Public Assessment Report

UK PAR

NICORETTE INVISI 10 MG PATCH
NICORETTE INVISI 15 MG PATCH
NICORETTE INVISI 25 MG PATCH

(Nicotine)

UK Licence No: PL 15513/0159-0161

McNeil Products Limited
LAY SUMMARY

Nicorette invisi 10 mg patch
Nicorette invisi 15 mg patch
Nicorette invisi 25 mg patch

(Nicotine)

The products may be referred to as ‘Nicorette invisi patch’ or ‘Nicorette invisi patches’ in this report.

This is a summary of the Public Assessment Report (PAR) for Nicorette invisi 10 mg, 15 mg and 25 mg patches (PL 15513/0159-0161). It explains how the applications for Nicorette invisi patches were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Nicorette invisi patches.

For practical information about using Nicorette invisi patches, patients should read the package leaflet or contact their doctor or pharmacist.

What are Nicorette invisi patches and what are they used for?
Nicorette invisi patches are a nicotine replacement therapy (NRT).

Nicorette invisi patches are used to relieve and/or prevent withdrawal symptoms and reduce the cravings a patient gets when he/she tries to stop smoking or when cutting down the number of cigarettes he/she smokes.

Ideally, the patient should always aim to stop smoking. The patient can achieve the aim to stop smoking by using the patches to completely replace all his/her cigarettes.

However, Nicorette invisi patches can also be used in other ways:
- if the patient feels unable to stop smoking completely, or wishes to increase the time to his/her next cigarette with the intention of cutting down the number of cigarettes he/she smokes.
- at those times when a patient cannot or does not want to smoke. For example, where a patient does not want to smoke and avoid harm to others e.g. children or family.
- for prolonged periods (greater than 16 hours) where smoking cigarettes is not allowed e.g. aeroplanes, work and social occasions.

Nicorette invisi patches may also help increase a patient’s motivation to quit.

When making a quit attempt, a behavioural support programme will increase a patient’s chances of success. Details of the behavioural support programme Nicorette ActiveStop are available in the package leaflet.

How do Nicorette invisi patches work?
The active substance in Nicorette invisi patches is nicotine.

When a patient stops smoking or cuts down the number of cigarettes he/she smokes, the body misses the nicotine that the patient has been absorbing. The patient may experience unpleasant feelings and a strong desire to smoke (craving). This indicates that the patient is dependent on nicotine. When a Nicorette invisi patch is applied to the skin, nicotine is released and passes into the body through the skin. The nicotine released is sufficient to relieve the unpleasant nicotine withdrawal symptoms. It will also help to stop the patient’s craving to smoke, but will not give the “buzz” the patient gets from smoking a cigarette.
How are Nicorette invisi patches used?
The patient should follow the instructions for use provided in the package leaflet.

Nicorette invisi patches are available in three strengths:

Each Nicorette invisi 25 mg patch releases 25 milligrams of nicotine, the active ingredient, over 16 hours.

Each Nicorette invisi 15 mg patch: Each patch releases 15 milligrams of nicotine, the active ingredient, over 16 hours.

Each Nicorette invisi 10 mg patch: Each patch releases 10 milligrams of nicotine, the active ingredient, over 16 hours

Nicorette invisi patches are applied to a completely clean, dry area of hairless skin on the front or side of the chest, upper arm or hip.

The patient should:
- avoid placing the patch onto any area of skin that is red, cut or irritated.
- not apply oil or talcum powder to the skin before putting on the patch as this may prevent it from sticking properly.

It is important that the patient does not use the same area on two consecutive days to help avoid irritating that site.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Nicorette invisi patches are obtained without a prescription, at pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist.

What benefits of Nicorette invisi patches have been shown in studies?
The Marketing Authorisation Holder (MAH; McNeil Products Limited), provided its own data on efficacy and safety studies. These studies have shown that Nicorette invisi patches are effective in the proposed indications.

In addition, the MAH (McNeil Products Limited) has provided data from the published literature on nicotine.

What are the possible side effects of Nicorette invisi patches?
Like all medicines, Nicorette invisi patches can cause side effects although not everybody gets them. As many of the effects are due to nicotine, they can also occur when nicotine is obtained by smoking.

Effects related to stopping smoking (nicotine withdrawal)
The patient may experience unwanted effects because by stopping smoking the patient reduces the amount of nicotine he/she is taking. These effects may also be experienced if the patient under uses Nicorette invisi patches before he/she is ready to reduce his/her nicotine intake.

These effects include:
- irritability or aggression
- feeling low
- anxiety
- restlessness
- poor concentration
- increased appetite or weight gain
- urges to smoke (craving)
- night time awakening or sleep disturbance
- lowering of heart rate

**Effects of too much nicotine**
The patient may also get these effects if he/she is not used to inhaling tobacco smoke.

**These effects include:**
- feeling faint
- feeling sick (nausea)
- headache

**Side-effects of Nicorette invisi patches**
When Nicorette invisi patch is used for the first time it may cause a mild skin reaction. This is usually redness or itching of the skin where the patch has been. This will usually disappear after a few days. Rarely the reaction may persist or if there is a more severe skin reaction, the patient should stop using the patches and consult a doctor, nurse or pharmacist.

If the patient notices any of the following allergic reactions (swelling of the mouth, lips, throat and tongue, itching of the skin, swelling of the skin, ulceration and inflammation of the lining of the mouth) stop taking Nicorette invisi patch and contact a doctor immediately.

**Very common side-effects:**
*(may affect more than 1 in 10 people)*
itching – this usually disappears within a few days

**Common side-effects:**
*(may affect up to 1 in 10 people)*
headache
dizziness
feeling sick (nausea)
sickness (vomiting)
hives (urticaria) or rash

For the full list of all side effects reported with Nicorette invisi patches, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why are Nicorette invisi patches approved?**
It was concluded that, in accordance with EU requirements that, for Nicorette invisi patches, the benefits are greater than its risks and it was recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Nicorette invisi patches?**
Safety information has been included in the Summaries of Product Characteristics and the package leaflet for Nicorette invisi patches, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.
Other information about Nicorette invisi patches.
Marketing Authorisations for Nicorette invisi patches (PL 15513/0159-0161) were granted in the UK to McNeil Products Limited on 02 December 2008.

The full PAR for Nicorette invisi patches follows this summary.

For more information about treatment with Nicorette invisi patches, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2016.
SCIENTIFIC DISCUSSION

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Scientific Discussion

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Nicorette invisi 10 mg, 15 mg and 25 mg patches to McNeil Products Limited on 2 December 2008. This medicine is on the general sales list (GSL) which means that it is available from both pharmacies and non-pharmacy outlets without prescription.

These are abridged, complex applications for transdermal patches containing 10mg, 15mg and 25mg of nicotine. These applications have been made under Article 8(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. This concerns line extensions to existing marketing authorisations granted to Pharmacia Limited for 10mg and 15mg Nicorette Transdermal Patches (PL 00032/0293-4). These applications are supported by a full file with literature to demonstrate well established use and comparative bioavailability with Nicorette Transdermal Patches. The legal basis of the file is the same as that for Nicorette Transdermal Patches and, as a line extension, cross refers to the same toxicology data.

These new Nicorette invisi patches have been developed from the currently licensed nicotine patches (Nicorette 5, 10 and 15mg transdermal patches) to:
- Reduce the area size of the patch to improve patient acceptability.
- To enable the new, higher strength of 25 mg on a reasonable patch area size.
- To improve nicotine utilization (increased proportion of bioavailable nicotine versus that contained in the patch).
- To introduce a translucent backing layer for a more discreet patch and better consumer compliance.

These products are used for the relief of nicotine withdrawal symptoms as an aid to smoking cessation in adults and children over 12 years of age.

II. QUALITY ASPECTS
ACTIVE SUBSTANCE
Nicotine
Ph. Eur. name:       Nicotine
Chemical name:      3-[(2S)-1-methylpyrrolidin-2-yl] pyridine
CAS Registry No: 54-11-5
Structural formula:

![Nicotine Structural Formula]

Molecular formula: C_{10}H_{14}N_{2}
Rel. molecular mass: 162.2
Chirality: Nicotine possesses one chiral centre at the pyrrole carbon attached to the pyridine. The drug substance is the S-(−)-isomer.

Nicotine is a colourless or brownish viscous liquid which is volatile and hygroscopic. It is soluble in water and miscible with ethanol.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active nicotine is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated, supporting the retest period and storage instructions.

**DRUG PRODUCT**

**Description and composition of the drug product**

The drug product is a transdermal patch containing nicotine. It is presented in three dosage strengths (10, 15 and 25 mg) with proportional nominal areas (9.0, 13.5 and 22.5 cm², respectively) and should be worn for 16 hours. This corresponds to a total amount of nicotine of 15.75, 23.62 and 39.37 mg per patch for the 10, 15 and 25 mg patches, respectively.

Other ingredients are medium-chain triglycerides, basic butylated methacrylate copolymer, polyethylenterephthalate film (PET), the acrylate matrix (comprising of acrylic adhesive solution, potassium hydroxide, croscarmellose sodium and aluminium acetylacetonate), the release liner (single side aluminium polyethylenterephthalate (PET) film, both sides siliconised) and printing ink solution (comprising of blending varnish, beige printing ink and brown printing ink).

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of polyethylenterephthalate film, acrylic adhesive solution, aluminium acetylacetonate, aluminium polyethylenterephthalate (PET) film (both sides siliconised), blending varnish, beige printing ink and brown printing ink, which are controlled by in-house specifications (in the absence of a Ph Eur monograph, this is acceptable). Satisfactory certificates of analysis have been provided for all excipients.

No excipients of human or animal origin are used to make this product.

No overages or novel excipients are used for this product.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

**Control of finished product**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

Each patch is packed in a heat-sealed laminate pouch consisting of paper, PET film and aluminium acrylnitrilecopolymer. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The 10 mg and 15 mg patches come in packets of 7 and 14 and the 25 mg patches come in packages of 2, 7 and 14. Not all pack sizes may be marketed.
Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set, which is satisfactory when the storage precaution “Do not store above 25° C” is applied.

Bioequivalence/bioavailability
A study was carried out comparing the proposed product (Nicorette invisi patches) to the reference product (Nicorette Transdermal Patches). This study confirmed bioequivalence between the two products.

Product literature
All product literature (SPC, PILs and labelling) are satisfactory.

Overall conclusions on quality
These products are satisfactory and Marketing Authorisations may be granted.

III. NON CLINICAL ASPECTS
INTRODUCTION
Original Nicorette Transdermal Patches are available in dosage strengths of 5, 10 and 15 mg and the nominal areas are 10, 20 and 30 cm², respectively, containing 0.83 mg nicotine per cm². The proposed products are semi-transparent, beige rectangular patches with nominal areas of 9.0, 13.5 and 22.5 cm² for the 10 mg, 15 mg and 25 mg strengths, respectively, containing 1.75 mg nicotine per cm². The dosage strengths for both the proposed Nicorette invisi patches and current Nicorette Transdermal Patches refer to the amount of nicotine that is absorbed systemically during a 16-hour period.

The proposed products represent a change in formulation to the existing transdermal patches. Furthermore, the 25 mg strength patch is also a new strength.

The active ingredient in both the originator product and the Nicorette invisi patch is identical and, therefore, cross refers to the same toxicological data. These data will not be reassessed here, although they will provide a basis on which to bridge and compare the results of the studies using the proposed products. The main non-clinical concerns for the proposed products are the toxicological implications of the increase in nicotine concentration (mg/cm²), a higher starting dose and the safety of the related substances and residual solvents in the products’ formulations.

GLP ASPECTS
The bridging non-clinical studies were conducted in accordance with GLP regulations. Reference is made to published data in the Non-Clinical Overview and it is presumed that these studies were conducted in compliance with the standards prevailing at that time.

PHARMACODYNAMICS
Nicotine is an agonist at both peripheral and central nervous system receptors with a well-established pharmacology, including adrenergic and cholinergic autonomic effects. The pharmacodynamic effects of nicotine have been well-documented in published literature. Based on the available data and established clinical experience with similar nicotine replacement therapy products, the pharmacological profile of nicotine, when used in a controlled manner, is well characterised and hence further studies have not been submitted nor are required.

PHARMACOKINETICS
The applicant has submitted several reviews that include information deemed relevant to these applications. No new non-clinical pharmacokinetic (Pk) studies with the Nicorette invisi patch formulations have been performed. This is acceptable since such data have been superseded by clinical Pk data. Results submitted from clinical biopharmaceutical studies have demonstrated Pk linearity over
the therapeutic dose range for both Nicorette invisi patches and the original Nicorette Patches. Furthermore, the two formulations were proven to be bioequivalent (refer to the Section IV, Clinical Aspects for further details). Given that the new, higher-dose patch is bioequivalent to the existing patch (bioequivalence established between Nicorette invisi 25 mg patch and the original patch via simultaneous use of one 10 mg plus one 15 mg patch), there are no concerns regarding safety and there is no need to justify the higher dose strength using non-clinical toxicity data as it is within the dose range in the currently approved SPC.

The absorption, distribution, metabolism and excretion profiles of nicotine are well known and will not be re-assessed here. Since comparable clinical plasma concentrations are achieved following administration of the Nicorette invisi patch in comparison to the original product, it is acceptable to cross refer to the pharmaco-toxicological data previously assessed for the Nicorette Patch.

With respect to the Pk profile of the ‘more pharmacologically active’ (s)-isomer of nicotine, the applicant has referred to published scientific literature results. Investigations (non-GLP) in dogs and rabbits have demonstrated that both (r)- and (s)-nicotine are rapidly metabolised and have similar disposition kinetics, although the metabolism of the (r)-isomer is slightly faster than that of the (s)-isomer in dogs. Following i.v. administration, higher mean plasma levels were recorded initially for the (s)-isomer but levels were comparable after several minutes. This was attributed to the smaller volume of distribution of (s)-nicotine. In rabbits, conversion to the predominant metabolite cotinine (fractional turnover ~0.5) was similar for both enantiomers (Jacob et al. 1988).

From a non-clinical point of view, the SPC sections 5.1 and 5.2 are satisfactory.

TOXICOLOGY
The non-clinical safety studies on the Nicorette Transdermal Patches have been submitted previously and give background safety data on single- and repeat-dose toxicity, skin irritation and sensitization. These data are included again to support the current application but will not be re-assessed here, although they will provide a basis on which to bridge and compare the results of the studies using the Nicorette invisi patches.

From the original studies, single-dose data in rats show a margin of safety of approximately 10 times the proposed higher clinical dose. Repeat-dose data in dogs show a margin of safety of approximately 4 times the higher strength clinical dose. A large clinical trial in over 3000 subjects showed an acceptable clinical safety profile for the 25mg strength dose and is discussed in the clinical assessment.

No new single dose toxicity studies, repeated dose toxicity studies, genotoxicity studies, carcinogenicity studies or reproductive and developmental toxicity studies were carried out, and none were needed.

**Local tolerance**

**Irritancy studies**
Primary skin irritation studies in rabbits were performed to support the approval of the original formulation: Nicorette patches. Investigations in rabbits included effects of percutaneous administration of Nicorette patches (8.3 mg) versus placebo formulations (tolerance scale (TS) 10); Nicorette patches (5 mg) versus degraded Nicorette patches (5 mg) on intact or abraded sites (TS 11); repeated application (24 h/day for 28 days) of Nicorette patches (5 mg) on intact or abraded skin (TS 12) and the application of occluded nicotine solution (0 - 15%) on shaved or depilated skin (TS 13).

Single application of nicotine patches was associated with absent to well-defined erythema (reversible). Findings were comparable in placebo treatment groups. Notable dermal effects reported in the cumulative irritation study were very slight to moderate-severe erythema and slight oedema. Effects were not exacerbated by prior skin abrasion. Similarly, degraded Nicorette patches did not exacerbate local effects seen with Nicorette patches administered to intact or abraded skin (slight erythema and oedema). Shaved skin proved less sensitive to nicotine solution than depilated skin. A 3% solution of
nicotine slightly irritated depilated skin but not shaved skin. Necrosis was evident when solution of 12% concentration was applied to depilated skin.

A primary skin irritation study (TS 14) in rabbits with Nicorette invisi patches (7.3 mg) did not reveal any erythema or oedema for up to 168 hours following percutaneous administration (24 h). Furthermore, no systemic toxicity was observed and no macro / microscopic pathological findings reported.

A comparative investigation (TS 15) into the effects of repeated percutaneous administration (15 mg for 23 h/day) of Nicorette invisi patch (test), Nicorette (reference) and placebo formulations for 5 days (15mg nicotine/day) was scheduled in rabbits. Severe dermal irritation in one animal in each nicotine treatment group limited the study to two applications of nicotine due to animal welfare concerns. Reported findings were moderate to severe erythema and very slight to slight oedema (test); well-defined to moderate erythema and very slight to moderate oedema (reference). Placebo tests sites exhibited very slight to well defined erythema and very slight oedema.

Although study TS15 was terminated early, the reasons for this are justified. Reported levels of irritancy were comparable for the reference and proposed products and findings were reversible. Moreover, clinical safety studies demonstrated that Nicorette invisi patches are mild products with comparable cumulative irritation potential to placebo and the reference product.

**Dermal Sensitisation**

Data published in 1986 demonstrated that nicotine solution was not a dermal sensitisier in the Guinea Pig Maximization Study. The original patch has also been tested to determine its potential for delayed-type contact hypersensitivity and the results were published in 1990. No erythema or oedema was reported, hence, it was concluded that Nicorette did not induce delayed-type contact hypersensitivity. The applicant argues that, since nicotine solution and Nicorette are not dermal sensitizers and the excipients of the proposed products are currently commercially available and conform to relevant EU regulatory requirements and / or European Pharmacopoeial standards, no additional animal studies are considered warranted and the findings reported for Nicorette and nicotine solution should apply to the proposed products.

The applicant’s justification can be accepted in relation to the active ingredient, however, from a preclinical perspective, the dermal sensitisation potential of the formulation remains uncertain. The applicant has not presented preclinical data to investigate the hypersensitivity potential of the excipients included in the proposed products, especially when applied under occluded conditions. Compliance of the excipients with EU regulatory standards or relevant pharmacopoeial standards does not negate this fact. However, following a six week clinical investigation into the potential for Nicorette invisi patches to cause contact sensitization, it was concluded that Nicorette invisi 25 mg patches did not cause contact sensitisation. Therefore, these clinical findings supersede the need for further preclinical investigations.

Nicorette patches did not induce erythema, crust formation, oedema or other skin reactions in skin photosensitivity tests. Therefore the applicant argues that the same findings can be applied to the proposed formulation, which contains the same active ingredient and commercially available standardised excipients.

Again, this justification can be accepted for the active ingredient but not the excipients without further data to demonstrate individual qualification of photosensitisation potential. However, the absence of such data can be justified by the fact that the clinical study demonstrated that Nicorette invisi 25 mg patches was not associated with phototoxicity or photoallergenicity. No subject in this study experienced the characteristic crescendo reaction at challenge that is observed in allergic or photoallergic reactions. These clinical findings supersede the need for further preclinical investigations.
Other toxicity studies
No antigenicity, immunotoxicity, dependence or metabolites studies were performed and none were required for these applications.

STUDIES ON IMPURITIES
Drug Substance
Nicotine is described in a Ph. Eur. monograph. The manufacturer holds a Certificate of Suitability (CoS) for nicotine. The CoS demonstrates that the current monograph of Ph. Eur. is suitable to control the quality of nicotine. The limits applied in the drug substance specification are satisfactory from a preclinical point of view.

Excipients
Nicorette invisi patches contain excipients which comply with all relevant and applicable EU and US regulatory requirements and European Pharmacopoeial standards.

Ecotoxicity/environmental risk
These applications are essentially line extensions with a known active substance and, therefore, it is reasonable to conclude that marketing of these products will not change the overall use pattern of the existing market.

OVERALL CONCLUSIONS
These applications are satisfactory from a nonclinical point of view and marketing authorisations may be granted.

IV. CLINICAL ASPECTS
INTRODUCTION AND BACKGROUND
Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, *Nicotiana tabacum* and related species (Solanaceae). Tobacco leaves contain 0.5 to 8% nicotine combined as malate or citrate.

Nicotine is readily absorbed through mucous membranes and the skin; the bioavailability of oral nicotine is low due to extensive first pass metabolism. Nicotine is widely distributed; it crosses the blood brain barrier and the placenta and is found in breast milk. The elimination half life is about 1 to 2 hours. Nicotine is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP2A6 to cotine and nicotine-N-oxide. Nicotine and its metabolites are excreted in urine.

INDICATIONS
The applicant has submitted the following:

“Nicorette Patch is indicated for the relief of nicotine withdrawal symptoms as an aid to smoking cessation in adults and children over 12 years of age.
If possible, Nicorette Patch should be used in conjunction with a behavioural support programme.”

This is consistent with the indications of the original product and are, therefore, satisfactory.

DOSE & DOSE SCHEDULE
The proposed posology is consistent with that detailed in the SPC of the parent product and is in line with current guidelines. It is, therefore, acceptable.

CLINICAL PHARMACOLOGY
To support the application, the applicant has submitted three biopharmaceutical studies (note, in the following figures the abbreviation NNTP indicates Nicorette invisi patches as they were originally referred to as new nicotine transdermal patches).
(1) Open label, single dose, randomized, crossover study in 12 healthy smokers comparing nicotine delivery from ten different sized nicotine patch formulations. The study was designed to define the surface areas of the Nicorette invisi patch that would correspond to the amount of nicotine delivered by the three strengths of the reference product.

Study protocol
Twelve healthy smokers, five male and seven female, aged 21-44 years, who had smoked more that 15 cigarettes per day for more than 1 year were included in this study. Each subject wore one of 10 nicotine patches for 16 hours. A randomisation scheme was included in the report.

The dose of nicotine released from the patches was calculated as the amount of nicotine in unused patches minus the residual amount of nicotine in each used patch. The amount of nicotine released from the patches was plotted against patch area for the Nicorette patches and the Nicorette invisi patches separately. For each patch, a linear regression analysis was performed to evaluate the relationship between the amount of nicotine released and patch area.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nicorette (patch area – cm²)</th>
<th>Treatment</th>
<th>NNTP (patch area – cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>mean</td>
<td>9.8</td>
<td>15.9</td>
<td>25.7</td>
</tr>
<tr>
<td>median</td>
<td>9.9</td>
<td>15.6</td>
<td>25.9</td>
</tr>
<tr>
<td>stdev</td>
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<td>1.2</td>
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</tr>
<tr>
<td>min</td>
<td>7.9</td>
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<tr>
<td>max</td>
<td>11.3</td>
<td>17.9</td>
<td>29.2</td>
</tr>
</tbody>
</table>

There was a linear relationship between the amount of nicotine released and patch area for both types of patch. A linear regression equation calculated for the released amount of nicotine versus patch area demonstrated that the Nicorette invisi patch areas corresponding to Nicorette patch delivering 10, 15 and 25mg/16 hours were 10.1cm², 15.9 cm² and 27.3 cm², respectively.

(2) An open label, single dose, randomized, crossover study to demonstrate the linear pharmacokinetics of nicotine following application of the Nicorette invisi patch and the reference Nicorette patch. This study compared the relationship between dose, rate and extent of nicotine absorption between the NNTP and the Nicorette reference patch.

Study protocol
Eighteen healthy smokers, eight male and 10 female, aged 21-50 years, who smoked more than 15 cigarettes per day were included in this study. Three subjects withdrew their consent. Each subject received nicotine from one of six nicotine patches.

Blood samples were taken by non smoking personnel at pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 17, 20, 22, 24, 26 and 28 hours after administration of the products. There then followed a 48 hour washout period before cross over and repeat. Blood samples were analysed for nicotine concentrations by LC/MS/MS. The LOQ was 0.5ng/ml. AUC₁₆, AUC₂₄, AUC₀₋₉₉₉, Cmax, tmax and t½ were calculated according to normal standard procedures.

The nicotine dose was calculated by measuring the residual nicotine in the used patches as before. A linear model was applied to the data:
There was a linear relationship between released amount of nicotine and patch area for both formulations. There was also a strong linear relationship between dose and AUC\(_{(16)}/AUC\(_{(24)}/AUC\(_{(0-\text{inf})}/C_{\text{max}}\), indicating linear pharmacokinetics over the therapeutic dose range, as well as the entire dose range.

(3) Open label, randomised, two-period, single dose, cross-over, bioequivalence study comparing the test 25mg/16h Nicorette invisi patch versus reference 25mg/16h Nicorette patch.
Study protocol
Thirty healthy smokers, 17 male and 13 female, aged 22-46 years, who smoked more than 15 cigarettes per day were included in this study. Each subject received a 25mg/16h nicotine dose of one of two nicotine formulations.

The formulations were given following a controlled period of exclusion from any nicotine intake from 24 hours pre dose. Blood samples were taken at pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 17, 20, 22, 24, 26 and 28 hours after administration of the products. There then followed a 48 hour washout period before cross over and repeat.

The method of analysis was gas chromatography. The LOQ for nicotine was 0.5ng/ml. AUC(0-t.), AUC(0-inf), Cmax, tmax and t½ were calculated according to normal standard procedures.

Statistical evaluation was performed for AUC(0-t), AUCinf and Cmax with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric mean (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>1.10 ( 1.02 – 1.19 )</td>
</tr>
<tr>
<td>AUCt</td>
<td>0.99 ( 0.92 – 1.07 )</td>
</tr>
<tr>
<td>AUCinf</td>
<td>0.99 ( 0.92 – 1.08 )</td>
</tr>
</tbody>
</table>

Two subjects were excluded from analysis due to baseline plasma nicotine concentrations >5ng/ml. There were no serious adverse events recorded.

Conclusion The applicant’s claim of bioequivalence between Nicorette invisi patch 25mg/16h and Nicorette Patch 25mg/h is endorsed. The applicant has demonstrated linear pharmacokinetics over the therapeutic dose range and for each formulation, therefore, no further studies are required at the lower dose strengths.

EFFICACY
The applicant has submitted a clinical efficacy study to support the use of a higher strength patch than previously available.

A placebo controlled, double blind, randomised study in smoking cessation using 16 hour transdermal patch.

Study protocol
The study was a double-blind randomised placebo controlled trial with five parallel treatment groups: 25mg/16hours during 22 weeks; 25mg/16hours during 8 weeks; 15mg/16hours during 22 weeks; 15mg/16hours during 8 weeks and placebo. All treatment groups had an additional 4 weeks tapering period.

Objectives
- To confirm existing evidence that treatment with nicotine patches is effective in helping motivated smokers to quit.
- To investigate whether a 25mg nicotine patch dose applied daily for 16 hours was more effective than a 15mg patch dose applied daily for 16 hours.
- To investigate whether 22 weeks of full dose daily treatment, at each dose specified, gave a better result than eight weeks of full dose daily treatment.
- To measure frequency of side effects.
- To define characteristics of subjects who are most likely to benefit from the nicotine treatment.
Study Population
A total of 3575 subjects (1723 female, 1852 male) were included in the study. Thirty-three centres enrolled 100 subjects, three other centres enrolled 99, 96 and 80 in total. The inclusion criteria were as follows:
- Men or women aged 20-70 years.
- Smokers of more than 15 cigarettes per day.
- Smoking duration more than 3 years.
- Having tried to give up smoking at least once before.
- Personally motivated to stop smoking and indicating a willingness to follow through with the protocol, including follow up visits even if relapsing.

The exclusion criteria were:
- Myocardial infarction within the last three months.
- Pregnancy or nursing.
- Under psychiatric care or medication.
- Alcohol or any other drug problem.
- Use of any form of smokeless tobacco.
- Use of any NRT or other smoking cessation programme in the previous 6 months.
- Generalised chronic dermatological disorder.
- Severe COPD (FEV1 < 60% predicted).
- Severe cardiac arrhythmia.
- Unstable angina.

Subjects could withdraw voluntarily, or be removed if the investigator felt it to be medically necessary. Subjects who did not return for follow up or who continued to smoke were withdrawn. Subjects giving a CO reading of 10ppm or more in exhaled air after week two were to be considered for exclusion.

Subjects were randomised into one of the five treatment groups. The 25mg groups were weaned during two weeks on 15mg and two weeks on 10mg nicotine patches. The 15mg group were weaned during four weeks on 10mg patches.

No differences were seen between the treatment groups at baseline for the main demographic and baseline smoking parameters.

Study treatments
Treatments consisted of 25mg or 15mg nicotine patch treatments or placebo for eight or 22 weeks. The patches were applied to either the arm or hip in the morning and removed at bedtime. The active treatment period was followed off by a tapering period of four weeks.

Subjects randomised to 25mg wore two patches, one 15mg and one 10mg. The 15mg active group wore one 15mg and one placebo of the 10mg size. The placebo patches did not contain any nicotine but were otherwise identical in terms of sizes and appearance.

Study visits occurred on eight occasions during the 6 month trial and follow-ups at 12, 18 and 24 months from the start of the study.

Primary endpoints
The following main definition for success was used:

1. Continuous self reported complete abstinence from two weeks after quit day until 12 months, together with a carbon monoxide measurement of less than 10ppm.
Secondary endpoints
1. No smoking from entry to end point and a carbon monoxide measurement of less than 10ppm from visit two until endpoint.

2. Long term success, no smoking and a carbon monoxide measurement of less than 10ppm at visits six and twelve months.

3. Carbon monoxide of less than 10ppm at visit three and later, but occasional smoking allowed.

Randomisation
Subjects were allocated a number and treatment following a randomisation list drawn up by the sponsor under supervision of a committee member, using a computer programme. Randomisation was performed by centre to avoid skewness. Each individual received a sealed randomisation envelope to be held by the investigators, returned at the end of the study for checking before evaluation.

Blinding
The active and placebo patches were identical in appearance and packaging. Each package held identical labelling, with the only distinguishing marking being the patient number. The investigators were also blind to the treatment.

Statistical methods (including pre-specified interim analyses or other looks at the data)
Primary analysis was made from an intend-to-treat data set, including all subjects receiving medication. Whenever statistical methods were performed, they were two-tailed and at 5% significance level. The key measure of outcome was the % of subjects successfully abstaining from smoking at different times after the start of the treatment. This outcome was analysed using:

- Simple basic tabulations and success rate plots derived according to the Kaplan-Meier method.
- Logrank tests and associated methods for confidence limit calculations for the comparison of success rate curves, adjusting for such variables as age, sex, centre, cotinine level, etc.
- Proportional hazard modelling, which, in essence, is an extension of the logrank approach to continuous variables.

No adjustment for covariates was made. Influence of baseline factors on the probability of success has been studied in a separate analysis of prognostic factors. Drop outs were handled as an equivalent to resuming smoking, though this may have underestimated the total outcome.

Tabulation of the demographic characteristics of the whole study population with unbroken code was performed during the study and distributed to participating centres. This was not done until after inclusion of the last patient. No interim analyses were performed before the clean file meeting and the subsequent code breaking.

Results
The 12 months outcome in the combined active group was 14.2% vs 9.9% in the placebo group (p=0.0028).

There was no difference between 8 and 22 weeks of full treatment and no evidence of patch dose by duration interaction. No factor predicting better outcome with higher dose was identified.
The 12 month outcome per dose group was:
- 25mg = 15.7%
- 15mg = 12.7%
- Placebo = 9.9%

(25 vs. 15mg p=0.022, 15mg vs. placebo p= 0.047)
There was no difference between 8 and 22 weeks of full treatment and no evidence of patch dose by duration interaction. No factor predicting better outcome with higher dose was identified.
Safety Evaluation
The 1380 subjects exposed to the 25mg patch had a mean treatment duration of 12 weeks, resulting in 314 treatment years. For the 1375 subjects on the 15mg patch, the mean duration of treatment was 11 weeks, resulting in 297 treatment years.

Side effects examined in detail included nightmares/vivid dreams, and the occurrence of mouth ulcers.

Nightmares/ vivid dreams
No increase in the frequency of nightmares occurred between baseline and week one. Thereafter, there did appear to be an increase in the frequency of those reporting at least one episode of a nightmare. However, there does not appear to be a dose relation in this occurrence.
Mouth ulceration

As expected, the frequency of mouth ulceration increased after the smoking cessation attempt, though there was no clear dose relation:

**Table 21a**

Frequencies of vivid dreams at baseline and number of subjects having at least one reported event of vivid dream from baseline to week 1, 2, 4, 8

<table>
<thead>
<tr>
<th>Week</th>
<th>N (25 mg)</th>
<th>% (25 mg)</th>
<th>N (15 mg)</th>
<th>% (15 mg)</th>
<th>N (Placebo)</th>
<th>% (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>262</td>
<td>18</td>
<td>268</td>
<td>19</td>
<td>121</td>
<td>17</td>
</tr>
<tr>
<td>BL - Week 1</td>
<td>281</td>
<td>20</td>
<td>262</td>
<td>18</td>
<td>109</td>
<td>15</td>
</tr>
<tr>
<td>BL - Week 2</td>
<td>459</td>
<td>32</td>
<td>433</td>
<td>30</td>
<td>181</td>
<td>25</td>
</tr>
<tr>
<td>BL - Week 4</td>
<td>579</td>
<td>40</td>
<td>549</td>
<td>38</td>
<td>227</td>
<td>32</td>
</tr>
<tr>
<td>BL - Week 8</td>
<td>646</td>
<td>45</td>
<td>608</td>
<td>42</td>
<td>243</td>
<td>34</td>
</tr>
</tbody>
</table>

**Table 21b**

Frequencies of vivid dreams among complete abstinent subjects from baseline to week 8

<table>
<thead>
<tr>
<th>Week</th>
<th>N (25 mg)</th>
<th>% (25 mg)</th>
<th>N (15 mg)</th>
<th>% (15 mg)</th>
<th>N (Placebo)</th>
<th>% (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL - Week 8</td>
<td>285</td>
<td>48</td>
<td>310</td>
<td>48</td>
<td>70</td>
<td>47</td>
</tr>
</tbody>
</table>

51 (95)
In addition, an open ended question was asked enabling subjects to report any unusual symptoms they had experienced. Here, it was found that a dose dependent difference in nausea and vomiting existed, though no other dose dependent effects were seen. Tachycardia was more frequent in the active groups versus placebo, though there was no difference between 25mg and 15mg strengths.

There were four deaths during the study period, none of which were due to the study medication: two myocardial infarctions; one boating accident; and one cardiac arrhythmia secondary to thyrotoxicosis.

There were four episodes of myocardial infarction, two of which proved fatal.

### Myocardial infarctions

<table>
<thead>
<tr>
<th>Center Code</th>
<th>Subj. No.</th>
<th>Sex</th>
<th>Age</th>
<th>No. of cig/day at enrollment</th>
<th>On study treatment at the event</th>
<th>Event date</th>
<th>Treatment group</th>
<th>Causality (investigators assessment)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF1</td>
<td>730</td>
<td>M</td>
<td>58</td>
<td>45</td>
<td>No (stopped 2.5 months earlier) started smoking</td>
<td>23/7-94</td>
<td>15mg/8w</td>
<td>unlikely</td>
<td>Fatal</td>
</tr>
<tr>
<td>F2</td>
<td>2651</td>
<td>M</td>
<td>50</td>
<td>22</td>
<td>Off treatment since a few weeks</td>
<td>Jan 95</td>
<td>15mg/22w</td>
<td>unlikely</td>
<td>Fatal</td>
</tr>
<tr>
<td>S1</td>
<td>2863</td>
<td>M</td>
<td>59</td>
<td>18</td>
<td>Probably</td>
<td>28/2-94</td>
<td>25mg/22w</td>
<td>-</td>
<td>Fatal</td>
</tr>
</tbody>
</table>

No further serious episodes occurred which could be linked to the study medication.

**Efficacy conclusions**

The active nicotine patch treatment is better than placebo.

Treatment with 25mg nicotine patches is more effective than 15mg patches for smokers who smoke more than 15 cigarettes per day and are motivated to quit. No factor predicting better outcome with higher dose was identified. Treatment duration longer than eight weeks plus four weeks tapering does not improve outcome.

**Conclusion** There would appear to be evidence that the outcome in terms of smoking cessation is improved for those smokers of more than 15 cigarettes per day who use 25mg patches versus those using 15mg. It also would seem apparent that there is no benefit in continuing treatment for longer than eight weeks, plus four weeks tapering. This advice has been incorporated into the Summary of Product Characteristics (SPC) posology appropriately.

**SAFETY**

The applicant has provided four clinical pharmacology studies designed to assess the potential for Nicorette invisi patches to cause skin problems:

1. **A study to assess the potential for Nicorette invisi patches 25mg to cause photoirritancy or photoallergenicity in 42 healthy smokers.** This was a double blind, repeat patch test, placebo controlled, blank controlled, single centre study with randomised assignment of two treatments to two test sites within the respective test zones for induction and challenge.

**Study protocol**

Forty-two healthy smokers, 22 male and 21 female, aged 21-58 years, who smoked more than 10 cigarettes per day and were of skin phototypes I, II or III were included in this study. Each subject wore one of two patches - active or placebo - in one of two test zones of skin for 16 hours, daily for 23 days. The blank area was the area of skin below the patch sites. A randomisation scheme was included in the report. The following formulations were administered:
Test: Transdermal Therapeutic System (TTS) Nicotine 25mg/16h. Patch size 22.5cm²

Placebo: TTS containing all the ingredients of test except nicotine. Patch size 22.5cm²

At Screening I (within 21 days before first application), screening examinations (medical history, physical examination, baseline skin evaluation, skin prototype assessment according to Fitzpatrick classification) were performed. In addition, a urine pregnancy test in women of childbearing potential was performed. The UVB irradiation for minimal erythema dose (MED) determination was performed after Screening I was completed, and eligibility for study participation was verified by the investigator, or his or her designee. The following day (Screening II), 16 to 26 h after MED irradiation, the MED for UVB was determined.

The study was conducted in three phases; two treatment phases and one rest phase. During the first treatment phase of 23 days, the phototoxic potential was assessed and induction for photoallergenicity testing ("Induction Phase") was performed in altogether 15 ambulatory visits. The investigational product was applied six times during 24±2 h to the skin (Visits 1, 5, 7, 9, 11, and 13). After patch removal at Visit 2, the patch test sites were evaluated for skin irritation (local patch tolerability). Thereafter, the test sites (the skin under placebo patch, active patch and a blank (untreated) skin site), were irradiated with 0.5 x MED UVB and 10 J/cm² UVA.

Within 30±5 min after start of irradiation, the test sites were scored for skin irritation for immediate response to UVA. Dermal reading of irradiated areas for determination of phototoxic potential was performed at Visits 3, 4, and 5. Visit 5 marked the end of the photoirritation assessments and the start of the induction phase for photoallergenicity with new patch applications to the same sites as before. At Visits 6, 8, 10, 12, and 14, the patch test sites were evaluated for skin irritation (local patch tolerability) and, thereafter, the three test sites were irradiated with 3 x MED UVB. At Visits 7, 9, 11, 13, and 15, dermal reading of irradiated areas was performed for safety analysis.

The first visit (Visit 16) of the second treatment phase ("Photoallergenicity Challenge Phase") took place at least 14 days after the last irradiation ("Rest Phase"). The subjects received one application of the investigational products, which remained on the skin for 24±2 h. After patch removal and patch test site evaluation (local patch tolerability) at Visit 17, one site each of patched and blank skin was irradiated with 4 J/cm² UVA and with 0.5 x MED UVB. Within 30±5 min after the start of irradiation, the test sites were scored for skin irritation for immediate response to UVA. Dermal reading of irradiated areas for determination of photoallergenicity was performed at Visits 18, 19, and 20 for late response to examine for a ‘crescendo reaction’ (i.e. increase of erythema between 24 and 72 h after irradiation with UVA and UVB).

Before each patch removal, adherence of the patches was evaluated. After each patch removal, the local tolerability of the patches was assessed using skin irritation scores. Immediate response to UVA irradiation was assessed after each UVA irradiation using skin irritation scores.

At Visit 20, after the last evaluation of the dermal reaction, the subjects were discharged from the study. In women of childbearing potential, a urine pregnancy test was performed before discharge.

The duration of the study for each subject was approximately 6 weeks.

The primary endpoints were the cumulative individual irritation scores (IIS). IIS was the combination of the irritation score, rated 0=none to 7=strong, and the superficial effects score, rated A=none to H=petechial erosions or scabs. The alphabetical score was converted to a numerical score A=0, H=7.

For the statistical analysis of the phototoxic potential, CIIS values for the first 72 hours after removal of the first patch were used. For analysis of the photoallergic potential, the CIIS values for the 72 hours following removal of the patch in the challenge phase were used, looking in particular for a
characteristic crescendo reaction at challenge. Differences in CIIS values among test sites were evaluated using a two way ANOVA.

The results were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Active patch</th>
<th>Placebo patch</th>
<th>Blank site</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>41</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.46 (0.67)</td>
<td>1.07 (1.23)</td>
<td>0.73 (1.06)</td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
<td>0-4</td>
<td>0-4</td>
<td>0-4</td>
</tr>
<tr>
<td>90% CI for mean</td>
<td>[0.23-0.69]</td>
<td>[0.75-1.40]</td>
<td>[0.50-1.07]</td>
</tr>
</tbody>
</table>

One subject was excluded from analysis due to incomplete dermal readings as a result of premature withdrawal.

<table>
<thead>
<tr>
<th></th>
<th>Active patch</th>
<th>Placebo patch</th>
<th>Blank site</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>39</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.33 (0.58)</td>
<td>0.51 (0.85)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
<td>0-2</td>
<td>0-3</td>
<td>0-0</td>
</tr>
<tr>
<td>90% CI for mean</td>
<td>[0.16-0.49]</td>
<td>[0.28-0.74]</td>
<td></td>
</tr>
</tbody>
</table>

No subject experienced the characteristic crescendo reaction at challenge that is observed on photoallergic reactions. Three subjects were excluded from analysis due to incomplete dermal readings as a result of premature withdrawal.

The results of this study confirm that the safety profile of Nicorette invisi patches with regards to potential to cause skin problems is reasonable.

(2) Study to assess the potential for Nicorette invisi patches 25mg to cause skin sensitization in healthy smokers. Double blind, multiple dose, within subject comparison, single centre study with randomised assignment of two treatments to two test sites.

Study protocol
Two hundred and fifty-seven healthy smokers, 119 male and 138 female, aged 18-63 years, who smoked more than 10 cigarettes per day and were of skin phototypes I, II or III were included in this study. During the induction phase, each subject wore one of two patches - active or placebo - in one of two test zones of skin for 48 hours (72 hours over the weekends), three times weekly for 3 weeks (nine applications). Skin reactions were observed at baseline and within 15 min of patch removal. There followed a rest phase of 14 days before a challenge phase with application of the patches to new skin sites for 48 hours. Evaluation of the skin reactions was made by a trained and blinded observer at 30min, 24h, 48h and 72h after patch removal. The blank area was the area of skin below the patch sites. A randomisation scheme was included in the report. The following formulations were administered:

Test: Transdermal Therapeutic System (TTS) Nicotine 25mg/16h. Patch size 22.5cm²

Placebo: TTS containing all the ingredients of test except nicotine. Patch size 22.5cm²

The primary endpoints were the cumulative individual irritation scores (CIIS). The CIIS were the combination of the irritation score, rated 0=none to 7= strong, and the superficial effects score, rated A=
none to H= petechial erosions or scabs. The alphabetical score was converted to a numerical score A= 0, H= 7.

Differences of CIIS values among test sites were evaluated using a two way ANOVA.

<table>
<thead>
<tr>
<th>Table 1. Descriptive Statistics of Cumulative Post-baseline Challenge Phase Individual Irritation Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Descriptive Statistics of Average Post-Baseline vs. Baseline Challenge Phase Individual Irritation Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum-Maximum</td>
</tr>
</tbody>
</table>

Of the 257 subjects randomized, 207 completed the entire course of the study and 205 fulfilled the criteria for inclusion into the evaluation of skin sensitization potential. Fifty subjects were withdrawn prematurely, 18 withdrew consent, 17 were noncompliant, eight had poor patch adherence, six withdrew due to adverse events and one had a positive breath alcohol test.

There were no statistically significant differences between treatment groups.

**Assessor’s comment**

These results are satisfactory and display close similarity between treatment and placebo, which is to be expected.

(3) Study to assess the potential for Nicorette invisi patches 15mg to cause skin irritation in healthy smokers. (4) Study to assess the potential for Nicorette invisi patches 25mg to cause skin irritation in healthy smokers. These were double blind, repeat dose, randomised, within subject comparison, single centre studies designed to assess the potential for Nicorette invisi patches to cause skin irritancy in healthy smokers. The studies were identical, except for the treatment regimen.

In Study 3, subjects received Nicorette invisi patches 15mg, matching placebo and Nicorette Patch 15mg. In Study 4, subjects received Nicorette invisi patches 25mg, matching placebo and a positive control: sodium lauryl sulphate 0.1% w/v solution. Each subject was assigned a randomised distribution of the three patches. Each treatment was applied to the same location on a daily basis for a total of 22 days (21 applications). Skin reactions were evaluated approximately 24 hours after each application by a trained investigator.

IIS values were calculated as before. Cumulative Irritation Scores (CIS, the sum of all IIS for all subjects), cumulative irritation scores for 10 subjects (CIS10), CIIS, frequency index (FI) for IIS and time to irritation scores were calculated. Data were summarised using descriptive statistics and treatment effects were evaluated using a two way ANOVA.
Table 2.7.2.6. The CIS₁₀ (95% CI), CIIS (mean ± SD), standardized class, FI for IIS ≥ 1 and ≥ 2 by treatment group [Study A6431082]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Group (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNTP 15 mg</td>
</tr>
<tr>
<td>CIS₁₀</td>
<td>172.1 (95% CI 150-194)</td>
</tr>
<tr>
<td>CIIS</td>
<td>17.2 ± 7.9**</td>
</tr>
<tr>
<td>Standardized Class*</td>
<td>2</td>
</tr>
<tr>
<td>FI for IIS ≥ 1</td>
<td>0.63**</td>
</tr>
<tr>
<td>FI for IIS ≥ 2</td>
<td>0.19**</td>
</tr>
</tbody>
</table>

*Class adapted from Berger and Bowman [13]; Class 2, CIS₁₀ ranging from 50 to 199, indicating that product probably mild in normal use, with evidence of slight potential for very mild cumulative irritation under conditions of test

** P<0.001 for test versus placebo, test versus Nicorette® and Nicorette® versus placebo

Table 2.7.2.7 The CIS₁₀ (95% CI), CIIS (mean ± SD), standardized class, FI for IIS ≥ 1, ≥ 2 and ≥ 3 by treatment group [Study A6431083]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Group (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNTP 25 mg</td>
</tr>
<tr>
<td>CIS₁₀</td>
<td>77.4 (95% CI 55-102)</td>
</tr>
<tr>
<td>CIIS</td>
<td>7.7 ± 7.9**</td>
</tr>
<tr>
<td>Standardized Class*</td>
<td>2</td>
</tr>
<tr>
<td>FI for IIS ≥ 1</td>
<td>0.35**</td>
</tr>
<tr>
<td>FI for IIS ≥ 2</td>
<td>0.02**</td>
</tr>
<tr>
<td>FI for IIS ≥ 3</td>
<td>0.00**</td>
</tr>
</tbody>
</table>

*Class adapted from Berger and Bowman [13]; Class 2, CIS₁₀ ranging from 50 to 199, indicating that product probably mild in normal use, with slight potential for very mild cumulative irritation under conditions of test; Class 3, CIS₁₀ ranging from 200 to 449, indicating that product possibly mild in normal use, with evidence of moderate potential for mild cumulative irritation under conditions of test

** P<0.001 for SLS versus NNTP 25 mg and placebo

Conclusion
These results are satisfactory and show that the proposed products have an acceptable safety profile with regards to skin irritation.

EXPERT REPORTS
A satisfactory expert report is provided by an appropriately qualified individual.

PRODUCT LITERATURE
All product literature (SPCs, PILs and labelling) are satisfactory. The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

OVERALL CONCLUSION
It is recommended that Marketing Authorisations can be granted.
V. USER CONSULTATION
The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI. OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT
QUALITY
The important quality characteristics of Nicorette invisi 10 mg, 15 mg and 25 mg patches are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
The non-clinical data referred to from previous studies and generated specifically in support of these applications is satisfactory. The data confirm that Nicorette invisi patches have an acceptable safety profile.

EFFICACY
The efficacy of nicotine patches is well established. The clinical studies generated in support of these applications are satisfactory and demonstrate that these products have an acceptable efficacy and safety profile.

The SPC, PIL and labelling are satisfactory and consistent with those for the existing licensed products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Nicorette invisi 10 mg, 15 mg and 25 mg patches. The risk: benefit ratio is, therefore, considered to be positive.
In accordance with Directive 2010/84/EU, the current version of the SmPCs and package leaflets are available on the MHRA website. The current labelling is presented below:
Nicorette invis 10 mg, 15 mg and 25 mg patch

Pouch front and back

nicorette
Invisi 10mg patch
nicotine
16 hours
transdermal patch

Each patch contains nicotine 15.75 mg releasing 10 mg nicotine over 16 hours.
9.0 cm² = 15.75 mg.
Keep out of reach and sight of children.
Contains one patch.

Batch No:          Use before:  8008613

2648
Nicorette invisí 10 mg, 15 mg and 25 mg patch

Nicorette invisí 15 mg patch

For preventing cravings and nicotine withdrawal symptoms throughout the day.
Nicorette invisi 10 mg, 15 mg and 25 mg patch

Pouch: Front and back
Nicorette invis 25 mg patch

Use:
Nicorette invis 25 mg patch is used to relieve and/or prevent withdrawal symptoms and reduce the craving you get when you try to stop smoking or when cutting down the number of cigarettes you smoke. It provides a safer alternative to smoking for both the individual and those around them.

Method of action:
Nicorette invis patch is absorbed through the skin and the nicotine in the patch is released slowly. Nicotine in the patch reaches the bloodstream and is transported to your brain, where it reaches levels similar to those achieved when you smoke.

Warning:
Do not exceed the stated dose.

You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counselor or a support programme.

Contra-indications:
The product is not recommended for use by pregnant or breastfeeding women.

Precautions:
- Do not use if you are allergic to any of the ingredients listed below.
- You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counselor or a support programme.

Contenido:
The pack contains seven 25 mg transdermal patches, each containing nicotine 1.58 mg.

Instructions:
- Read the enclosed leaflet for instructions.
- Do not store above 25°C.
- Dispose of the product in the household waste.

nicorette invis
25 mg patch
Nicorette invis 10 mg, 15 mg and 25 mg patch

Pouch: Front and back

nicorette
invis 25mg patch
nicotine
16 hours
transdermal patch

Each patch contains nicotine 39.37 mg releasing 25 mg nicotine over 16 hours. 22.5 cm² = 39.37 mg.

Keep out of reach and sight of children.

Contains one patch.

Batch No: Use before: 2008310

2650
**STEPS TAKEN AFTER THE INITIAL PROCEDURE – SUMMARY**

The following table lists non-safety update to the Marketing Authorisations for Nicorette invisi 10 mg, 15 mg and 25 mg patch (PL 15513/0159-0161) that have been approved by the MHRA since the products were first licensed. This is not a complete list of the post authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>04 August 2010</td>
<td>Type IB</td>
<td>To update the therapeutic indication of the product with consequential changes to Sections 4.1, 4.2, 4.6 and 5.1 of the Summaries of Product Characteristics (SmPCs), the Patient Information Leaflet and cartons at the request of the MHRA. In addition, Sections 4.3, 4.4 and 4.8 of the SmPCs have been updated with the name Nicorette invisi patch.</td>
<td>Approved on 14 October 2010</td>
</tr>
<tr>
<td>28 April 2016</td>
<td>Type IB</td>
<td>To update Section 5.1 of the Summaries of product Characteristics to include Anatomical Therapeutic Chemical (ATC) code in line with the current Quality Review of Documents (QRD) template.</td>
<td>Approved on 25 May 2016</td>
</tr>
</tbody>
</table>
ANNEX 1

Our Reference:

PL 15513/0159, Application 41
PL 15513/0160, Application 41
PL 15513/0161, Application 44

Product(s):

Nicorette invis 10 mg patch
Nicorette invis 15 mg patch
Nicorette invis 25 mg patch

Marketing Authorisation Holder:

McNeil Products Limited

Active Ingredient(s):

Nicotine

Type of Procedure:

National

Submission Type:

Variation

Submission Category:

Type IB

Submission Complexity:

Standard

Reason:

To update Section 5.1 of the Summaries of Product Characteristics to include Anatomical Therapeutic Chemical (ATC) code in line with the current Quality Review of Documents (QRD) template.

Supporting Evidence

Revised SmPC fragment (section 5.1)

Evaluation

The proposed change to the SmPCs is satisfactory.

Conclusion

The proposed change to the SmPCs is considered acceptable and there are no objections to approval.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision – Approved on 25 May 2016.