Voke 0.45mg Inhaler
PL 39589/0001
Nicotine 0.45mg Inhaler
PL 39589/0002

UKPAR

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LAY SUMMARY

Voke 0.45mg Inhaler
Nicotine 0.45mg Inhaler
(nicotine)

This is a summary of the Public Assessment Report (PAR) for Voke/Nicotine 0.45mg Inhalers (PL 39589/0001-2). It explains how the marketing authorisation applications for Voke/Nicotine 0.45mg Inhalers 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 Voke/Nicotine 0.45mg Inhalers.

For practical information about using Voke/Nicotine 0.45mg Inhalers, patients should read the package leaflet or contact their doctor or pharmacist.

What are Voke/Nicotine 0.45mg Inhalers and what are they for?

Voke/Nicotine 0.45mg Inhalers are intended for use as nicotine replacement therapy. These inhalers are nicotine inhalation devices that are used in a similar way to smoking and are a substitute for the nicotine that you normally get from cigarettes. They are an alternative to smoking.

It is the toxins in cigarette smoke, such as tar, lead, cyanide and ammonia, that cause smoking-related disease and death; not the nicotine. By using these products, you and those around you, will not be exposed to the serious health risk associated with these toxins.

For the full health benefits, you should use these products to help you stop smoking completely. If you're not ready to do this, they can also help you cut down. Alternatively you can use these inhalers when you are unable to smoke or want to avoid causing harm to others, e.g. children, friends or family.

Voke/Nicotine 0.45mg Inhalers are a 'hybrid' medicines. This means they are similar to a reference medicine already authorised in the European Union (EU) called Nicorette Inhalator, which was originally granted to Pharmacia Laboratories Limited on 15 July 1997. Following a change of authorisation holder, the current marketing authorisation holder is McNeil Products Limited (PL 15513/0179).

How are Voke/Nicotine 0.45mg Inhalers used?

The frequency with which you use these products and the length of time they last will depend on how many cigarettes you previously smoked and how strong they were.

The recommended dose:
Adults aged over 18 years: as needed; up to a maximum of two full packs per day.

For further information on how Voke/Nicotine 0.45mg Inhaler are used, please refer to the package leaflets and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Voke/Nicotine 0.45mg Inhalers can be obtained by adults without a prescription, at pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist.

How do the Voke/Nicotine 0.45mg Inhalers work?

When you use these inhalers, nicotine is released and passes into the air you breathe and into your body, just like a cigarette but without the harmful chemicals in the smoke. You can use these products as you would a cigarette and inhale as much as desired.

The benefits of stopping smoking far outweigh any potential risk from using these inhalers. There are no circumstances in which it is safer to smoke than to use these products.

Since these products replace nicotine from smoking, they can help relieve nicotine withdrawal symptoms such as irritability, low mood, anxiety, restlessness and cravings when used in place of cigarettes.

How have Voke/Nicotine 0.45mg Inhalers been studied?

The Company (Kind Consumer Limited) provided data from the published literature on the use of inhaled nicotine for smoking cessation.

One additional study, composed of four parts, was performed to determine the pharmacokinetics and tolerability of the inhaled nicotine from this product versus the reference medicine, Nicorette Inhalator (McNeil Products Limited).

What are the benefits and risks of Voke/Nicotine 0.45mg Inhalers?

Because Voke/Nicotine 0.45mg Inhalers are hybrid applications and considered to be therapeutically equivalent, to the reference product Nicorette Inhalator (McNeil Products Limited), the benefits and risks are taken as being the same as those of the reference medicine.

Why are Voke/Nicotine 0.45mg Inhalers approved?

The use of nicotine in smoking cessation is well-established and there are a number of approved products on the market. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Voke/Nicotine 0.45mg Inhalers outweigh the risks and the grant of Marketing Authorisations was recommended.

What measures are being taken to ensure the safe and effective use of Voke/Nicotine 0.45mg Inhalers?

Safety information has been included in the Summaries of Product Characteristics and the package leaflets for Voke/Nicotine 0.45mg Inhalers, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Voke/Nicotine 0.45mg Inhalers.

Marketing Authorisations were granted in the UK on 11 September 2014.

The full PAR for Voke/Nicotine 0.45mg Inhaler follows this summary.

For more information about treatment with Voke/Nicotine 0.45mg Inhaler, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2014.

Voke 0.45mg Inhaler
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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Kind Consumer Limited Marketing Authorisations (licences) for the medicinal products Voke/Nicotine 0.45mg Inhaler (PL 39589/0001-2) on 11 September 2014. These products are on the General Sales List (GSL) and are used to relieve and/or prevent cravings and nicotine withdrawal symptoms associated with tobacco dependence. They are indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them. These products are also indicated in pregnant and lactating women making a quit attempt.

These applications were submitted as abridged applications according to Article 10(3) of Directive 2001/83/EC, as amended, so-called hybrid applications. The reference product for this application was Nicorette Inhalator, which was licensed to McNeil Products Limited on 30 August 2000.

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% of nicotine combined as malate or citrate.

No new non-clinical studies were conducted, which is acceptable given that these are hybrid applications.

One clinical study, composed of four parts, was performed to determine the pharmacokinetics and tolerability of the inhaled nicotine products versus the reference medicine, Nicorette Inhalator (McNeil Products Limited).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products.

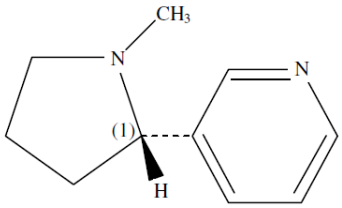
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE– Nicotine

INN: Nicotine (pharmaceutical grade)

Chemical name: 3(1-methyl-2-pyrrolidinyl) pyridine
1-methyl-2-(3-pyridyl) pyrrolidine
β-pyridyl-α-N-methyl-pyrrolidine

Structure:



Molecular formula: $C_{10}H_{14}N_2$

Molecular weight: 162.24

Appearance: Colourless or brownish viscous liquid, volatile, hygroscopic

Solubility: soluble in water, miscible in alcohol

Nicotine is the subject of a European Pharmacopoeia monograph.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance nicotine.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance. 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.

The specifications and batch analytical test results are provided and are satisfactory.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

An appropriate retest period has been proposed based on stability data submitted for the active substance.

MEDICINAL PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients propylene glycol, ethanol, saccharin, levomenthol and HFA134a. With the exception of HFA134a, all excipients are controlled by their respective European Pharmacopoeia monograph. A suitable specification has been provided for HFA134a, which complies with the requirements of the CPMP/IPACT-I "Results of the Co-ordinated Review of 1,1,1,2-tetrafluoroethane HFA 134a" considered to be the standard to be applied for this propellant.

None of the excipients used contain material of animal or human origin.

Pharmaceutical development

The aim of the pharmaceutical development was to develop a stable formulation of nicotine in HFA propellant that could be considered comparable to Nicorette Inhalator (McNeil Products Limited).

A satisfactory account of the pharmaceutical development has been provided.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on production-scale batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. 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

The finished product is stored in a pressurised aluminium canister with a continuous delivery valve. The finished product is delivered to the user using a polybutylene terephthalate inhalation stick-shaped device, with a breath-operated valve which is charged from the canister. One pack contains one stick device and one canister. A canister contains twenty charges for the stick. Pack sizes are 1, 2x1 and 5x1 packs.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 12 months (unopened) and 7 days (opened) was set. The following storage conditions apply to these products:

- Store below 25°C.
- Do not expose to temperatures higher than 50°C.
- Store away from heat or direct sunlight.

- As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.
- The canister contains a pressurised liquid, do not puncture, break or burn even when empty.
- Do not attempt to light the stick.

Bioequivalence/bioavailability
One clinical study, composed of four parts, was performed to determine the pharmacokinetics and tolerability of the inhaled nicotine products versus the reference medicine, Nicorette Inhalator (McNeil Products Limited).

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labelling are pharmaceutically acceptable.

A 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, as amended. 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.

Marketing Authorisation Application (MAA) forms
The MAA forms are pharmaceutically satisfactory.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

NON-CLINICAL ASSESSMENT

These applications were submitted as abridged applications, according to Article 10(3) of Directive 2001/83/EC, as amended, so-called hybrid applications.

No new non-clinical studies were conducted, which is acceptable given that these are hybrid applications containing an active substance that has been used for many years. Since nicotine is a well-established product, the applicant has provided a discussion on the non-clinical characteristics of nicotine and so there is no need for an extensive re-assessment here. The assessment has focussed on the evaluation of the safety of the drug substance and product via the inhalation route, including degradants/ impurities, use of excipients and potential exposure to leachables/extractables from the device.

No concerns have been raised in respect to the impurities/degradants in the finished product.

The applicant has provided an up-to-date and in-depth review of relevant literature for excipients present in these products. Levels of ethanol, propylene glycol and saccharin

are below acceptable daily intake (ADI) limits established by UK Health and Safety Executive (HSE) and the Joint Expert Committee on Food Additives (JECFA). Levels of menthol are below the JECFA ADI of 4 mg/kg/day for menthol (WHO 1999). Although the above limits are derived from mainly oral studies, it is considered that there is sufficient safety margin that this may be of limited concern. Some data are presented from rat and monkey inhalation studies with propylene glycol, these studies do not highlight any significant systemic effects at low doses (160 mg/m^3), reductions in leucocytes are noted at higher levels of exposure (>1000 mg/m^3) in female rats. Overall considering the JECFA ADI and the limited inhalation toxicity studies, the maximum daily exposure to 138 mg propylene glycol is considered unlikely to cause concern.

Exposure to the propellant HFA-134a was reviewed using inhalation studies in rodents; where the exposure to a no effect dose of 88 g/kg body weight was more than a hundred-fold more than the potential daily exposure via Voke/Nicotine Inhaler.

Overall no non-clinical concerns are raised with respect to excipients, concern over propylene glycol use is within established limits and any potential concern is limited due to a minimum age of 18 years for users of these products.

The applicant has provided details of potential unknown extractables and leachables, and performed leachables studies – including metal ion analysis. These reveal no new concerns, and overall the data are considered to be satisfactory and the risk of extractables and leachables containing compounds considered to be of high carcinogenic risk is low.

No environmental risk assessment has been submitted with these applications. As these products are intended for substitution with an already marketed product, no increase in environmental burden is anticipated.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical dossier.

The grant of marketing authorisations is recommended.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of nicotine as an active in the treatment of tobacco dependence is well-established and is not described in further detail in this report.

The clinical development program for the Voke/Nicotine Inhaler comprises a single pharmacokinetic study, supported by a comprehensive literature review of the pharmacokinetics, safety and efficacy of nicotine replacement therapy (NRT) and cigarettes, and no further clinical efficacy studies have been conducted with the Voke Inhaler.

The efficacy of nicotine replacement therapy (NRT) is also well-established and not described in further detail in this report. No new efficacy data are provided. However,

the pharmacokinetic study included some pharmacodynamic measures regarding effect on cravings, which are considered below.

Study KC001

In this study the name 'Oxette' is given to the Voke Inhaler.

Study design

The study was performed in four parts:

- Part A was a randomised, single-blind, multi-dose study to determine the arterial pharmacokinetics of orally inhaled nicotine delivered via the Oxette Nicotine Inhaler device at three doses of nicotine 0.028% w/w (low), 0.056% w/w (medium - the dose of nicotine used in the final product) and 0.084% w/w (high).
- Part B was a randomised, open-label/single-blind, three-way crossover study to determine the venous pharmacokinetics of orally inhaled nicotine at two dose levels delivered via the Oxette Nicotine Inhaler device in comparison to the Nicorette Inhaler (10 mg).
- Part C was an open-label study to determine the tolerability and venous pharmacokinetics of repeat high doses of orally inhaled nicotine (0.084%w/w nicotine) delivered via the Oxette Nicotine Inhaler device at one dose level of nicotine.
- Part D was a randomised, open-label, two-way crossover study to determine the venous pharmacokinetics of orally inhaled nicotine at the medium dose level (0.056%w/w) delivered via the Oxette Nicotine Inhaler device in comparison to the Nicorette Inhaler (10 mg).

An active treatment control (Nicorette Inhaler 10 mg) was used in Parts B and D of the study. A cross-over design was used in Part B of the study to allow direct comparison between two nicotine dose levels inhaled via the Oxette Nicotine Inhaler, and the Nicorette Inhaler 10 mg, which was used as a control. A cross-over design was also used in Part D of the study to allow direct comparison between medium nicotine dose level (0.056%w/w) inhaled via the Oxette Nicotine Inhaler, and the Nicorette Inhaler 10 mg, which was used as a control.

In Part A, the participants received two dose levels of the Oxette Nicotine Inhaler. The study design ensured that the lower of the two dose levels was received first and, therefore, the doses were not in random order. A washout period of at least 5 hours was included in Part A of the study to ensure that nicotine from the first dose had reached baseline levels through excretion before the second dose was inhaled.

The design of Part C of the study was to investigate in-use pharmacokinetics where repeated refills of the device were taken over the course of a day.

Following a 12-hour nicotine abstinence period, subjects received their first trial medication.

Part A

Part A enrolled 18 subjects, all of whom completed the trial. Participants were randomised to receive two of three dose levels of nicotine in one day. The nicotine

dose levels were 0.028% w/w (low), 0.056% w/w (medium) and 0.084% w/w (high). The 18 participants were divided equally into three groups, with each group containing six participants. The first group received the low dose followed by the medium dose; the second group received the low dose followed by the high dose; and the third group received the medium dose followed by the high dose.

Each enrolled participant received the first dose of nicotine via the Oxette Nicotine Inhaler device. The participant inhaled the entire contents of the inhaler, taking one inhalation every 15 seconds until the device was empty, but taking no longer than 4 minutes to complete the dose. The maximum time was estimated based on the Oxette Nicotine Inhaler device containing approximately eight inhalations per dose, inhaling every 15 seconds.

The dose time was to be recorded as the time when the participant took the first inhalation.

Then each enrolled participant received the second dose of nicotine via the Oxette Nicotine Inhaler device. The participant inhaled the entire contents of the inhaler taking one inhalation every 15 seconds until the device was empty, but taking no longer than 4 minutes to complete the dose as before.

Arterial blood sampling was performed pre-dose and 2, 4, 6, 8, 10, 15, 20, 40, 60, 120, 180, 240 and 300 minutes after the start of inhalation for both treatment periods.

Participants were to be given a standard light breakfast to be completed 1 hour before the first dose, and a standard light lunch to be completed at least 1 hour before the second dose. Fluids were not to be allowed from at least 1 hour before dosing to 1 hour after dosing.

Test products

Low	Oxette® Nicotine Inhaler, 0.028%w/w nicotine
Medium	Oxette® Nicotine Inhaler, 0.056%/w/w nicotine
High	Oxette® Nicotine Inhaler 0.084%w/w nicotine

Population(s) studied

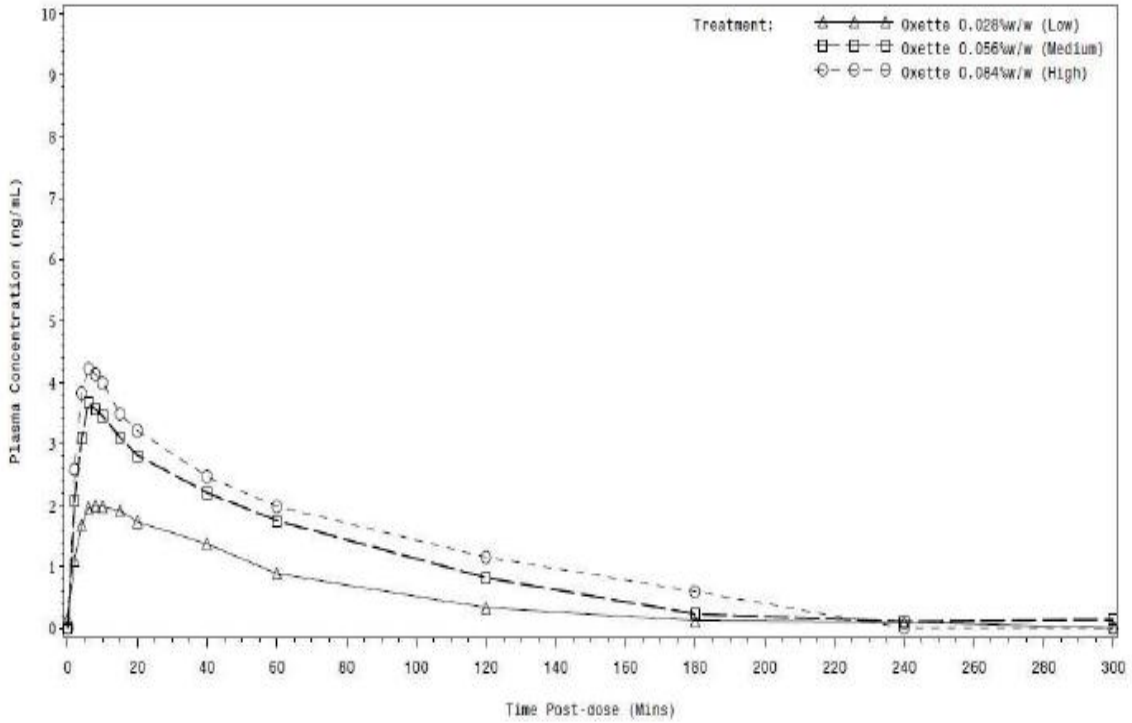
18 healthy subjects, 10 male and 8 female aged 21-53 years, who smoked >10 cigarettes/day were included in the study. All 18 subjects completed the study.

Pharmacokinetic Variables

The following pharmacokinetic parameters were calculated and presented descriptively: C_{max}; t_{max} and AUC_t.

Results

Mean Arterial Plasma Nicotine Concentrations over time (linear)(ng/mL)



Time (Post-dose)	Oxette 0.028%w/w (low)		Oxette 0.056%w/w (medium)		Oxette 0.084%w/w (high)	
	Mean	*Std Dev*	Mean	*Std Dev*	Mean	*Std Dev*
Pre-dose	0.15	*0.52*	0.00	*0.00*	0.00	*0.00*
2 mins	1.10	*0.78*	2.06	*0.92*	2.59	*1.18*
4 mins	1.68	*0.70*	3.09	*1.06*	3.83	*1.09*
6 mins	1.95	*0.59*	3.66	*1.17*	4.23	*1.14*
8 mins	1.99	*0.62*	3.56	*1.00*	4.13	*1.16*
10 mins	1.98	*0.83*	3.45	*0.94*	4.00	*1.08*
15 mins	1.91	*0.62*	3.10	*0.77*	3.49	*0.86*
20 mins	1.73	*0.85*	2.81	*0.72*	3.21	*0.87*
40 mins	1.37	*0.68*	2.20	*0.56*	2.46	*0.69*
60 mins	0.89	*0.80*	1.75	*0.72*	1.98	*0.52*
120 mins	0.33	*0.63*	0.82	*0.77*	1.16	*0.74*
180 mins	0.12	*0.42*	0.23	*0.55*	0.59	*0.63*
240 mins	0.10	*0.33*	0.10	*0.35*	0.00	*0.00*
300 mins	0.00	*0.00*	0.14	*0.47*	0.00	*0.00*

Summary of mean pharmacokinetic parameters by treatment - Part A

Treatment	C_{max} (ng/mL)		T_{max} (min)		AUC_{last} (min*ng/mL)		AUC_{all} (min*ng/mL)	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Oxette® 0.028%w/w (low)	2.113	0.671	10.2	3.9	118.6	127.3	145.7	132.5
Oxette® 0.056%w/w (medium)	3.733	1.131	7.3	1.6	241.7	152.6	274.4	146.5
Oxette® 0.084%w/w (high)	4.380	1.186	6.5	1.9	296.9	124.6	334.4	124.2

There were no deaths, serious adverse events or other significant adverse events in this study. A total of 56 treatment emergent adverse events (TEAEs) were reported by 16 (89%) of the 18 participants for the duration of the study. Sixteen (16) participants reported 47 TEAEs that were assessed as "related" to study medication, 2 participants reported 2 TEAEs that were assessed as "moderate" and 1 participant reported 1 TEAE that was assessed as "moderate and related" to study medication. This adverse event was "tingling of lips and tongue" which was reported immediately after administration of the high dose of Oxette (0.084%w/w), and was resolved within nine minutes.

The most frequently occurring TEAEs amongst the 18 participants in Part A were oral paraesthesia (12 participants; 67%), vessel puncture site haematoma (6 participants; 33%), dizziness (3 participants; 17%), headache (3 participants; 17%), cough (3 participants; 17%), dry throat (3 participants; 17%), and throat irritation (3 participants; 17%). There were no differences in the frequency of adverse events between dose strengths.

Eleven reports of oral paraesthesia were graded as "mild" and one was graded as "moderate". Eleven of the reports of oral paraesthesia were assessed as "definitely related" and one was assessed as "probably related" to investigational product. All six reports of vessel puncture site haematoma were graded as "mild" and assessed as "not related" to investigational product. All reports of cough, dry throat and throat irritation were graded as "mild" and were assessed as "definitely, probably or possibly related" to investigational product**.**

Conclusions

The inhalers are seen to be essentially dose proportional with regard to pharmacokinetic parameters and released dose, arterial C_{max} occurring between 6-8 minutes.

From an initial view of product safety profile, the adverse events were mild or moderate in severity and known to be related to nicotine replacement products.

It is noted that there was no significant difference between dose strengths with regard to adverse event profile.

Part B

Part B enrolled 24 subjects. Each participant attended the clinical trial unit on three consecutive days and was randomised to receive one complete refill of the Oxette Nicotine Inhaler device at one nicotine dose level on one day, one complete refill of the Oxette Nicotine Inhaler device at a second nicotine dose level on a second day, and one treatment of Nicorette Inhaler (10 mg) on a third day.

Oxette® Nicotine Inhaler device: The participants were to inhale the entire contents of the inhaler taking one inhalation every 15 seconds until the device was empty, but taking no longer than 4 minutes to complete the dose as for part A. The dose time was to be recorded as the time when the participant takes the first inhalation.

Nicorette® Inhaler: The participants were to use the Nicorette Inhaler in-line with the manufacturer's prescribing information. Participants were instructed to take four inhalations every minute for 20 minutes. The maximal dose was expected to be achieved after 20 minutes of continuous use with deep inhalations.

Venous blood sampling was performed pre-dose and 2, 4, 7, 10, 15, 20, 30, 40, 50, 60, 120, 180, 240 and 300 minutes after the start of inhalation for all three treatment periods.

Participants were given a standard light breakfast to be completed one hour before dosing. Fluids were not to be allowed from at least one hour before dosing to one hour after dosing.

Test and reference products

Test:	
Medium	Oxette® Nicotine Inhaler, 0.056%/w/ nicotine
High	Oxette® Nicotine Inhaler, 0.084%w/w nicotine
Reference:	Nicorette Inhaler (10 mg)

Population(s) studied

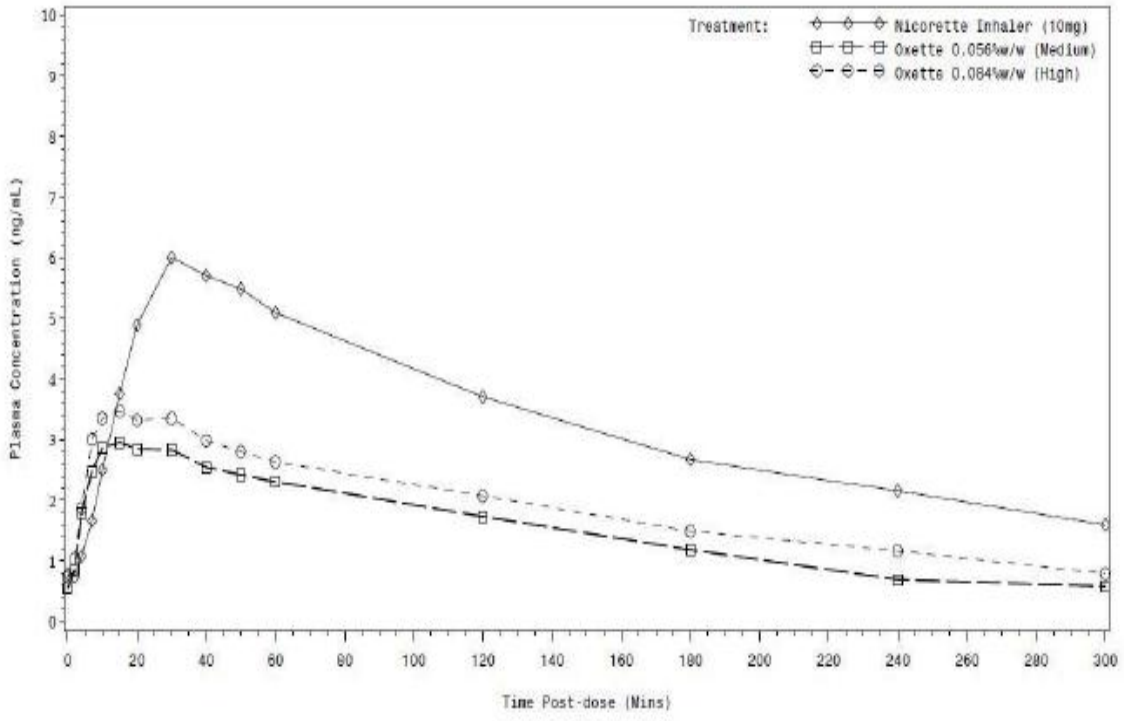
24 healthy subjects, 14 male and 10 female aged 21-53 years, who smoked >10 cigarettes/day were included in the study. 23 subjects completed the study. Subject B002 withdrew consent before receiving either dose of the Oxette® Inhaler and dropped out of the study.

Pharmacokinetic Variables

C_{max}; t_{max} and AUC_t.

Results

Mean Venous Plasma Nicotine Concentrations over time (linear)(ng/mL)



Time (Post-dose)	Oxette 0.056%w/w (medium)		Oxette 0.084%w/w (high)		Nicorette Inhaler 10 mg	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Pre-dose	0.55	0.82	0.73	1.09	0.78	0.97
2 mins	0.86	1.05	1.03	1.21	0.73	0.95
4 mins	1.79	1.49	1.87	1.54	1.08	0.96
7 mins	2.49	1.38	3.01	1.68	1.66	1.17
10 mins	2.87	1.15	3.35	1.61	2.50	1.55
15 mins	2.96	1.09	3.47	1.42	3.76	2.14
20 mins	2.85	1.00	3.32	1.26	4.89	2.46
30 mins	2.84	1.00	3.35	1.45	6.01	2.84
40 mins	2.55	0.93	2.99	1.32	5.70	2.65
50 mins	2.42	0.94	2.80	1.34	5.49	2.49
60 mins	2.30	0.93	2.64	1.24	5.09	2.44
120 mins	1.73	0.90	2.07	1.18	3.71	1.91
180 mins	1.18	0.95	1.49	1.17	2.68	1.53
240 mins	0.69	0.89	1.16	1.00	2.15	1.32
300 mins	0.58	0.83	0.79	0.96	1.59	1.17

Summary of mean pharmacokinetic parameters by treatment – Part B

Treatment	C_{max} (ng/mL)		T_{max} (min)		AUC_{last} (min*ng/mL)		AUC_{all} (min*ng/mL)	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Oxette® 0.056%w/w (medium)	3.284	1.238	18.7	8.6	430.8	273.8	453.3	259.0
Oxette® 0.084%w/w (high)	3.915	1.640	19.2	11.8	545.3	334.4	563.0	322.9
Nicorette® Inhaler 10 mg	6.566	2.965	38.0	11.8	977.7	498.7	987.7	487.7

For C_{max} and Area Under the Curve (AUC), the geometric means of the ratio of test/reference within subject, along with 90% confidence intervals (i.e. the two one-sided 95% confidence limits), are provided in Table 14.2.5.8-9, for parts B and D, respectively. Table 14.2.5.10 shows the geometric means of the ratio of test/reference between subjects, along with 90% confidence intervals (i.e. the two one-sided 95% confidence limits), for Part D vs Part B.

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Table 14.2.5.8
Comparison Between Treatments of Pharmacokinetic Parameters, Part B
Per Protocol Pharmacokinetic Population
(n=23, omitting B002)

Reference = Nicorette Inhaler (10mg)

Test Treatment	Parameter	--- LS Means --- Test	--- LS Means --- Reference	Ratio* of LS Means	One-sided 95% CLs for Ratio* --- of LS Means ---- Lower 95% CL	Upper 95% CL	Intra-subject CV (%)
Oxette 0.056%w/w (Medium)	Tmax (min)	18.7	39.0	-20.2	-24.6	-15.9	
	AUC(0-10) (min*ng/mL)	14.9	9.5	156.4%	117.8%	207.8%	47.3
	AUCall (min*ng/mL)	386.5	842.4	45.9%	37.2%	56.6%	36.0
	AUClast (min*ng/mL)	351.1	819.1	42.9%	33.9%	54.2%	40.4
	Cmax (ng/mL)	3.08	5.90	52.2%	43.8%	62.2%	30.2
Oxette 0.084%w/w (High)	Tmax (min)	19.4	39.0	-19.5	-24.0	-15.1	
	AUC(0-10) (min*ng/mL)	19.2	9.5	202.2%	151.4%	270.0%	47.3
	AUCall (min*ng/mL)	516.3	842.4	61.3%	49.5%	75.9%	36.0
	AUClast (min*ng/mL)	483.4	819.1	59.0%	46.5%	75.0%	40.4
	Cmax (ng/mL)	3.87	5.90	65.5%	54.8%	78.4%	30.2

Key: * = Difference for Tmax;
Note:
Comparison by analysis of variance performed on log-transformed parameters
using SAS Proc GLM with model: <parameter> = Treatment Period Sequence Subject(Sequence)

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Table 14.2.5.9
Comparison Between Treatments of Pharmacokinetic Parameters, Part D
Per Protocol Pharmacokinetic Population
(n=24)

Reference = Nicorette Inhaler (10mg)

Test Treatment	Parameter	--- LS Means --- Test	--- LS Means --- Reference	Ratio* of LS Means	One-sided 95% CLs for Ratio* --- of LS Means --- Lower 95% CL	Upper 95% CL	Intra-subject CV (%)
Oxette 0.056%w/w (Medium)	Tmax (min)	21.0	36.3	-15.3	-20.4	-10.3	
	AUC(0-10) (min*ng/mL)	13.9	9.3	149.9%	110.6%	203.3%	53.8
	AUCall (min*ng/mL)	347.1	780.5	44.5%	32.4%	61.0%	63.6
	AUClast (min*ng/mL)	295.4	754.7	39.1%	27.1%	56.6%	74.2
	Cmax (ng/mL)	3.22	6.24	51.6%	41.2%	64.5%	45.2

Key: * = Difference for Tmax;
Note:
Comparison by analysis of variance performed on log-transformed parameters
using SAS Proc GLM with model: <parameter> = Treatment Period Sequence Subject(Sequence)

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Table 14.2.5.10
Comparison of Pharmacokinetic Parameters (Venous) for Oxette Medium, Part D vs Part B

Parameter	--- LS Means --- Part D	--- LS Means --- Part B	Ratio* of LS Means	One-sided 95% CLs for Ratio* --- of LS Means --- Lower 95% CL	Upper 95% CL	Intra-subject CV (%)
Tmax (min)	21.0	18.7	-2.3	-7.8	3.3	
AUC(0-10) (min*ng/mL)	13.5	14.8	109.6%	73.5%	163.5%	80.7
AUCall (min*ng/mL)	347.1	386.7	111.4%	80.7%	153.8%	65.8
AUClast (min*ng/mL)	295.4	351.2	118.9%	79.7%	177.5%	81.7
Cmax (ng/mL)	3.22	3.08	95.5%	77.9%	117.2%	41.8

Key: * = Difference for Tmax;
Note:
Comparison by analysis of variance performed on log-transformed parameters
using SAS Proc GLM with model: <parameter> = Part

The plasma samples obtained during the study were analysed using validated LC/MS/MS. Nicotine-d3-salicylate salt was used as internal standard.

Ratio of test/reference with 90% confidence intervals have been provided for Part B, Part D and Part B vs Part D for Oxette medium (product to be marketed).

In the protocol Oxette was given every 15 seconds for a maximum of 4 minutes when Nicorette was used every 15 seconds for 20 minutes.

The tables below give the nicotine concentrations for both products. After 4 minutes the plasma nicotine concentrations (ng/ml) with the proposed product was higher than with Nicorette (about 70% in Part B and 30% in Part D), and again after 7 minutes to become similar after 10 minutes.

Part B

Time (Post-dose)	Oxette 0.056%w/w (medium)		Oxette 0.084%w/w (high)		Nicorette Inhaler 10 mg	
	Mean	*Std Dev*	Mean	*Std Dev*	Mean	*Std Dev*
Pre-dose	0.55	*0.82*	0.73	*1.09*	0.78	*0.97*
2 mins	0.86	*1.05*	1.03	*1.21*	0.73	*0.95*
4 mins	1.79	*1.49*	1.87	*1.54*	1.08	*0.96*
7 mins	2.49	*1.38*	3.01	*1.68*	1.66	*1.17*
10 mins	2.87	*1.15*	3.35	*1.61*	2.50	*1.55*
15 mins	2.96	*1.09*	3.47	*1.42*	3.76	*2.14*

Part D

Time (Post-dose)	Oxette 0.056%w/w (medium)		Nicorette Inhaler 10 mg	
	Mean	*Std Dev*	Mean	*Std Dev*
Pre-dose	0.61	*1.09*	0.64	*1.05*
2 mins	0.84	*1.15*	0.69	*0.99*
4 mins	1.32	*1.33*	1.00	*1.19*
7 mins	2.45	*1.70*	1.81	*1.76*
10 mins	2.95	*1.56*	2.91	*2.34*

The ratio of Test/Reference for AUC_{0-10} is 156.4% (117.8-207.8) in Part B and 149.9% (110.6-203.3) in Part D, making the proposed product at least as good as Nicorette for nicotine delivery in the time used, or in the direct aftermath.

When comparing the results with Oxette 0.056 %w/w in Part B and D, nicotine delivery was higher in the first part although no direct explanation has been given, with a very high variability for AUC, especially for AUC_{0-10}. This is reflected by slightly better results regarding craving in Part B as compared to Part D. This has been commented on by the applicant in the below:

> A summary of Oxette® dose inhaled by Part and treatment for all participants administered Oxette® is provided in Tables 11-3 of the KC001 Clinical Study Report. From this table the data for Parts B and D have been extracted below.

Table 19: (Parts B and D only) KC001 Clinical Study Report

Part	Treatment	Number of Doses	Amount Inhaled (g)				
			Mean	SD	Median	Min	Max
B	Oxette 0.056%w/w (Medium)	23	0.9472	0.2051	1.0062	0.4236	1.1075
B	Oxette 0.084%w/w (High)	23	0.8610	0.3005	0.9440	0.0254	1.1932
B (per protocol)	Oxette 0.056%w/w (Medium)	20	1.0187	0.0845	1.0429	0.8113	1.1075
B (per protocol)	Oxette 0.084%w/w (High)	20	0.9461	0.2012	0.9956	0.4443	1.1932
D	Oxette 0.056%w/w (Medium)	24	0.7074	0.3028	0.7607	0.1044	1.1404
D (per protocol)	Oxette 0.056%w/w (Medium)	20	0.8112	0.2051	0.8329	0.4239	1.1404

As can be seen in the table above, the mean inhaled weight for the 0.056%w/w dose in Part B is around 33% higher than for the medium strength in Part D. It is notable that in this comparison the maximum weight inhaled in Parts B and D is very similar (actually numerically higher for Part D) but the minimum weight is also a lot lower in part D (greater than four-fold). Unsurprisingly this increases the standard deviation (SD) from 0.2 to 0.3.

The correlation between the inhaled weight of formulation (x-axis) and the plasma nicotine AUC $_{0\text{-}10}$ (y-axis) for the 0.056%w/w dose in parts B and D can be seen in the Figure 11 below.

There is a trend for the plasma nicotine AUC $_{0\text{-}10}$ to increase with increasing inhaled weight of formulation, but there is considerable variability in the data and 4 individuals can be identified in part D who inhaled a very low weight of formulation.

This data can also be represented in a scatter plot (Figure 12) of inhaled weight of formulation (x axis) against craving AUC (y-axis) for the 0.056%w/w dose in parts B and D.

Figure 11: Plasma Nicotine AUC $_{0\text{-}10}$ for 0.056% w/w dose in parts B and D

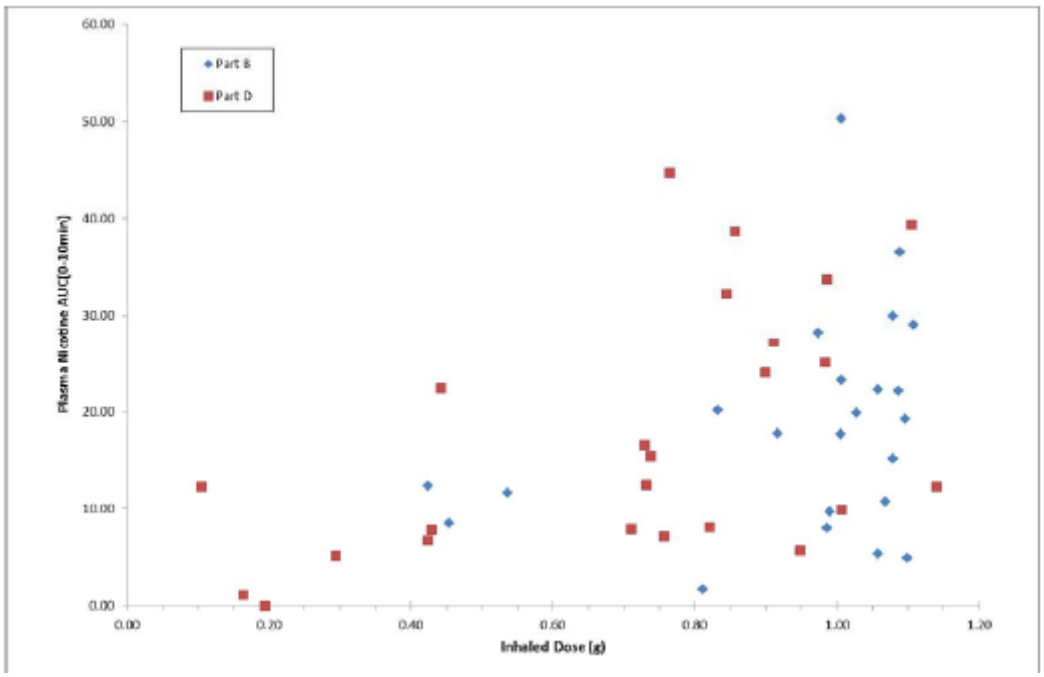
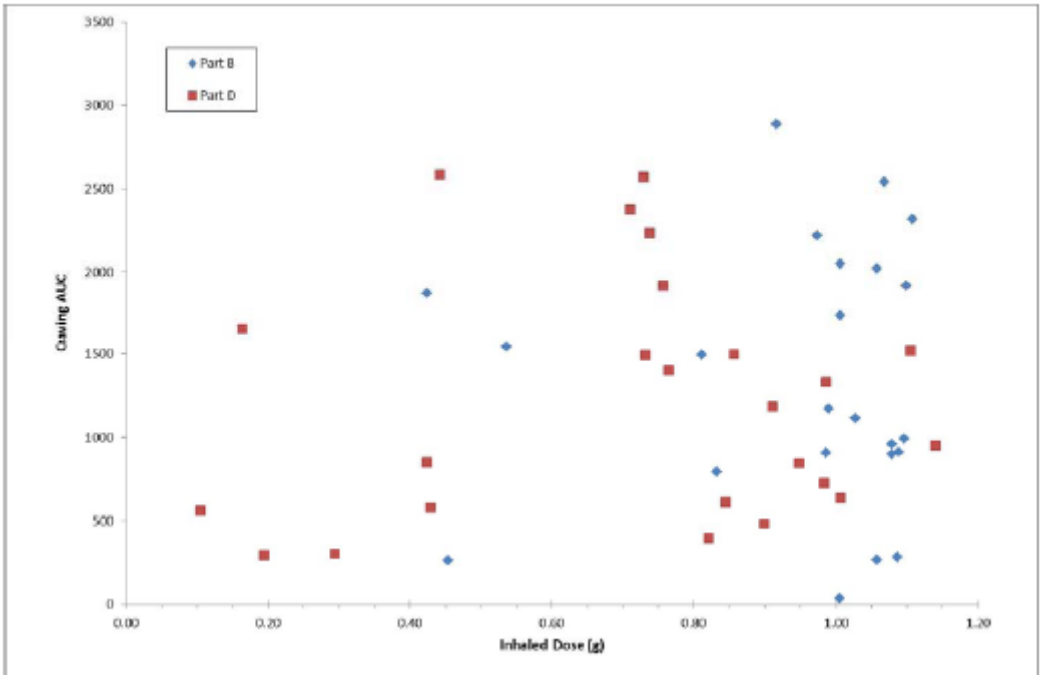


Figure 12: Craving AUC for 0.056% w/w dose in parts B and D



From this scatter plot there is generally a poor correlation between inhaled weight of formulation and craving AUC and the 4 individuals in part D with very low inhaled doses are clearly identified.

The impact of the data from these 4 individuals' results in the mean weight of formulation inhaled in part D being 0.7074g if they are included and 0.8112g if they are excluded. The mean inhaled weight for the 0.056%w/w dose in Part B is then approximately 16% higher than the medium strength in Part D rather than 33% when they are included.

From the two scatter plots presented above it can be seen that there is no evidence for a systematic difference between the data generated for participants in parts B and D – both the inhaled weight of formulation and the craving AUC and plasma nicotine AUC $_{0\text{-}10}$ are similarly variable in both parts of the study. This is likely to reflect the variability in inhalation technique that was noted during the study conduct. Although the protocol specified taking one inhalation every 15 seconds – the depth of inhalation was subject dependent – this may explain both the variability of the nicotine pharmacokinetics – especially AUC $_{0\text{-}10}$ coupled with the variability of the subjective sensation of craving relief.

There were no deaths, serious adverse events or other significant adverse events in this study. For Part B, a total of 87 treatment-emergent adverse events (TEAEs) were reported by 23 (96%) of the 24 participants for the duration of the study. Twenty three (23) participants reported 79 TEAEs that were assessed as "related" to study medication, 2 participants reported 2 TEAEs that were assessed as "moderate" and 1 participant reported 1 TEAE that was assessed as "moderate and related" to study medication. This adverse event was "local numbness" which was reported 4 minutes after administration of Nicorette Inhaler 10 mg, and was resolved within fifteen minutes.

The most frequently occurring TEAEs among the 24 participants in Part B were oral paraesthesia (15 participants; 63%), throat irritation (11 participants; 46%) and oral hypoaesthesia (6 participants; 25%). All fifteen reports of oral paraesthesia were graded as "mild", and assessed as "probably related" to investigational product. All

eleven reports of throat irritation were graded as “mild”, three of which were assessed as “definitely related” and eight were assessed as “probably related” to investigational product. Five reports of oral hypoaesthesia were graded as “mild” and one was graded as “moderate”. All six reports of oral hypoaesthesia were assessed as “probably related” to investigational product.

Conclusion
This study provides a comparative estimate of pharmacokinetics between two doses of the Oxette Inhaler and Nicorette 10mg Inhalator. It is seen that Oxette at dose proposed for marketing achieves a C_{max} approximately half and an AUC_{0-10} comparable with that of the reference, Nicorette Inhaler 10mg.

It is noted that adverse events were more frequently reported in the Oxette treatment groups than with Nicorette. The percentage of subjects reported at least one TEAE was 74%, 91% and 58% for the 0.056% w/w, 0.084% w/w Oxette Inhalers and Nicorette inhaler, respectively.

Part C
Part C enrolled 18 subjects, all of whom completed the trial. Each participant received repeat doses of nicotine over the period of one day. All participants received the same dose of nicotine via the Oxette Nicotine Inhaler device. One complete refill of Oxette Nicotine Inhaler device was inhaled every hour for 12 hours.

Oxette® Nicotine Inhaler device: The participant was to inhale the entire contents of the inhaler taking one inhalation every 15 seconds until the device was empty, but taking no longer than 4 minutes to complete the dose as for part A. The dose time was to be recorded as the time when the participant takes the first inhalation.

Venous blood sampling was performed pre-dose and 2, 4, 7, 10, 15, 20, 30, 40, 50, 60, 120, 180, 240 and 300 minutes after the start of inhalation for all three treatment periods.

Participants were given a standard light breakfast to be completed 1 hour before dosing. Fluids were to be allowed throughout the course of the dosing day.

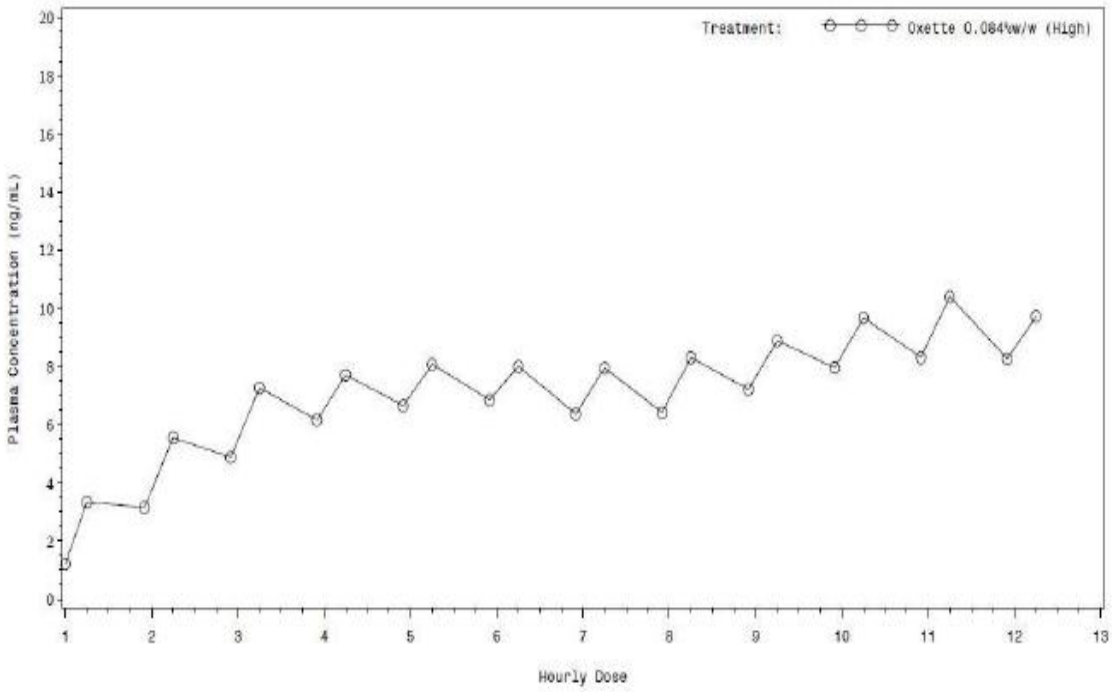
Test product
High Oxette® Nicotine Inhaler 0.084%w/w nicotine

Population(s) studied
18 healthy subjects, 13 male and 5 female aged 21-52 years, who smoked >10 cigarettes/day were included in the study. All 18 subjects completed the study.

Pharmacokinetic Variables
C_{max}; t_{max} and AUC_t peak and trough concentrations.

Results

Mean Venous Plasma Nicotine Concentrations over time (linear)(ng/mL)



Dose	5 Mins Pre-Dose		15 Mins Post-Dose	
	Mean	*Std Dev*	Mean	*Std Dev*
1	1.21	*0.98*	3.33	*1.27*
2	3.15	*1.24*	5.55	*2.08*
3	4.88	*1.71*	7.26	*2.31*
4	6.16	*2.17*	7.71	*2.15*
5	6.65	*2.36*	8.07	*2.48*
6	6.85	*2.38*	8.00	*2.44*
7	6.36	*2.60*	7.95	*2.83*
8	6.42	*2.41*	8.31	*2.82*
9	7.21	*2.45*	8.88	*2.70*
10	7.96	*2.70*	9.68	*3.13*
11	8.31	*3.05*	10.40	*3.68*
12	8.27	*3.00*	9.72	*3.47*

There were no deaths, serious adverse events or other significant adverse events in this study. A total of 104 treatment-emergent adverse events (TEAEs) were reported by 17 (94%) of the 18 participants for the duration of the study. Seventeen (17) participants reported 97 TEAEs that were assessed as “related” to study medication, 2 participants reported 2 TEAEs that were assessed as “moderate” and 1 participant reported 1 TEAE that was assessed as “moderate and related” to study medication.

This adverse event was "emesis" which was reported twenty minutes after the 11th hourly administration of the high dose of Oxette (0.084%w/w), and was resolved within one hour.

Conclusions
Plasma nicotine concentration appears to continually rise with repeated use, achieving an approximate steady state venous plasma concentration between 8-10ng/mL. This can be compared relative to the typical venous plasma nicotine concentration of a cigarette of between 15-30ng/mL.

It is also noted that almost all of the subjects experienced a TEAE, although these were mild in nature and consistent with other forms of nicotine-replacement therapy.

Part D
The dose level chosen for Part D was the 0.056%w/w nicotine as this is the proposed to-be-marketed formulation.

Part D enrolled 24 subjects. Each participant attended the clinical trial unit to be confined for two consecutive days, and was randomised to receive one complete refill of Oxette Nicotine Inhaler device at the medium dose level (0.056%w/w) on one day, and one treatment of Nicorette Inhaler (10 mg) on another day. The order in which treatment was to be received was to be randomised.

Oxette® Nicotine Inhaler device: The participant was to inhale the entire contents of the inhaler taking one inhalation every 15 seconds until the device was empty, but taking no longer than 4 minutes to complete the dose as for part A. The dose time was to be recorded as the time when the participant takes the first inhalation.

Nicorette® Inhaler: The participant was to use the Nicorette Inhaler in line with the manufacturer's prescribing information. Participants were instructed to take 4 inhalations every minute for 20 minutes. The maximum dose was expected to be achieved after 20 minutes of continuous use with deep inhalations.

Venous blood sampling was performed pre-dose and 2, 4, 7, 10, 15, 20, 30, 40, 50, 60, 120, 180, 240 and 300 minutes after the start of inhalation for both treatment periods.

Participants were given a standard light breakfast to be completed one hour before dosing. Fluids were not to be allowed from at least one hour before dosing to one hour after dosing.

Test and reference products
Test:
Medium Oxette® Nicotine Inhaler, 0.056%/w/w nicotine

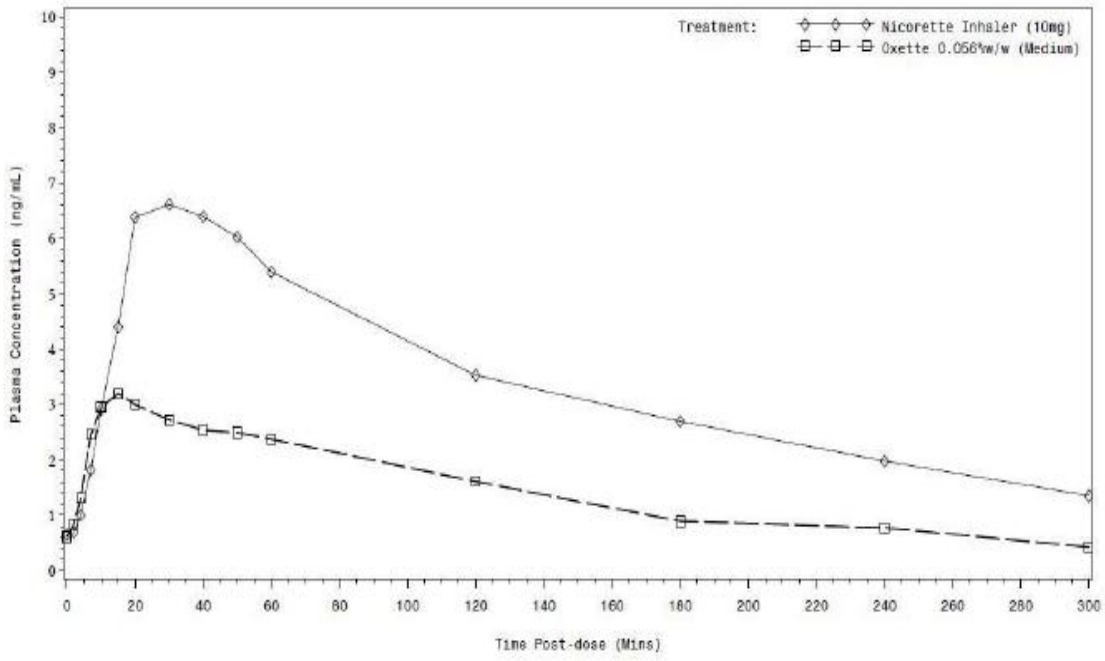
Reference: Nicorette Inhaler (10 mg)

Population(s) studied
24 healthy subjects, 13 male and 11 female aged 18-55 years, who smoked >10 cigarettes/day were included in the study. All 24 subjects completed the study.

Pharmacokinetic Variables
C_{max}; t_{max} and AUC_t.

Results

Mean Venous Plasma Nicotine Concentrations over time (linear)(ng/mL)



Time (Post-dose)	Oxette 0.056%w/w (medium)		Nicorette Inhaler 10 mg	
	Mean	*Std Dev*	Mean	*Std Dev*
Pre-dose	0.61	*1.09*	0.64	*1.05*
2 mins	0.84	*1.15*	0.69	*0.99*
4 mins	1.32	*1.33*	1.00	*1.19*
7 mins	2.45	*1.70*	1.81	*1.76*
10 mins	2.95	*1.56*	2.91	*2.34*
15 mins	3.20	*1.47*	4.40	*2.90*
20 mins	2.99	*1.36*	6.38	*4.87*
30 mins	2.72	*1.03*	6.61	*3.73*
40 mins	2.53	*1.11*	6.39	*3.48*
50 mins	2.49	*1.15*	6.02	*3.16*
60 mins	2.37	*0.95*	5.39	*3.00*
120 mins	1.61	*1.00*	3.52	*1.91*
180 mins	0.89	*1.06*	2.69	*1.74*
240 mins	0.77	*1.00*	1.98	*1.62*
300 mins	0.42	*0.84*	1.35	*1.22*

Summary of mean pharmacokinetic parameters by treatment - Part D

Treatment	C_{max} (ng/mL)		T_{max} (min)		AUC_{last} (min*ng/mL)		AUC_{all} (min*ng/mL)	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Oxette® 0.056%w/w (medium)	3.519	1.378	21.0	13.5	406.1	298.9	433.2	284.6
Nicorette® Inhaler 10 mg	7.628	4.718	36.3	12.4	991.5	595.4	1002.6	584.5

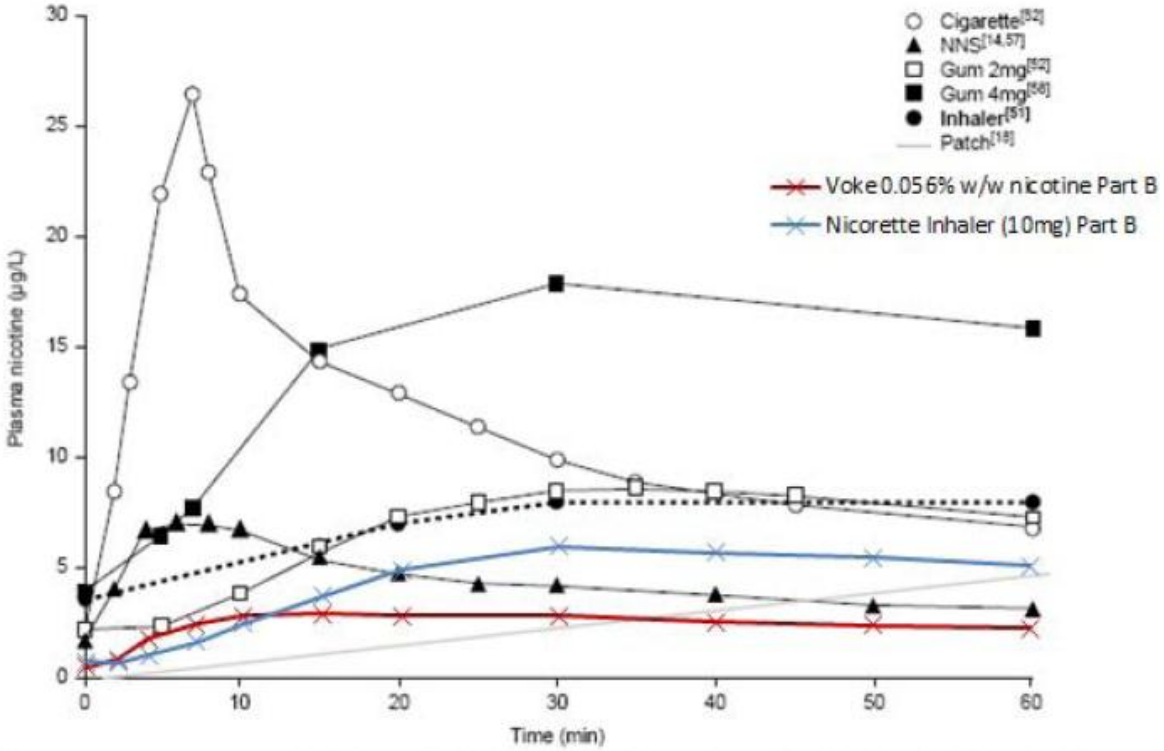
AUC and C_{max} have been presented as a ratio of Test/Reference with 90% confidence intervals above in Part B of the study.

There were no deaths, serious adverse events or other significant adverse events in this study. A total of 61 treatment-emergent adverse events (TEAEs) were reported by 22 (92%) of the 24 participants for the duration of the study. Nineteen (19) participants reported 50 TEAEs that were assessed as "related" to study medication, however, all were of mild severity.

Overall Conclusions on Pharmacokinetics

The pharmacokinetics of nicotine are well-known and not discussed in further detail in this report. Regarding the Voke Inhaler, pharmacokinetic data from three different dose strengths of the Voke Inhaler have been presented. The current applications concern the 'medium strength' tested, 0.056% w/w nicotine.

It is seen that Oxette at dose proposed for marketing achieves a C_{max} approximately half and an AUC_{0-10} comparable with that of the reference, Nicorette Inhaler 10mg. The clinical expert provides further comparative data of the single dose pharmacokinetic profile of the 0.056% w/w inhaler (taken from Part B of the study) relative to other already approved forms of nicotine replacement therapy:



Venous plasma nicotine concentrations for a single cigarette[52] and single doses of the following 'acute' nicotine delivery systems: nicotine nasal spray (NNS),[14,57] nicotine 2mg gum,[52] nicotine 4mg gum[55] and nicotine inhaler.[51] The course of the first hour of transdermal administration is also represented.[18] There are only 3 time-points for the inhaler preparation. Intake time varies with the cigarette smoked over 5 minutes, gum chewed over 30 minutes, inhaler used over 20 minutes (80 puffs). (**insert**) The course of 2 nicotine patches (16 and 24 hours) represented in hours over a 24-hour period.[18]

It is noted that the venous nicotine concentrations achieved by the 0.056%w/w inhaler are substantially lower than those found with other nicotine replacement therapy delivery systems. Therefore the extrapolation of efficacy from other nicotine replacement therapy dosage forms is not straightforward based on pharmacokinetics alone.

The rationale for selecting the medium strength (0.056%w/w nicotine) as the initial to-be-marketed formulation was based on the statistically superior effect on craving compared to the Nicorette Inhaler in the AUC analysis in Part B as well as the arterial pharmacokinetics seen in Part A of study KC001, where the medium strength achieved arterial plasma nicotine concentrations that approached those of the high strength. Part B of the study revealed that the percentage of subjects who reported at least one TEAE was 74%, 91% and 58% for the 0.056% w/w, 0.084% w/w Oxette Inhalers and Nicorette inhaler respectively.

Further evidence to support the efficacy of the Oxette Inhaler is discussed below.

EFFICACY

The efficacy of nicotine replacement therapy and that of the Nicorette Inhaler to which this application makes reference is well-established and will not be discussed further in this report.

Study KC001 also included repeated assessments of craving using a visual analogue scale (VAS) and the Brief Questionnaire of Smoking Urges (QSU-Brief or QSU-B) in all four parts. Parts B and D of the study allowed a direct comparison of the relief of cravings between Oxette and Nicorette.

Participants were asked to assess their level of craving using a 0-10 point VAS when asked "How strong is your craving for cigarettes?" and requested to place a vertical 'line' to indicate their level of craving on a scale of 0 to 10 (no craving being a 0 and strong craving being 10). In Part B, individual craving VAS scores were taken pre-dose and 4, 20, 40, 60, 120, 180, 240 and 300 minutes post-dose. In Part D, individual craving VAS scores were taken pre-dose and 2, 4, 10, 20, 40, 60, 120, 180, 240 and 300 minutes post dose.

Using the QSU-B, at various time points, participants were asked to assess "how do you feel right now" with regard to ten statements on a scale of 1 to 7 (1=strongly disagree to 7=strongly agree)":

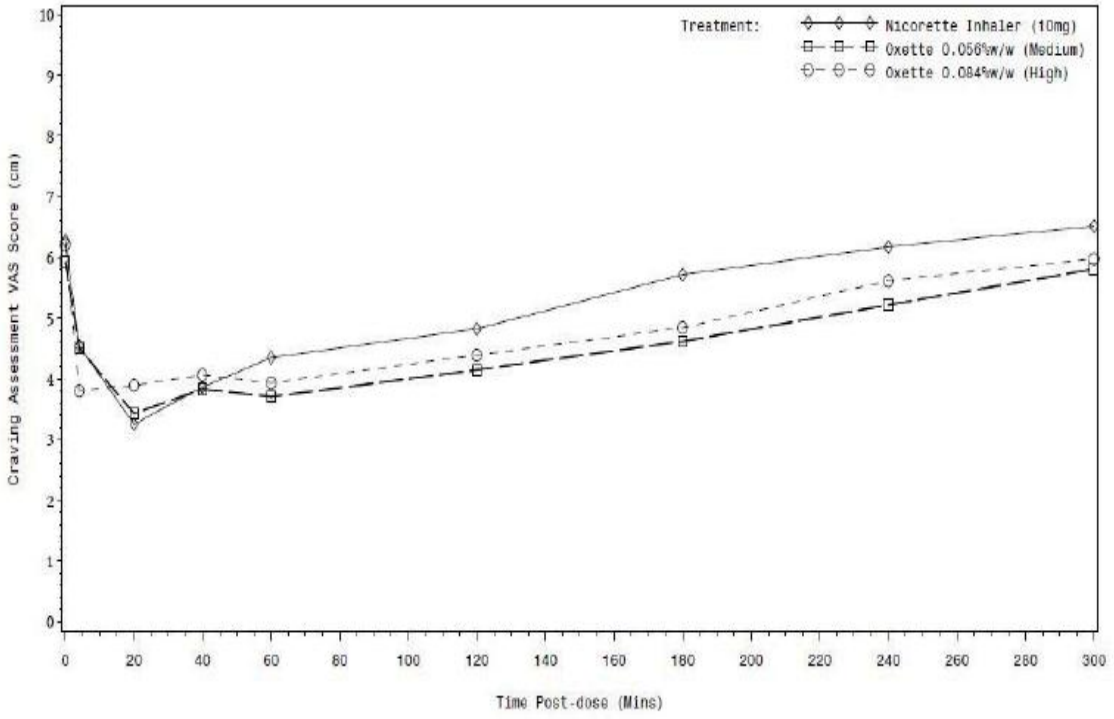
1. I have a desire for a cigarette right now.
2. Nothing would be better than smoking a cigarette right now.
3. If it were possible I would probably smoke now.
4. I could control things better right now if I could smoke.
5. All I want right now is a cigarette.
6. I have an urge for a cigarette.
7. A cigarette would taste good now.
8. I would do almost anything for a cigarette now.
9. Smoking would make me less depressed.
10. I am going to smoke as soon as possible.

The QSU-Brief total score was determined as the average of the 10 responses to the questions above. Component scores were determined for the Desire and Anticipation subscales as follows:

Desire = (Q1 + Q3 + Q6 + Q7 + Q10)/5
Anticipation = (Q2 + Q4 + Q5 + Q8 + Q9)/5

MEAN CRAVING VISUAL ANALOGUE SCALE SCORES (PART B)

Time (Post-dose)	Oxette 0.056%w/w (medium)		Oxette 0.084%w/w (high)		Nicorette Inhaler (10 mg)	
	Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Pre-dose	5.93	2.66	6.22	2.79	6.28	2.25
4 mins	4.50	2.63	3.80	2.86	4.54	2.43
20 mins	3.43	2.29	3.89	2.97	3.25	2.46
40 mins	3.83	2.44	4.07	2.83	3.86	2.48
60 mins	3.70	2.65	3.93	2.54	4.35	2.38
120 mins	4.15	2.78	4.39	2.89	4.83	2.36
180 mins	4.62	2.91	4.84	2.90	5.72	2.15
240 mins	5.22	3.14	5.62	2.84	6.18	2.38
300 mins	5.81	2.84	5.98	2.86	6.52	2.44



The lowest mean craving VAS score was at 20 minutes post-dose for both 0.056%w/w Oxette (medium) and Nicorette Inhaler 10 mg. The mean craving VAS scores then increased over time in a similar way for all three treatment groups reaching near baseline levels at 300 minutes post-dose.

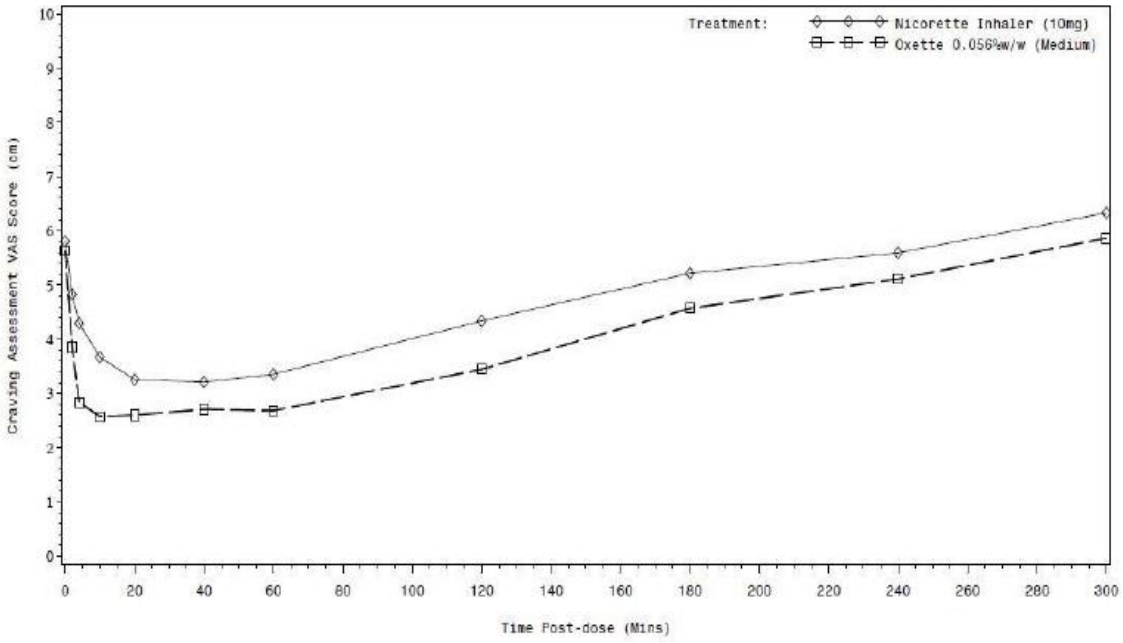
PER-PROTOCOL MEAN QSU-BRIEF COMPONENT AND TOTAL SCORES OVER TIME BY TREATMENT (PART B)

Treatment	Study Time	Anticipation		Desire		Total	
		Mean	Mean Change from pre-dose	Mean	Mean Change from pre-dose	Mean	Mean Change from pre-dose
Oxette® 0.056%w/w (medium)	Pre-dose	3.58	N/A	5.02	N/A	4.30	N/A
	20 mins	2.46	-1.12	3.41	-1.61	2.94	-1.36
	40 mins	2.75	-0.83	3.65	-1.37	3.21	-1.09
	60 mins	2.83	-0.86	3.84	-1.22	3.34	-1.04
	120 mins	2.95	-0.63	3.97	-1.05	3.46	-0.84
	180 mins	3.12	-0.46	4.25	-0.77	3.68	-0.62
	240 mins	3.36	-0.22	4.53	-0.49	3.94	-0.36
	300 mins	3.64	0.09	4.93	-0.12	4.28	-0.01
Oxette® 0.084%w/w (high)	Pre-dose	3.81	N/A	5.21	N/A	4.49	N/A
	20 mins	2.70	-1.11	3.63	-1.58	3.17	-1.33
	40 mins	2.72	-1.09	3.86	-1.35	3.29	-1.20
	60 mins	2.97	-0.84	3.97	-1.24	3.48	-1.02
	120 mins	3.01	-0.80	4.21	-1.00	3.60	-0.89
	180 mins	3.18	-0.63	4.51	-0.70	3.85	-0.65
	240 mins	3.47	-0.34	4.79	-0.42	4.13	-0.36
	300 mins	3.67	-0.05	4.97	-0.22	4.32	-0.12
Nicorette® Inhaler 10 mg	Pre-dose	3.77	N/A	5.26	N/A	4.52	N/A
	20 mins	2.39	-1.38	3.36	-1.90	2.87	-1.64
	40 mins	2.83	-0.94	3.71	-1.55	3.27	-1.25
	60 mins	2.92	-0.85	4.06	-1.20	3.49	-1.02
	120 mins	3.17	-0.60	4.25	-1.01	3.71	-0.80
	180 mins	3.42	-0.35	4.77	-0.49	4.10	-0.42
	240 mins	3.84	0.07	5.04	-0.22	4.44	-0.08
	300 mins	4.02	0.25	5.28	0.02	4.65	0.14

The mean QSU-Brief total scores for all three treatment groups in Part B were at their lowest at the 20 minute post-dose time point, with a slightly higher reduction following administration of the Nicorette Inhaler 10 mg. The mean QSU-Brief total scores then rose steadily and reached near baseline values at 300 minutes post-dose.

MEAN CRAVING VISUAL ANALOGUE SCALE SCORES (PART D)

Time (Post-dose)	Oxette 0.056%w/w (medium)		Nicorette Inhaler (10 mg)	
	Mean	Std Dev	Mean	Std Dev
Pre-dose	5.63	2.50	5.80	2.95
4 mins	2.83	2.54	4.29	2.80
20 mins	2.60	2.70	3.25	3.03
40 mins	2.70	2.79	3.21	2.93
60 mins	2.68	2.72	3.35	3.22
120 mins	3.44	2.72	4.34	3.14
180 mins	4.57	2.49	5.22	3.03
240 mins	5.11	2.73	5.59	3.14
300 mins	5.86	2.86	6.33	2.99



The mean craving VAS scores for both treatment groups in Part D were reduced at 4 minutes post-dose, however the lowest mean craving VAS score was at 20 minutes post-dose for 0.056%w/w Oxette (medium) and 40 minutes post-dose for Nicorette Inhaler 10 mg. The mean VAS scores then increased over time in a similar way for both treatments reaching slightly above baseline levels at 300 minutes post-dose. The mean craving VAS scores were consistently lower following administration of Oxette than Nicorette, and remained lower for Oxette for the duration of the study.

PER PROTOCOL MEAN QSU-BRIEF COMPONENT AND TOTAL SCORES OVER TIME BY TREATMENT (PART D)

Treatment	Study Time	Anticipation		Desire		Total	
		Mean	Mean Change from pre-dose	Mean	Mean Change from pre-dose	Mean	Mean Change from pre-dose
Oxette® 0.056%w/w (medium)	Pre-dose	3.23	N/A	5.43	N/A	4.33	N/A
	20 mins	2.36	-0.91	3.91	-1.69	3.14	-1.29
	40 mins	2.27	-1.00	3.88	-1.72	3.07	-1.36
	60 mins	2.27	-1.00	4.07	-1.53	3.17	-1.27
	120 mins	2.51	-0.76	4.44	-1.16	3.49	-0.95
	180 mins	2.93	-0.34	5.25	-0.35	4.10	-0.33
	240 mins	3.13	-0.14	5.40	-0.20	4.25	-0.19
	300 mins	3.48	0.21	5.76	0.16	4.62	0.18

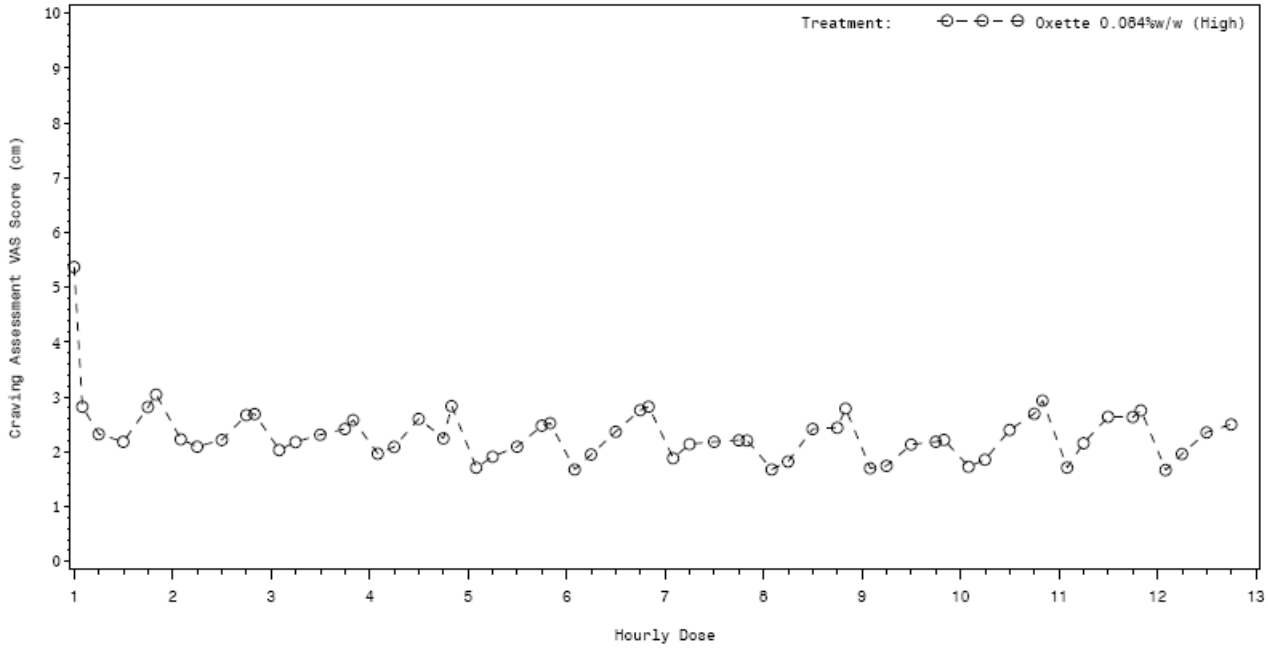
Treatment	Study Time	Anticipation		Desire		Total	
		Mean	Mean Change from pre-dose	Mean	Mean Change from pre-dose	Mean	Mean Change from pre-dose
Nicorette® Inhaler 10 mg	Pre-dose	3.51	N/A	5.61	N/A	4.56	N/A
	20 mins	2.50	-0.91	3.77	-1.78	3.13	-1.35
	40 mins	2.36	-1.05	4.00	-1.55	3.18	-1.30
	60 mins	2.52	-0.89	4.16	-1.39	3.34	-1.14
	120 mins	2.77	-0.64	4.75	-0.80	3.76	-0.72
	180 mins	3.02	-0.39	5.21	-0.35	4.10	-0.38
	240 mins	2.98	-0.43	5.32	-0.23	4.16	-0.32
	300 mins	3.60	0.11	5.82	0.17	4.72	0.14

The mean QSU-Brief total scores for both treatment groups in Part D were reduced by the 20 minute post-dose time points, with a very similar level of reduction. The mean QSU-Brief total scores then rose steadily and reached near baseline values at 300 minutes post-dose. The QSU-Brief component and total scores were at their lowest 20 and 40 minutes post dose for both treatments administered in Part D of the study.

The effect of multiple doses of the Oxette Inhaler over the course of a day has been investigated in Part C of study KC001. Part C was an open label study to evaluate the tolerability and venous pharmacokinetics of repeat doses of orally inhaled nicotine via the Oxette Inhaler. Eighteen (18) participants were enrolled into Part C. Each participant inhaled one complete refill (dose) of the Oxette Inhaler every hour for 12 hours with the first dosing taking place at approximately 8 am. Craving was assessed prior to each dose and at 5, 15, 30 and 45 minutes post dose. Figure 14.2.1.7 below

included within the Clinical Overview (page 30, figure 18) shows that inhaling repeated refills of the Voke Inhaler had a reproducible effect on craving with craving being reduced from baseline with the first inhalation – then increasing just prior to the next refill, followed by another period of craving suppression.

Figure 14.2.1.7
Mean Craving Scores Over Time by Dose, Part C



Unlike Parts B and D of Study KC001 where the Nicorette Inhaler 10mg was used as a comparator product, Part C only involved the Oxette Inhaler (0.084% w/w nicotine), thus any assessment of craving effect between the two products over multiple doses will require a literature-based comparison. Lunell (1995) investigated the effect of the Nicorette Inhalator (referred to as the vapour inhaler) on craving over a 2 day period of smoking abstinence. Subjects were requested to maintain their normal daily activities, and to use no less than 5 and no more than 15 cartridges containing 10mg nicotine per study day. It was entirely at the discretion of the subject when he/she would self-administer the Inhalator during the day.

Both active and placebo Inhalators were used in this study. Subjects were assessed for urge to smoke and missing cigarette (each on a 10cm VAS score) and the two scores were combined to give a score out of 20.

VAS ratings were done at 08.00, 11.00, 15.00, 18.00 and 22.00 h on the first study day and at 08.00, 11.00, 15.00 and 18.00 h on Day 2. Two inhalation techniques were used, with no difference found between the two ('pulmonary' and 'buccal' techniques). The 'pulmonary mode' corresponds to the inhalation regimen also used in Parts B & D of Study KC001.

The figure below shows the craving score (out of 20), for the Nicorette Inhalator using on average 12 cartridges over the day and a placebo control. It can be seen that when compared to placebo, craving is reduced by approximately 40-50% over the course of the 2 days.

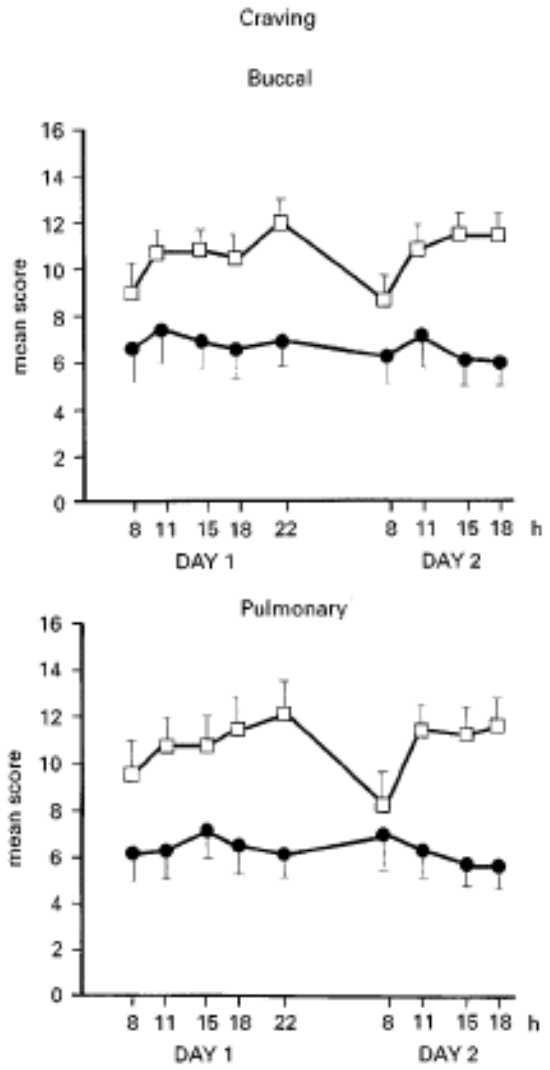
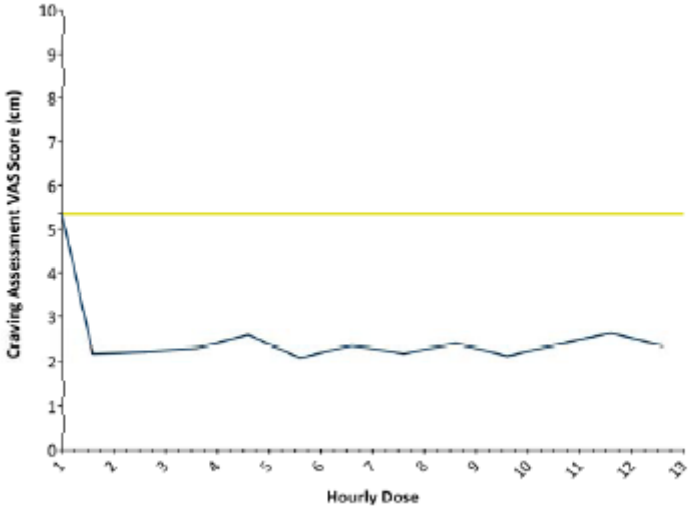


Fig. 1 The effect of nicotine vapour inhalation on total craving score during a two-day smoke-free period. Rating of craving for cigarettes was made after treatment with active (●) and placebo (□) inhaler using buccal (*upper graph*) and pulmonary (*lower graph*) inhalation techniques. Subjects were allowed to use the inhaler from the time of waking. The first rating was done at 08.00 h. Mean with SEM, $n = 15$. The difference between active and placebo inhaler treatment was statistically significant ($P < 0.005$) at all time-points except for 08.00 h on both days

In the absence of a placebo group in Part C of Study KC001, a comparison with the Nicorette data described above can only be descriptive. Re-plotting the Part C data from KC001 to only show the 30 minutes post dose craving scores indicates that over the course of a day craving is reduced by approximately 50% from first pre-dose baseline reading.

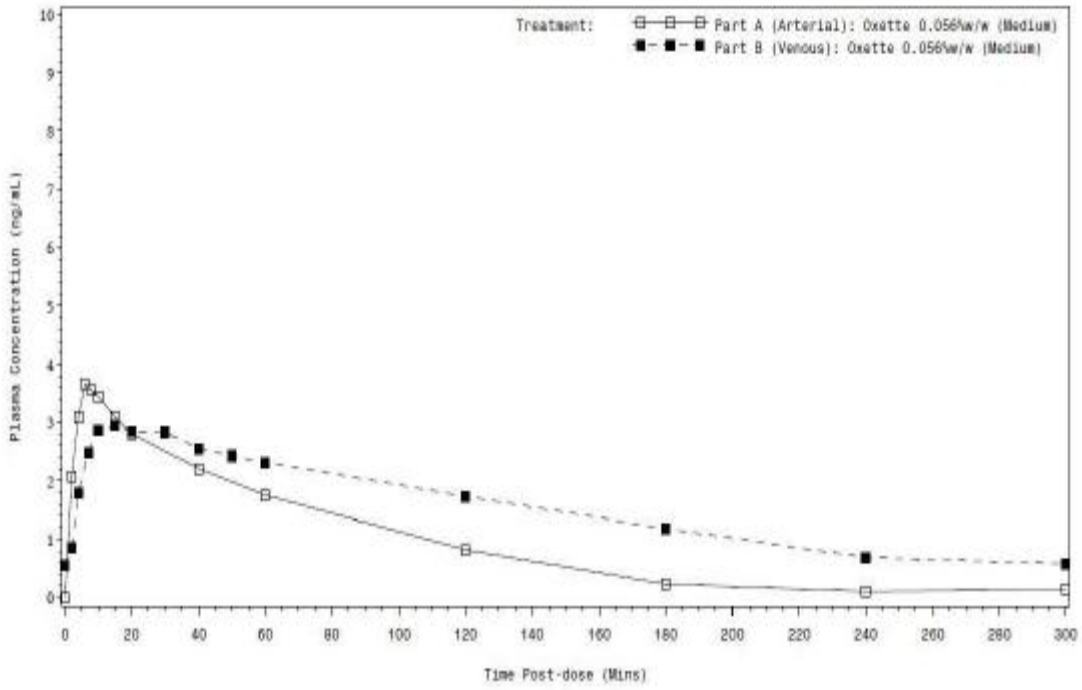


In terms of a nicotine exposure an average of 12 cartridges containing 10mg each were used in the Lunell et al. study per day, i.e. 120mg nicotine of which approximately 48mg is expected to be extracted by inhalation By comparison the 12 doses of the Oxette Nicotine Inhaler (high) 0.084% w/w nicotine would contain a total nicotine dose of approximately (0.67mg x 12) 8mg nicotine.

Perhaps surprisingly, given the far lower venous nicotine concentrations achieved by the 0.056%w/w inhaler relative to the Nicorette Inhalator, very similar reductions in craving are seen following single doses of both products.

The Nicorette Inhalator generates a vapour that results in predominantly oromucosal deposition and absorption, hence the relatively slow delivery of nicotine with a T_{max} of 38.0 minutes compared with 18.7 minutes for the medium strength Oxette. The faster delivery by the Oxette probably represents a greater degree of pulmonary absorption which is evidenced by the comparison of the arterial and venous pharmacokinetics (taken from Part A and B of study KC001):

ARTERIAL VERSES VENOUS MEAN PLASMA NICOTINE CONCENTRATIONS OVER TIME BY TREATMENT, OXETTE® 0.056%W/W (LINEAR)



The pattern of the appearance of nicotine in arterial blood followed by a delayed appearance in venous blood is consistent with a proportion of the nicotine being absorbed through the lungs into pulmonary venous blood with subsequent systemic circulation. This also results in a shorter T_{max} for Oxette compared to the inhalator which seems to correspond to earlier relief of cravings, as seen in Study Part D.

Therefore, despite producing lower plasma nicotine AUC and C_{max}, the shorter T_{max} might explain the similar effect to Nicorette Inhalator with regard to craving relief. This is reassuring in terms of the likely efficacy of the product. Maintenance of craving levels following multiple use over the course of a day in Part C is also reassuring.

SAFETY

The adverse events recorded in Study KC001 are detailed above. As described, almost all of the subjects enrolled in Study KC001 experienced a treatment emergent adverse event, although these were mild in nature and consistent with other forms of nicotine replacement therapy. There were no serious adverse events or deaths throughout the study, and no participants discontinued treatment due to an adverse event.

Oral paraesthesia was by far the most frequently reported TEAE that was related to Oxette in all parts of the study, with an overall of 51 participants (61%) reporting oral paraesthesia at least once. Eighteen (18) of the 83 participants (22%) reported throat irritation, 11 participants (13%) reported headache, and 9 participants (11%) reported oral hypoaesthesia as a TEAE that was related to Oxette. The remaining TEAEs occurred in less than 10% of the overall patient population.

EXPERT REPORTS
A clinical expert report has been written by a suitably qualified person and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)
The SmPCs are satisfactory and consistent with those for other similar products.

PATIENT INFORMATION LEAFLET (PIL)
The PILs are satisfactory and consistent with those for other similar products.

LABELLING
This is satisfactory

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A Risk Management Plan has been developed to ensure that Voke/Nicotine 0.45mg Inhalers are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the PIL for Voke/Nicotine 0.45mg Inhalers, including the appropriate precautions to be followed by healthcare professionals and patients.

A summary of the risk minimisation activities is presented below:

Risk	Routine risk minimisation activities	Additional risk minimisation activities
Identified		
None	NA	None
Potential		
Cardiovascular events	SPC and PIL	Post-marketing pharmacoepidemiologic prospective cohort study (Study NVPMS001).
Respiratory events	SPC and PIL	Post-marketing pharmacoepidemiologic prospective cohort study (Study NVPMS001).
Use in children or adolescents	SPC and PIL	Post-marketing pharmacoepidemiologic prospective cohort study (Study NVPMS001) and adolescent cohort surveillance study (Study NVPMS002).
Gateway to smoking	Communications will encourage stopping smoking completely to maximise health benefits of reduction.	Post-marketing pharmacoepidemiologic prospective cohort study (Study NVPMS001) and adolescent cohort surveillance study (Study NVPMS002).
Quitter relapse to Voke	Targeted consumer promotion towards adult smokers only	Post-marketing pharmacoepidemiologic prospective cohort study (Study NVPMS001).

APPLICATION FORMS (MAA)
These are satisfactory.

MEDICAL CONCLUSION
The grant of marketing authorisations is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Voke/Nicotine 0.45mg Inhalers 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
No new non-clinical data were submitted and none are required for applications of this type. There are no non-clinical issues in respect to impurities for these products. No non-clinical concerns are raised in respect to excipients, propylene glycol use is within established limits and any potential concern is limited due to a minimum age of 18 years for users of this product. Overall, the risk of extractables and leachables to contain compounds considered to be of high carcinogenic risk is low.

CLINICAL
One clinical study, composed of four parts, was performed to determine the pharmacokinetics and tolerability of the inhaled nicotine products versus the reference medicine, Nicorette Inhalator (McNeil Products Limited). Additionally, Parts B and D of this study measured the reduction in cravings of these products versus Nicorette Inhalator (McNeil Products Limited).

It is seen that Oxette at dose proposed for marketing achieves a C_{max} approximately half and an AUC_{0-10} comparable with that of the reference, Nicorette Inhaler 10mg. Comparison with other forms of NRT indicates that the Voke inhaler can expect to achieve far lower venous plasma concentrations of nicotine than other available nicotine replacement treatment dosage forms.

However, Voke/Nicotine 0.45mg Inhalers have a shorter T_{max} than the reference inhalator product and on the basis of a single-dose and multiple-dose administrations, appears to achieve earlier onset and comparable levels of craving relief.

SAFETY
The adverse event profile is similar to that established for other nicotine replacement treatment products.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The clinical data provided show comparable efficacy with the reference product. Extensive clinical experience with nicotine is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk ratio is considered to be positive.

Voke 0.45mg Inhaler
PL 39589/0001
Nicotine 0.45mg Inhaler
PL 39589/0002

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 02 November 2012.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 20 November 2012.
3	Following assessment of the application the MHRA requested further information on 26 February 2013, 07 January 2014 and 30 April 2014.
4	The applicant responded to the MHRA's requests, providing further information on 24 April 2013, 12 July 2013, 19 November 2013, 19 March 2014, and 20 May 2014, 25 June 2014 and 13 August 2014.
5	The application was determined on 11 September 2014.

Voke 0.45mg Inhaler
PL 39589/0001
Nicotine 0.45mg Inhaler
PL 39589/0002

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics and Patient Information Leaflet

The current approved versions of the SmPC and PIL are available on the MHRA website.

Labelling

PARTICULARS TO APPEAR ON THE PACKAGING

CARTON/PACK BODY

1. NAME OF THE MEDICINAL PRODUCT

Nicotine 0.45mg Inhaler
Nicotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

nicotine 0.45mg

3. LIST OF EXCIPIENTS

Also contains propylene glycol, ethanol, levomenthol, saccharin and HFA134a (a CFC-free propellant).

4. PHARMACEUTICAL FORM AND CONTENTS

20 0.45mg charges
Contents: 1 stick and 1 pressurised canister containing 20 charges, each containing 0.45mg nicotine, equivalent to a delivered dose of 0.43mg nicotine, except for the first charge which delivers less (see leaflet for details).

2x1 packs:
2 x 20 0.45mg charges
Contents: This multipack contains 2 packs, each containing 1 stick and 1 pressurised canister containing 20 charges. Each charge contains 0.45mg nicotine, equivalent to a delivered dose of 0.43mg nicotine, except for the first charge which delivers less (see leaflet for details).
5x1 packs:
5 x 20 0.45mg charges
Contents: This multipack contains 5 packs, each containing 1 stick and 1 pressurised canister containing 20 charges. Each charge contains 0.45mg nicotine, equivalent to a delivered dose of 0.43mg nicotine, except for the first charge which delivers less (see leaflet for details).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Nicotine 0.45mg Inhaler can help with cravings when you stop smoking or cut down or replace the number of cigarettes you smoke. This is a safer alternative for you and those around you. You should aim to stop smoking and this may help your motivation to quit. Nicotine Inhaler is for adults over 18 years of age.

CLICK open the side door. Remove the stick. Hold the pack upright. Insert white end into the port at the base of the Nicotine 0.45mg Inhlaer pack, push firmly, CHARGE for five seconds and release. Charge new sticks twice. Draw gently through the filter end to activate and INHALE.

Maximum daily dose 2 packs.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Once opened discard after 7 days. Pressurised can. Do not puncture, break or burn even when empty. Do not expose to temperatures higher than 50°C. Store away from heat or direct sunlight.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kind Consumer Ltd.
79 Clerkenwell Rd
London EC1R 5AR

12. MARKETING AUTHORISATION NUMBER(S)

PL 39589/0002

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

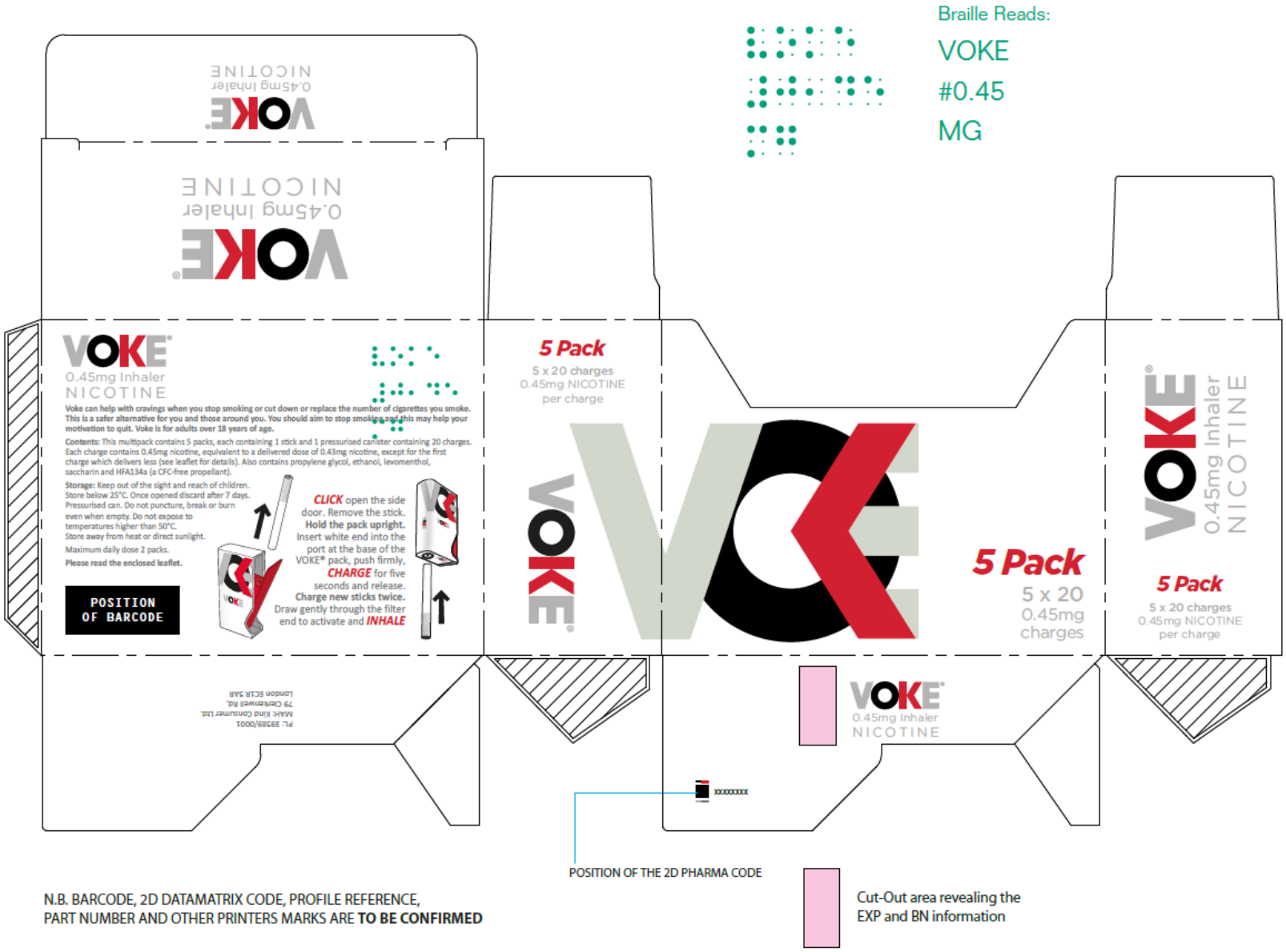
15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nicotine 0.45 mg Inhaler

POSITION OF THE 2D PHARMA CODE


VOKE
0.45mg Inhaler
NICOTINE
Twin Pack
2 x 20
0.45mg
charges
Twin Pack
2 x 20 charges
0.45mg NICOTINE
per charge
Voke can help with cravings when you stop smoking or cut down or replace the number of cigarettes you smoke. This is a safer alternative for you and those around you. You should aim to stop smoking and this may help your motivation to quit. Voke is for adults over 18 years of age.
Contents: This multipack contains 2 packs, each containing 1 stick and 1 pressurised canister containing 20 charges. Each charge contains 0.45mg nicotine, equivalent to a delivered dose of 0.43mg nicotine, except for the first charge which delivers less (see leaflet for details). Also contains propylene glycol, ethanol, levomenthol, saccharin and HFA134a (a CFC-free propellant).
Storage: Keep out of the sight and reach of children. Store below 25°C. Once opened discard after 7 days. Pressurised can. Do not puncture, break or burn even when empty. Do not expose to temperatures higher than 50°C. Store away from heat or direct sunlight.
Maximum daily dose 2 packs.
Please read the enclosed leaflet.
POSITION OF BARCODE
PL: 39589/0001
MAH: Kind Consumer Ltd.
79 Clerkenwell Rd,
London EC1R 5AR
CLICK open the side door. Remove the stick. Hold the pack upright. Insert white end into the port at the base of the VOKE® pack, push firmly, CHARGE for five seconds and release. Charge new sticks twice. Draw gently through the filter end to activate and INHALE
XXXXXXXX
XXXXXXXX
POSITION OF THE 2D PHARMA CODE


Braille Reads:
VOKE
#0.45
MG
VOKE
0.45mg Inhaler
NICOTINE
VOKE
0.45mg Inhaler
NICOTINE
VOKE
0.45mg Inhaler
NICOTINE
Voke can help with cravings when you stop smoking or cut down or replace the number of cigarettes you smoke. This is a safer alternative for you and those around you. You should aim to stop smoking and this may help your motivation to quit. Voke is for adults over 18 years of age.
Contents: This multipack contains 5 packs, each containing 1 stick and 1 pressurised canister containing 20 charges. Each charge contains 0.45mg nicotine, equivalent to a delivered dose of 0.43mg nicotine, except for the first charge which delivers less (see leaflet for details). Also contains propylene glycol, ethanol, levomenthol, saccharin and HFA134a (a CFC-free propellant).
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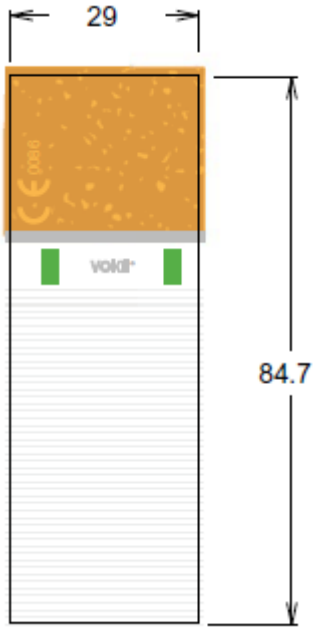
Maximum daily dose 2 packs.
Please read the enclosed leaflet.
POSITION OF BARCODE
CLICK open the side door. Remove the stick. Hold the pack upright. Insert white end into the port at the base of the VOKE® pack, push firmly, CHARGE for five seconds and release. Charge new sticks twice. Draw gently through the filter end to activate and INHALE
PL 39389/0001
MAK Kind Consumer Ltd.
79 Chiswell Rd.
London EC1R 5AR
5 Pack
5 x 20 charges
0.45mg NICOTINE
per charge
VOKE
5 Pack
5 x 20
0.45mg
charges
VOKE
0.45mg Inhaler
NICOTINE
5 Pack
5 x 20 charges
0.45mg NICOTINE
per charge
xxxxxxx
POSITION OF THE 2D PHARMA CODE
N.B. BARCODE, 2D DATAMATRIX CODE, PROFILE REFERENCE, PART NUMBER AND OTHER PRINTERS MARKS ARE TO BE CONFIRMED
Cut-Out area revealing the EXP and BN information


29
84.7
voke