with a 10cm² release area; release rate 7 mg/24 h (approx); branding CWC.

All three presentations are round with a yellowish-ochre backing foil. Each patch is packaged individually in a heat sealed multilaminar sachet. All presentations contain information on Nicotinell and how to use it. They are available in boxes of 3, 7, 14, 21, 28 or 35 patches (not all pack sizes may be marketed)

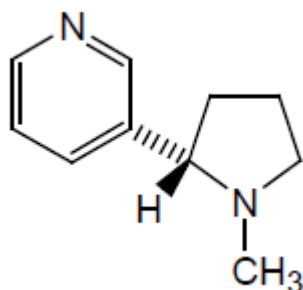
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Remove used patch, fold it in half, sticky side inwards, replace in the original sachet and discard of carefully, keeping it out of reach of children or pets.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical name: S-3-(1-methyl-2-pyrrolidinyl) pyridine

Molecular formula: C₁₄H₁₆N₂

Molecular weight: 162.26

CAS number

54-11-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled.

8 SPONSOR

Perrigo Australia
25-29 Delawney Street,
WA, 6021, Australia
Contact: 1800 805 546

9 DATE OF FIRST APPROVAL

23 April 1993

10 DATE OF REVISION

15 November 2018

SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|------------------------|--|
| N/A | PI reformatted to align with new form. |
| 4.4 | Additional warnings added. |