Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

e-Voke 10mg Electronic Inhaler
PL 42601/0003

e-Voke 15mg Electronic Inhaler
PL 42601/0004

(Nicotine)

UKPAR

Nicovations Limited

e-Voke 10mg Electronic Inhaler
PL 42601/0003

e-Voke 15mg Electronic Inhaler
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LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for e-Voke 10mg and 15mg Electronic Inhaler (termed 'e-Voke Electronic Inhaler' in this document). It explains how the marketing authorisation applications for e-Voke Electronic Inhaler 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 e-Voke Electronic Inhaler.

For practical information about using e-Voke Electronic Inhaler, patients should read the package leaflet or contact their doctor or pharmacist.

What is e-Voke Electronic Inhaler and what is it for?

e-Voke Electronic Inhaler is used to relieve and /or prevent withdrawal symptoms and reduce the cravings smokers get when they try to stop smoking or when they cut down the number of cigarettes that they smoke. e-Voke Inhalation Cartridges (called cartridges) are for use only with e-Voke Electronic Inhaler (called inhaler).

How does e-Voke Electronic Inhaler work?

e-Voke contains nicotine. It belongs to a group of medicines known as nicotine replacement therapy (NRT).

When smokers stop smoking or cut down the number of cigarettes they smoke, their body misses the nicotine that they have been getting from cigarettes. They may experience unpleasant feelings and a strong desire to smoke (craving). The nicotine they get from using e-Voke replaces the nicotine that they were getting from cigarettes. This relieves the unpleasant withdrawal symptoms. It will also help to stop their craving to smoke.

Benefits from using NRT instead of smoking

Nicotine replacement therapy, such as e-Voke, can help relieve nicotine withdrawal symptoms such as irritability, low mood, anxiety, restlessness and cravings when used in place of cigarettes. NRT may benefit smokers who want to quit, by helping to control weight gain that may be experienced when trying to stop 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. The benefits of stopping smoking clearly outweigh any potential risk from using nicotine from NRT.

How is e-Voke Electronic Inhaler used?

For adults aged 18 years and over:

- 10 inhalations: typically the amount needed before cravings will go away.

- 10 inhalations: contain approximately 0.38mg or 0.56mg of nicotine depending on the cartridge strength, although the actual amount will vary depending on how deeply a user inhales. How often there is need to use the inhaler depends on how many cigarettes used to be smoked.
- 130 inhalations: is about the amount in each cartridge. This depends on the depth and length of user inhalations.
- 5 cartridges per day: the maximum you should use. It is up to you how many inhalations you use and how often you use them.

If a smoker is able to stop smoking they should use e-Voke, when needed, in place of cigarettes. As soon as they can, they should reduce the number of cartridges they use until they have stopped using them completely. They should continue using e-Voke until cravings for nicotine disappear.

If a smoker has quit smoking and wants to stop using e-Voke, but is finding this difficult they should contact their doctor, pharmacist or nurse for advice.

e-Voke is made up of: e-Voke Electronic Inhaler (inhaler) and Inhalation Cartridges (cartridges). The cartridges must not be used with any other electronic inhaler. There is a risk of serious injury if the cartridges are used in other delivery devices.

How has e-Voke Electronic Inhaler been studied?

Nicovations Limited has provided data from the published literature on the use of inhaled nicotine for smoking cessation. In addition, a clinical study has been provided, comparing the blood nicotine levels in subjects using e-Voke 10mg and 15mg Electronic Inhaler versus the reference product Nicorette 15mg Inhalator and after smoking a cigarette.

What are the benefits and risks of e-Voke Electronic Inhaler?

Because e-Voke Inhalers use the same doses of nicotine as other NRT products on the market, the benefits and risks are taken as being the same as those for other NRT products.

Why is e-Voke Electronic Inhaler approved?

The use of nicotine in smoking cessation is well-established and there are a number of approved products on the market. In addition, the clinical study submitted showed that using e-Voke Electronic Inhaler resulted in comparable blood nicotine levels than using Nicorette Inhalator. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of e-Voke Electronic Inhaler outweigh the risks and the grant of Marketing Authorisations was recommended.

What measures are being taken to ensure the safe and effective use of e-Voke Electronic Inhaler?

Safety information has been included in the Summaries of Product Characteristics and the package leaflets for e-Voke Electronic Inhaler, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about e-Voke Electronic Inhaler.

Marketing Authorisations were granted in the UK on 16 November 2015 to Nicoventures Trading Limited (PL 40317/0001-2). Following a change of authorisation holder that was

granted on 19 November 2015, the current marketing authorisation holder is Nicovations Limited (PL 42601/0003-4).

The full PAR for e-Voke Electronic Inhaler follows this summary.

For more information about treatment with e-Voke Electronic Inhaler, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2015.

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INTRODUCTION

The MHRA granted Nicoventures Trading Limited Marketing Authorisations (licences) for the medicinal products e-Voke 10mg and 15mg Electronic Inhaler (PL 40317/0001-2) on 16 November 2015. These products are on the General Sales List (GSL), and are used to relieve and/or prevent withdrawal symptoms and reduce the cravings 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. e-Voke is also indicated in pregnant and lactating women making a quit attempt.

These applications were submitted as hybrid applications according to Article 10(3) of Directive 2001/83/EC, as amended. The reference product for this application was Nicorette 10mg Inhalator (PL 15513/0358), which was licensed to McNeil Products Limited (formerly Pharmacia 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. Since e-Voke inhaler is intended for substitution with products already on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

One clinical study was performed, comparing the blood nicotine levels in subjects using e-Voke 10mg and 15mg Electronic Inhaler versus the reference product Nicorette 15mg Inhalator and after smoking a cigarette.

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.

Following a change of authorisation holder that was granted on 19 November 2015, the current marketing authorisation holder is Nicovations Limited (PL 42601/0003-4).

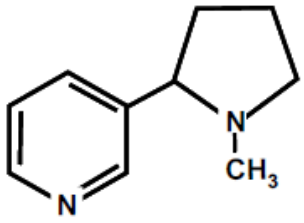
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE– Nicotine

INN: Nicotine

Chemical name: 3-[(2S)-1-methylpyrrolidin-2-yl]pyridine
(S)-3-(1-Methyl-2-pyrrolidinyl)pyridine
ß-Pyridyl-α-N-methyl pyrrolidine

Structure:



Nicotine

Molecular formula: $C_{10}H_{14}N_2$
Molecular weight: 162.24
Appearance: Colourless or yellow-brownish viscous liquid, very hygroscopic
Solubility: soluble in water, miscible in alcohol

Nicotine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of nicotine are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

MEDICINAL PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients glycerol and water for injections.

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, safe formulation of nicotine that could be used in a delivery device interchangeably with the reference product Nicorette 10mg Inhalator (McNeil Products Limited).

The delivery of nicotine from the inhalation cartridge is controlled by the inhaler delivery device. The device is breath activated by the user.

The delivery device is a Class IIa medical device. The device has been assessed against the requirements of the Medical Devices Directive 93/42/EEC and complies with the relevant annexes. The manufacturing of the device is controlled through an ISO 13485:2003 certified quality management system. Additional controls are in place through certification against the Medical Devices Directive Annex 5.

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 commercial-scale batches. The results are satisfactory.

Finished product specification

The finished product specifications are 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

e-Voke inhalation cartridge is a colourless polypropylene cartridge, containing a polyurethane foam matrix, which is sealed with an aluminium/polyethylene co-extrusion foil. This cartridge is contained within a light brown polypropylene mouthpiece, which is packed in polyethylene terephthalate/polyester/aluminium blisters.

e-Voke Electronic Inhaler comprises a stainless steel vaporiser and battery unit with a clear polypropylene protective cap which fits over the vaporiser and is removed before use. A USB charger is also provided to recharge the battery.

Each blister contains five cartridges.

Pack sizes:
One e-Voke Electronic Inhaler and five inhalation cartridges
Replacement cartridge packs: 5, 10 or 20 inhalation cartridges.

Not all pack sizes may be marketed. However, the marketing authorisation holder has agreed to provide mock-ups to the MHRA for approval before marketing any pack size.

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, the following shelf-lives and storage conditions have been accepted:
<u>e-Voke inhalation cartridges:</u>
24 months.

In-use shelf life: Once inserted into the mouthpiece the cartridge should be disposed of within 24 hours.

<u>e-Voke Electronic Inhaler:</u>
2 years

In-use shelf life: 6 weeks

Storage conditions: Store below 25°C. Protect from light.

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

As the general safety of the drug substance nicotine has been well-documented over many years of extensive clinical use, the effects of nicotine are well-known and there are several approved nicotine-containing medicinal products on the market (including Nicorette Inhalator, Nicorette Nasal Spray). Therefore, the non-clinical data are based exclusively on literature references and no new non-clinical studies have been performed in support of this application.

One clinical study has been submitted with these applications; a comparative bioavailability study comparing the bioavailability of nicotine when delivered using the proposed 10mg and 15mg Inhalation Cartridge versus the reference product Nicorette 15 mg Inhalator and after smoking a cigarette (Benson & Hedges Gold). It was determined that plasma concentrations of nicotine following administration using the e-Voke Inhaler products were higher than those observed after use of the reference product (Nicorette 15mg Inhalator) and is likely to be similar to, or less than, exposure resulting from smoking a cigarette. Thus, any risk from nicotine exposure, associated with e-Voke Inhaler use should at worst be equivalent to the risks already experienced by the smoker. However, nicotine is generally considered to be non-mutagenic, and expert opinion from the European Food Safety Authority (EFSA), the World Health Organisation's International Programme on Chemical Safety (IPCS) and the International Agency for Research on Cancer (IARC) do not classify nicotine as a carcinogen, tumour initiator, tumour promoter or co-carcinogen. Therefore, it is plausible that the use of e-Voke Inhaler would pose a more favourable outcome for users as an alternative to continuing smoking because of the absence of tobacco combustion products.

Based on the established safety profile of nicotine, this assessment placed emphasis on the novel method of delivery of the drug substance (vaporisation then inhalation) and hence relevant animal inhalation studies and the exposure to potential leachables and extractables in order to establish that the polyurethane foam that contains the nicotine is fit for purpose.

It has been demonstrated that the user will be exposed to inhaled water vapour, which is considered harmless and also to inhaled glycerol. Calculation suggest that the exposure to inhaled glycerol, if the product is used as indicated, is acceptable for the adult patient population and supported by the known toxicology of inhaled glycerol.

As a result of recent concerns raised about the use of nicotine-containing products in children, the decision has been taken to restrict the use of e-Voke Inhalers to adults only. The Summaries of Product Characteristics (SmPCs) contraindicate the use of the product in children and adolescents under the age of 18 years. This can be accepted from a non-clinical perspective.

In December 2011 the MHRA advised that 'a justification for the absence of local tolerance testing in line with guidance [Guideline on Non-clinical Local Tolerance testing of Medicinal Products (CPMP/SWP/2145/00)] should be included in the non-clinical overview along with a discussion of the likely toxicity of the excipients. This critical discussion together with clinical experience with the proposed excipients (demonstration of previous use in inhaled products) may obviate the need for specific non-clinical studies.'

Nicotine and glycerol are found in other licensed medicines that deliver these to the buccal, throat, trachea and lungs. Moreover, there are no safety signals in the bibliographic search conducted that indicate a local tolerability concern with glycerol or new concerns associated with nicotine. The unlicensed version of these products (Intellicig) was available on the market for several years with no reports of local tolerance issues and there were no reported local tolerance issues following the relative bioavailability study –hence the absence of specific non-clinical local tolerance data can be accepted at this time from a non-clinical perspective.

The safety margin for all potentially leachable and extractable substances was generally acceptable. A separate toxicological assessment has been performed to review the toxicology of EHDPP. Data suggests it appears at low total levels with adequate safety margins at the inhaled No Observed Adverse Event Concentration (NOAEC). Regarding the 'newly identified' leachable DPP; the amount present in the vapour generated by this electronic cigarette is reportedly independent of the concentration of this leachable in the cartridge (based on studies with cartridges spiked with DPP). Limits have been introduced for the level of DPP and EHDPP based on the aforementioned safety factors in the foam specification to be determined by extractables testing in order to control the amount that may leach into the product formulation. These are acceptable.

There were no non-clinical concerns relating to the drug substance or drug product impurity profile, including the residual solvents and degradation products.

Since e-Voke inhaler is intended for substitution with products already on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

CLINICAL ASSESSMENT

INTRODUCTION

A bioavailability study supported by a literature review of the pharmacokinetics, safety and efficacy of nicotine replacement therapies (NRTs) and cigarettes were submitted with these applications.

CLINICAL PHARMACOLOGY

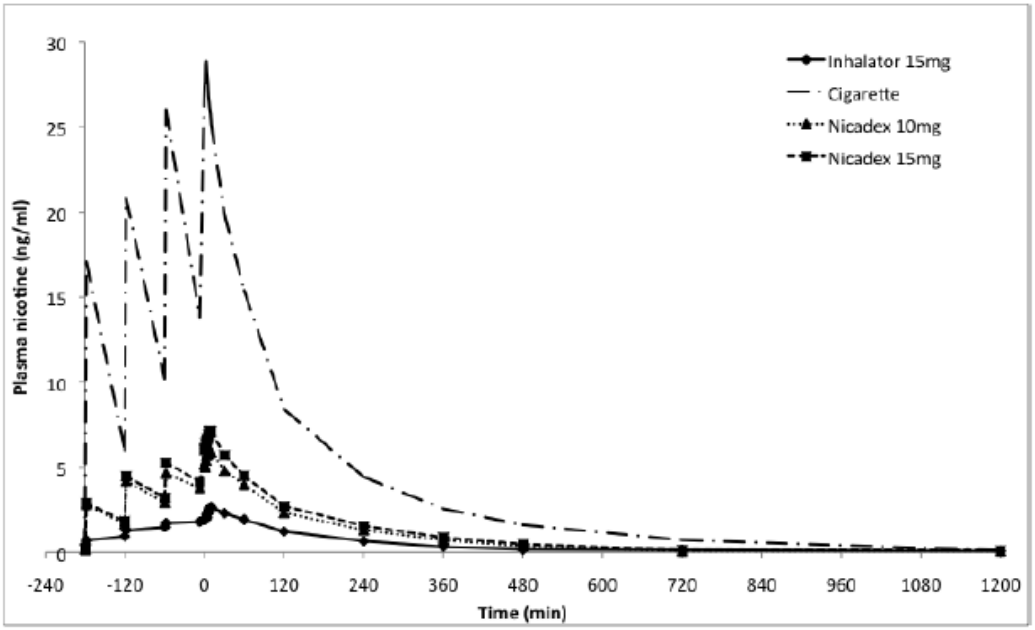
In support of these applications, the below pharmacokinetic study was submitted:

A randomised four-way crossover, relative bioavailability study of nicotine delivered by an electronic cigarette, Nicorette Inhalator and cigarette smoking

In the clinical study, nicotine plasma concentrations were evaluated in 24 healthy male smokers following the use of e-Voke Inhaler 10mg, e-Voke Inhaler 15mg, Nicorette 15 mg Inhalator (as reference product) and a standard cigarette. Subjects were instructed to take ten inhalations at 30 seconds intervals (i.e. approximately 4.5 minutes). Another three administrations were done at 1-hour intervals. Each treatment was administered in a crossover manner over 4 days (one treatment per day). The study was conducted in a Phase I clinical trials unit, where participant were confined for the duration of the study. As a result, all food and fluid intake could be regulated and monitored. During the study, no subjects dropped out and hence there were no replacements used. It is also confirmed that no additional subjects were dosed, other than those reported.

To take into account a possible non-zero baseline for the nicotine level, the study design included four doses, the plasma concentrations were derived taking into account the concentration at the start of the dosing.

Mean plasma concentration-time curves for nicotine using the electronic cigarette (Nicorette Inalator, e-Voke [Nicadex] 10mg Inhaler or e-Voke [Nicadex] 15mg Inhaler) versus standard cigarette



The concentrations for the cigarette and the Nicorette inhalator are comparable to data available in the literature.

Summary of the Statistical Analysis of Relative Bioavailability

	Treatment				Comparisons **				
	CN Electronic Cigarette		Nicorette Inhalator	Cigarette *					
Nicotine Strength	10 mg (CN 10) (N = 24)	15 mg (CN 15) (N = 24)	15 mg (Nicorette) (N = 24)	0.9 – 1.0 mg (Cigarette) (N = 24)	CN 10 vs Cigarette	CN 15 vs Cigarette	CN 10 vs Nicorette	CN 15 vs Nicorette	CN 15 vs CN 10
	Geometric LSmean				Geometric LSMean Ratio (%) (90% C.I.)				
C_{max} (ng/mL)	5.9389	7.0240	2.5748	29.6920	20.00 (18.07 – 22.14)	23.66 (21.37 – 26.18)	230.65 (208.40 – 255.28)	272.80 (246.48 – 301.92)	118.27 (106.86 – 130.90)
AUC_{0-t} (ng.min/mL)	846.29	1033.13	351.63	3603.96	23.48 (20.02 – 27.54)	28.67 (24.44 – 33.62)	240.67 (205.21 – 282.26)	293.81 (250.52 – 344.57)	122.08 (104.09 – 143.17)
$AUC_{0-\infty}$ (ng.min/mL)	990.60	1198.00	505.85	3780.88	26.20 (22.77 – 30.14)	31.69 (27.54 – 36.45)	195.83 (169.87 – 225.75)	236.83 (205.44 – 273.02)	120.94 (105.12 – 139.14)
	Median				Median Difference (p-value) (95% C.I.)				
t_{max} (min) ***	8	8	9.5	2.5	4.5 (0.0002) (3 - 6)	5 (0.0001) (3 – 7)	-3 (0.0173) (-6 – -0.5)	-3 (0.0130) (-6 – -0.5)	0.5 (0.5755) (-1.5 – 2.5)

* Cigarette was Benson & Hedges Gold
** Results obtained using a mixed effects ANOVA with fixed effects of study period, sequence and treatment and a random effect of subject (sequence) (excl. t_{max}).
*** t_{max} results obtained using the method of Campbell and Gardner and the Wilcoxon Matched Pairs test.

The nicotine levels obtained after the use of Nicadex 10 mg or 15 mg fall between those of the Nicorette inhalator and of a cigarette. The pharmacokinetic profiles obtained in the study are consistent with previous knowledge on buccal absorption from the Nicorette Inhalator product, and also suggest a combination of buccal and pulmonary absorption following use of the e-Voke Inhaler.

No pharmacodynamic data were presented, although it is assumed that a higher concentration of nicotine overall coupled with a higher C_{max} would have additional benefit as compared with Nicorette Inhalator.

Carbon monoxide (CO) and carboxyhaemoglobin levels were determined at screening and each study day. On dosing days, this was done prior to the first administration of nicotine. Self-reported smoking activity of the participants ranged from 10 to 20 cigarettes per day. The mean CO level and % carboxyhaemoglobin at each timepoint is shown in the following table as mean (range) and standard deviation.

	CO (ppm)	Carboxyhaemoglobin (%)
Screening	14.5 (4-25) 5.99	3.0 (1.3-4.6) 0.96
Day 0 (baseline)	19.5 (5-35) 7.17	3.8 (1.4-6.2) 1.15
Day 1	6.8 (3-10) 1.72	1.7 (1.3-2.2) 0.28
Day 2	3.3 (1-5) 1.04	1.2 (0.8-1.4) 0.16
Day 3	2.8 (1-5) 0.96	1.1 (0.8-1.4) 0.15
Day 4	2.9 (1-5) 1.03	1.1 (0.8-1.4) 0.15
Day 5 (post-study)	2.5 (1-5) 0.88	1.0 (0.8-1.4) 0.13

At screening, the CO level was 14.5 ppm (range 4 to 25). The level was similar on Day 0 (baseline) at 19.5 ppm (range 5 to 35). However, once the study participants had been confined within the research unit, the levels of CO decreased markedly (daily means ranging from 2.5 to 6.8 ppm), consistent with abstinence from smoking. A similar pattern was seen with carboxyhaemoglobin. At screening, the carboxyhaemoglobin level was 3.0% (range 1.3 to 4.6). The level was similar on Day 0 (baseline) at 3.8% (range 1.4-6.2). However, once the study participants had been confined within the research unit, the levels of carboxyhaemoglobin decreased markedly (mean ranging from 1.0 to 1.7%) again consistent with abstinence from smoking.

The inclusion of a craving scale at the design stage of the study was considered, but was not included. There were two reasons for this:

1. Each participant in the study had four nicotine administrations, 1 hour apart, on each of four dosing days. The logistical organisation of the study activities was already considered to be difficult, given the number of blood samples to be taken and the number of assessments to be made to monitor subject safety. Inclusion of an additional assessment was considered to over-complicate the study activities, and would have risked either interfering with other study assessments or of these not being completed fully.
2. The alternative, to use a craving scale before the first administration of nicotine on each dosing day (i.e. before the intensive activity planned for later in the day), was also considered. However, a population of smokers was chosen for the study who would be expected to have cravings each morning following an enforced period of abstinence from smoking. For example, the first nicotine administration on each dosing day was approximately 20 hours after the last administration (or after they had last smoked before entering the clinical trial unit). It was considered, therefore, that the use of a craving scale at this time would be futile and would only confirm that a population of smokers, when forced to be abstinent for an afternoon, an evening and overnight, would have cravings.

In the study, the results of the Fagerström Test for Nicotine Dependence confirmed that all subjects were (as expected) nicotine dependent, reinforcing the decision not to test for craving following forced abstinence.

As expected, cigarette smoking resulted in a high peak concentration of plasma nicotine resulting from rapid pulmonary absorption. Peak plasma concentrations of nicotine following use of the comparator product Nicorette Inhalator are considerably lower than those seen with cigarette smoking. The peak plasma nicotine concentrations for the e-Voke products fell between those of cigarette smoking and the reference product Nicorette Inhalator. This indicates that the pharmacokinetics of e-Voke 10mg and 15mg Inhalers can be considered at least comparable with those of the reference product Nicorette Inhalator.

EFFICACY
No new efficacy data were submitted and none were required for these applications.

SAFETY
The data generated in the bioavailability study showed that the peak plasma levels of nicotine in the e-Voke Inhaler products are lower than those with normal cigarette use. This indicates that these products can be considered at least as safe in terms of nicotine consumption as cigarette smoking.

The safety data are reassuring as there doesn't appear to be additional adverse event reporting following four administrations of the proposed products over a period of 3 hours.

The use of this product has been restricted to adults only.

Suitable warnings have been added to the SmPCs with regards to lung, throat or bronchospastic disease.

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 e-Voke 10mg and 15mg Inhalers are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the PIL.

A summary of the risk minimisation activities is presented below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Ineffective disposal of product	The Summary of Product Characteristics provides adequate guidance on the effective disposal of the spent used capsules: ***6.6 Special precautions for disposal and other handling*** *Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Keep away from animals. the e-VokeElectronic Inhaler should not be disposed of in household waste. It should be returned to the pharmacy or place of purchase for disposal.* The Patient Information Leaflet provides adequate guidance to consumers: ***Keep e-Voke in a safe place out of the sight and reach of children and animals.*** *Store in the original packaging to protect from light.Do not store above 25°C. Do not store e-Voke in your pocket.* *Do not use this medicine after the expiry date (EXP) which is stated on the pack. The expiry date refers to the last day of that month. After this date return any unused medicine to your nearest pharmacy for safe disposal.* *Dispose of any cartridge that has been attached to the e-Voke vaporiser for 24 hours even if it has not been used.* *The e-Voke-inhaler should be disposed of and replaced after it has been used for 6 weeks.* ***How to dispose of e-Voke Inhalation Cartridges*** ***It is very important that you dispose of e-Voke sensibly and safely as the empty cartridge and inhaler still contains some nicotine.** This nicotine may not be available for inhalation but could be harmful to children or pets.* *Put used e-Voke cartridges back in the pack and then dispose of them with your household rubbish.* *the e-Voke-inhaler should not be disposed of in your household waste. It must be returned to the pharmacy or place of purchase for disposal.* *Do not throw away any medicines via waste water. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.*	None
Lipoid pneumonia	Routine pharmacovigilance, including targeted follow up of all reports of adverse events suggestive of lipoid pneumonia (Annex 7).	None
Gateway to smoking in adolescents	Routine pharmacovigilance to determine risk.	None
Relapse to smoking in former smokers	Routine pharmacovigilance to determine risk.	None
Use in non-smoking adults	Routine pharmacovigilance to determine risk.	None

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 e-Voke 10mg and 15mg 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. No non-clinical concerns are raised in respect to excipients. There were no non-clinical concerns relating to the drug substance or drug product impurity profile, including the residual solvents and degradation products.

CLINICAL

A randomised four-way crossover, bioavailability study was conducted to study the effects of nicotine delivered by these products versus the reference product (Nicorette Inhalator) and cigarette smoking.

The peak plasma nicotine concentrations for the e-Voke products fell between those of the reference product and those from cigarette smoking. From these results it can be determined that e-Voke electronic inhalers are at least comparable with the reference product (Nicorette Inhalator) and as safe (in terms of nicotine consumption) as cigarettes.

SAFETY

No new or unexpected safety concerns arose from these applications.

The SmPCs, PILs and labelling are satisfactory, and contain suitable reference to use in adults only and use in patients with lung, throat or bronchospastic disease.

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.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The currently approved labels are provided below:

e-VOKE 10mg
White/Red
+ Existing Stick

Braille Reads: e-VOKE #10 MG

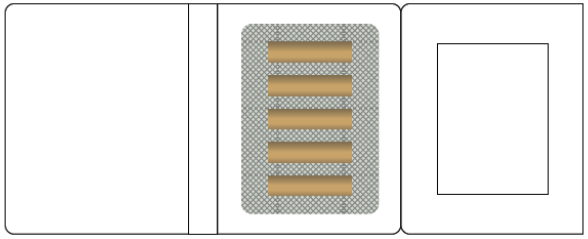
INSIDE PACKAGING

REFILL PACK (OUTSIDE, OPENED OUT FLAT)

FOAM RUBBER INSERT + USB CHARGER

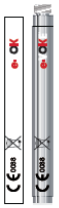
REFILL PACK (FRONT FACE)

REFILL PACK (INSIDE, OPENED OUT FLAT)



BLISTER PACK (REVERSE)

INHALER LABEL



Version 7
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e-VOKE 15mg
Option D. Grey/Black
+ Existing Stick

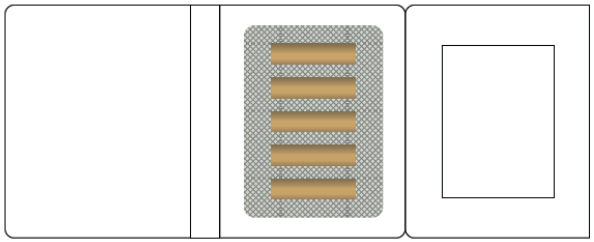
Braille Reads:
e-VOKE
#15
MG

REFILL PACK (OUTSIDE, OPENED OUT FLAT)

FOAM RUBBER INSERT + USB CHARGER

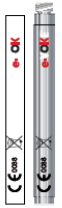
REFILL PACK (FRONT FACE)

REFILL PACK (INSIDE, OPENED OUT FLAT)



BLISTER PACK (REVERSE)

INHALER LABEL



Version 7
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e-Voke 10mg Electronic Inhaler
PL 42601/0003

e-Voke 15mg Electronic Inhaler
PL 42601/0004

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome