



Northern Treatment
Advisory Group

e-Voke[®] electronic cigarette for smoking cessation and reduction

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Summary

- Electronic cigarettes (e-cigarettes) are battery-powered devices which vaporise a liquid, normally containing nicotine, intended for inhalation. They are currently used by 2.6 million people in the UK, most of whom are current or former cigarette smokers.
- E-cigarettes are currently regulated as consumer products, but legislation to be implemented this year will require that available products meet safety and quality standards. Products not meeting the new standards can instead apply for a medicines marketing authorisation.
- The e-Voke[®] (Nicovations Ltd) is the first e-cigarette to receive a marketing authorisation in the UK. It is licensed as a GSL product as an aid to smoking cessation, to aid smokers unwilling or unable to smoke, and as a safer alternative to smoking.
- The e-Voke is a rechargeable device with replaceable nicotine cartridges, available in 10 mg and 15 mg strengths. Each cartridge delivers approximately 130 inhalations, and is considered roughly equivalent to 13 cigarettes. Every 10 inhalations delivers 0.38 mg nicotine (10 mg strength) or 0.56 mg nicotine (15 mg strength).
- There are no published clinical trials of e-Voke. The marketing authorisation was granted on the basis of a clinical study in 24 healthy male smokers which demonstrated bioequivalence with the reference product, Nicorette 15 mg Inhalator. Nicotine exposure with the e-Voke was higher than with the Inhalator, but substantially lower than with smoking a cigarette. This study did not include any evidence for effectiveness in smoking cessation.
- There is a large body of literature on e-cigarettes in smoking cessation. Two recent meta-analyses found that there was no significant difference between e-cigarettes and comparators for smoking cessation. Comparators in these analyses varied, but included conventional nicotine replacement therapies.
- The pharmacokinetic study concluded that e-Voke was at least as safe as cigarette smoking in terms of nicotine exposure. No other safety events or outcomes were reported. Public Health England considers e-cigarettes to be 95% safer than conventional cigarette smoking.
- Serious toxic exposures to nicotine in e-cigarettes have been reported in the UK, but appear to be rare compared to the prevalence of e-cigarette use. Public Health England does not consider these devices to pose a risk of nicotine poisoning if used as intended.
- There is no cost currently available for e-Voke, and an anticipated launch date has not yet been set. Similar products already marketed vary considerably in price.

Introduction and background

Electronic cigarettes, or e-cigarettes, are a relatively new type of nicotine-delivery product which can be defined as any device designed for the delivery of nicotine vapour via a mouthpiece. There are a number of different designs, but all are battery-powered devices which heat a nicotine-containing liquid to produce a vapour which is then inhaled.^{1,2} E-cigarettes are commonly sold as smoking cessation aids or harm reduction tools on the basis that inhaling a pure nicotine vapour is likely to be less harmful than smoking cigarettes.

There is a great deal of variability in the design and function of the available e-cigarettes. The harm-reduction charity Action on Smoking and Health (ASH) classifies the available devices as follows:²

- Cig-a-likes are early generation products, designed to resemble a conventional cigarette. These may be entirely disposable, or rechargeable and re-fillable by means of pre-filled cartridges.
- Tank models are often colloquially known as vapes, or vape pens. Tank devices have a rechargeable battery and a reservoir that must be filled with liquid before use. The user therefore has a reasonable amount of control over the flavour and strength of the liquid used.
- Mods are more advanced devices which offer some customisation, such as a variable voltage setting to adjust the temperature of the vaporiser.

Liquids for refillable e-cigarettes can be purchased in a variety of strengths and may be flavoured or unflavoured. Some users mix their own liquids to precisely meet their desired specifications. Nicotine-free liquids are also available and appear to be used simply for the pleasure of inhaling the flavoured vapour.

ASH estimates that 2.6 million people in the UK currently use e-cigarettes. Around a third of these are former smokers, while most of the remainder use both e-cigarettes and tobacco products.² The prevalence of e-cigarette use among people who have never smoked is thought to be low, and has been estimated at around 0.2%.¹

UK legislation

Neither tobacco nor medicines legislation currently applies to e-cigarettes sold in the UK, which are therefore regulated only as consumer products.² However, from May 2016 the EU Tobacco Products Directive (TPD) will become part of UK law, and included in this legislation will be a number of legal requirements for e-cigarettes:^{3,4}

- Manufacturers must give the MHRA notice of at least 6 months before putting a new product on the UK market. Products already on the market will have until November 2017 to submit a notification.
- Cartridges, tanks and reservoirs will have a specified maximum volume and must be child-proof, tamper-proof and leak-proof.
- Liquids must use high-quality ingredients, and devices must deliver nicotine at consistent levels.

- Packets will be required to carry health warnings and packs must contain instructions for use, toxicity and addiction information, an ingredients list and information on the nicotine content.

The legislation will also prevent sale of products which either make medical claims or contain nicotine ≥ 20 mg/mL; these will be regulated as medicines and will require a marketing authorisation. Manufacturers of devices which comply with the TPD will also be able to voluntarily opt to apply for a medicines marketing authorisation. The regulations will be phased in over a period of a year. It is not clear how many existing products will be able to comply with the legislation and remain on the market.

Guidance and related advice

Public Health England (PHE) published an evidence summary in 2015 which found there is a place in UK smoking cessation policy for e-cigarettes, recommending them as an option for smokers who have tried other smoking cessation methods without success.¹ For smokers who are unwilling or unable to stop smoke, PHE state that e-cigarettes may be a viable option to reduce the burden of smoking-related morbidity and mortality. In line with ASH, the report found no evidence that e-cigarette use is undermining the long-term trend towards reduced cigarette smoking in the UK.

NICE have produced multiple guidelines on smoking cessation, prevention and harm reduction. Although none include specific recommendations on e-cigarettes, the broader policy recommendations on smoking cessation may apply.

- [PH1](#) Smoking: brief interventions and referrals
- [PH5](#) Smoking: workplace interventions
- [PH10](#) Stop smoking services
- [PH14](#) Smoking: preventing uptake in children and young people
- [PH23](#) Smoking prevention in schools
- [PH26](#) Smoking: stopping in pregnancy and after childbirth
- [PH45](#) Smoking harm reduction
- [PH48](#) Smoking: acute, maternity and mental health services

The e-Voke electronic cigarette

The e-Voke[®] device is the first electronic cigarette in the UK to seek regulatory approval as a medicine. The marketing authorisation is held by Nicovations Ltd, which is part of Nicoventures, a division of British American Tobacco. E-Voke is a hybrid medicine, and the reference product is the Nicorette[®] 15 mg Inhalator.

The e-Voke device consists of a stainless steel vaporiser and battery unit which are screwed together by the patient before first use.⁵ The battery is rechargeable, and must be unscrewed from the vaporiser in order to be charged with the supplied USB

adaptor. The battery is designed to last roughly 130 inhalations before needing to be recharged, and charging takes 2-3 hours.

Nicotine liquid is supplied in replaceable cartridges consisting of a nicotine reservoir and a mouthpiece. The user must remove a foil tab from the cartridge before use, then attach it to the vaporiser by pushing the two components together.^{6,7} The user will know when the cartridge needs to be replaced because the amount of vapour produced when they exhale will be reduced. Each cartridge supplies approximately 130 inhalations, approximately equal to 13 cigarettes. Each cartridge should be disposed of within 24 hours of opening, whether or not it is empty. The electronic inhaler has a shelf life of 2 years, but an in-use shelf life of 6 weeks. If patients still require nicotine replacement therapy after 6 weeks use of e-Voke, they will need a new inhaler device.

Refill cartridges are supplied in blister packs, and each replaceable cartridge contains 10 mg or 15 mg of nicotine in a water and glycerol solution.^{8,9} There are no flavourings or other excipients. The manufacturers advise that 10 inhalations are usually required to remove cigarette cravings, which supplies either 0.38 mg of nicotine (10 mg device) or 0.56 mg of nicotine (15 mg device). However, the device is not metered and the actual amount of nicotine delivered will depend on individual patient characteristics such as inhalation depth and length.

The e-Voke is switched on by unscrewing the battery unit from the vaporiser, then screwing the components back together. It is designed to enter a "sleep" mode if it is not used for 4 minutes, and must be switched back on by repeating the unscrewing and re-screwing procedure. There is no way to manually switch off the device.

In November 2015 e-Voke was licensed as a GSL product for the treatment of adults aged at least 18 year, including pregnant and lactating women:

- as an aid to smokers wishing to quit or reduce prior to quitting
- to assist smokers who are unwilling or unable to smoke
- as a safer alternative to smoking for smokers and those around them

There is not currently a planned launch date or price for e-Voke. The manufacturers are currently concentrating on plans to launch their inhalator-type product, Voke[®].¹⁰

This document will review the evidence for the e-Voke.

Evidence for the efficacy of e-Voke

There are no published trials of e-Voke, however a clinical study was submitted to support the marketing authorisation application.⁵ This was a pharmacokinetic study with a crossover design, comparing the bioavailability of nicotine when delivered by:

- e-Voke 10 mg or 15 mg cartridges
- Nicorette 15 mg Inhalator (reference product)
- Smoking a cigarette (Benson & Hedges Gold).

Participants (n=24) were healthy adult male smokers who smoked an average of 10-20 cigarettes per day, and who were confined to the study centre for the duration of

the trial. The regulatory document implies that participants were required to be abstinent from smoking during the trial, but does not explicitly state this.

The study had a randomised crossover design in which one product was assessed each day, such that each participant tested each product over the course of 4 days. Participants were instructed to take 10 inhalations of the assigned product with an interval of 30 seconds between each inhalation, for a total of 4.5 minutes. This process was repeated three more times at intervals of one hour. Plasma nicotine levels were tested prior to the first inhalation and then at regular intervals, although the precise timepoints were not specified.

Plasma nicotine levels were higher with e-Voke than the Nicorette 15 mg inhalator at all timepoints. Nicotine levels associated with cigarette smoking were considerably higher than all other methods (see table 1 below). Total nicotine exposure was higher with e-Voke than the inhalator, and substantially higher with cigarette smoking than either other method (see table 2 below). Peak plasma concentration was reached much more quickly with cigarette smoking.

Table 1: Nicotine exposure with different delivery mechanisms

| | e-Voke 10 mg | e-Voke 15 mg | Inhalator 15 mg | Cigarette |
|------------------------------|--------------|--------------|-----------------|-----------|
| C_{max} (ng/mL) | 5.9 | 7.0 | 2.6 | 29.7 |
| AUC_{0-4} (ng.min/mL) | 846.3 | 1033.1 | 351.6 | 3604.0 |
| $AUC_{0-\infty}$ (ng.min/mL) | 990.6 | 1198.0 | 505.9 | 3780.9 |
| Median t_{max} (min) | 8 | 8 | 9.5 | 2.5 |

Table 2: Difference in nicotine exposure with different delivery mechanisms (%)

| | e-Voke 10 mg vs. Inhalator | e-Voke 15 mg vs. Inhalator | e-Voke 10 mg vs. cigarette | e-Voke 15 mg vs. cigarette |
|-----------------------------------|-----------------------------|-----------------------------|----------------------------|----------------------------|
| C_{max} (ng/mL) | 230.7 (208.4 to 255.3) | 272.8 (246.5 to 301.9) | 20.0 (18.1 to 22.1) | 23.7 (21.4 to 26.2) |
| AUC_{0-4} (ng.min/mL) | 240.7 (205.2 to 282.3) | 293.8 (250.5 to 344.6) | 23.5 (20.0 to 27.5) | 28.7 (24.4 to 33.6) |
| $AUC_{0-\infty}$ (ng.min/mL) | 195.8 (169.9 to 225.8) | 236.8 (205.4 to 273.0) | 26.2 (22.8 to 30.1) | 31.7 (27.5 to 36.5) |
| Median difference (95% CI) | | | | |
| Median t_{max} (min) | -3, p=0.017 (-6 to -0.5) | -3, p=0.013 (-6 to -0.5) | 4.5, p=0.0002, (3 to 6) | 5, p=0.0001 (3 to 7) |

Carbon monoxide breath tests were also conducted during the trial, along with carboxyhaemoglobin testing. Both of these tests are used to estimate carbon monoxide exposure, and are frequently used in trials of smoking cessation products to biochemically confirm abstinence. Carbon monoxide levels vary in healthy adults,

with cut-offs for non-smokers set anywhere from 3-10 parts per million (ppm).¹¹ Similarly, normal carboxyhaemoglobin levels are variable, but the National Poisons Information Service considers 1-2% normal for non-smokers, while smokers typically have higher levels at around 5-10%.¹² In this study, mean exhaled carbon monoxide fell from 14.5 ppm at admission to 2.5 ppm at day 5 (post-study). Similarly, mean carboxyhaemoglobin levels fell from 3.0% to 1.0%. These levels are consistent with enforced abstinence from smoking during the study.

No data on cigarette cravings were collected, largely due to logistical concerns; it was not considered practical for study participants to complete multiple questionnaires on cravings each day. There is no published evidence comparing e-Voke to any other product in terms of efficacy for smoking cessation.

The reference product for the e-Voke marketing authorisation was Nicorette 15 mg Inhalator, which is a breath-actuated device with no electrical components. Nicorette 15 mg Inhalator was in turn licensed on the basis of bioequivalence to the Nicorette 10 mg Inhalator.¹³ The 10 mg Inhalator is no longer marketed, and no regulatory information could be located. It is therefore not clear what evidence of effectiveness was submitted in support of that marketing authorisation, and therefore underpins this chain of product licences.

Evidence for e-cigarettes in smoking cessation

The literature on e-cigarettes is rapidly evolving, and wide-ranging. While a complete review of the literature is outside the scope of this document, two recent meta-analyses give a good overview of the evidence.

Kalkhoran et al conducted a meta-analysis of studies evaluating the relationship between e-cigarette use and cigarette smoking cessation in adults.¹⁴ The review included studies which enrolled adults regardless of whether they had a desire to stop smoking. Definitions of quitting varied, and could be self-reported or biochemically validated. Comparators were variable, and in several cases simply included patients with no e-cigarette use during the study period. Other studies used nicotine replacement therapy or simple cigarette abstinence as a comparator.

A total of 20 studies were included in the meta-analysis, of which 15 were cohort studies, 3 were cross-sectional studies and 2 were clinical trials. It found that the odds of successfully quitting smoking were significantly lower among e-cigarette users than among non-users (odds ratio 0.72, 95% CI 0.57 to 0.91). When the analysis was restricted to smokers who actively wanted to stop using cigarettes, there was no significant difference between e-cigarettes and comparators (odds ratio 0.86, 95% CI 0.60 to 1.23).

One of the included clinical trials was an RCT which compared e-cigarettes with nicotine replacement therapy (NRT) for smoking cessation. It found that quit rates were numerically higher with e-cigarettes than NRT, but there was no significant difference. The second clinical trial was a non-randomised study which found that smoking cessation was more likely to be successful with e-cigarette use than without, but again the difference did not reach significance.

A Cochrane review published in 2014 included studies which compared e-cigarettes with placebo e-cigarettes, other smoking cessation aids (including NRT) or no intervention.¹⁵ The primary outcome was smoking abstinence, with biochemically validated abstinence preferred. The analysis included data from 22 studies but the main findings were based solely on the results of two RCTs, one of which was discussed briefly above.

The review found that smoking cessation was more likely with nicotine-containing e-cigarettes than with placebo devices (risk ratio 2.29, 95% CI 1.05 to 4.96), but found no difference between nicotine-containing e-cigarettes and conventional NRT (risk ratio 1.26, 95% CI 0.68 to 2.34). The review noted that the evidence was of overall low or very low quality.

Safety

Safety data on e-Voke specifically are extremely limited. The pharmacokinetic study which supported the marketing authorisation found that since peak plasma nicotine levels were lower than those associated with cigarette smoking, e-Voke could be considered at least as safe as cigarettes in terms of nicotine exposure.⁵ No other safety data were reported, other than a statement there was no additional adverse event reporting following the trial regimen of four administrations over three hours.

There are concerns about the safety of having concentrated nicotine products available in domestic situations, since concentrated nicotine is highly toxic by ingestion, inhalation and skin contact.¹² E-cigarettes therefore pose a risk not only by overdose of the vapour, but by any other exposures to the nicotine liquid whether intentional or accidental. The PHE position is that e-cigarettes do not pose a risk of nicotine poisoning if used as intended, however toxic exposures have been reported. NPIS reported receiving 241 telephone enquiries in 2014/15 regarding e-cigarettes and refill liquids, compared to 204 the previous year.¹⁶ The number of enquiries has been steadily increasing since 2007. Most enquiries related to patients who were either asymptomatic or had only minor features of toxicity, such as local irritation, nausea or vomiting. However several patients had moderate or severe toxicity, which can include features such as arrhythmia, coma, convulsions, and respiratory or cardiac arrest. It is not clear what proportion of these enquiries related to cig-a-like devices like the e-Voke.

Given the estimated prevalence of e-cigarette use it would therefore appear that the incidence of toxic nicotine exposure as a result of their use is low. The introduction of the TPD regulations is intended to further reduce these risks.

PHE consider e-cigarettes to be substantially safer than smoking tobacco.¹ This is based on a multi-criteria decision analysis performed by a committee composed of experts from a variety of backgrounds.¹⁷ The committee considered the relative harms of a variety of nicotine-containing products including cigarettes, cigars, pipes, smokeless tobacco, electronic nicotine delivery systems and nicotine replacement products. A variety of harms were considered, including mortality, morbidity, dependence, crime, and social and economic impacts. The group scored each product for each harm on a scale of 0 (no harm) to 100 (most harmful). At the end of

this process electronic nicotine delivery systems, including e-cigarettes, were found to be associated with approximately 5% of the harms of conventional cigarette smoking. Only nasal sprays, oral nicotine products and nicotine patches were considered less harmful.

Dosage and administration

Around 10 inhalations of e-Voke are estimated to be equivalent to one cigarette, and should be sufficient to remove cigarette cravings. This delivers either 0.38 mg nicotine (10 mg strength) or 0.56 mg nicotine (15 mg strength), although the device is not metered and dose will vary with the user's inhalation size and force. Each cartridge contains approximately 130 inhalations. The maximum daily dose is five e-Voke cartridges of either strength, roughly equivalent to 65 cigarettes.

E-Voke is licensed for use both to relieve cigarette cravings and to prevent cravings in situations where they are anticipated.^{8,9} Smokers aiming to quit completely should replace all cigarettes with e-Voke then gradually reduce use until they have stopped using any form of nicotine. Smokers who are not trying to quit should use e-Voke to prolong the intervals between smoking cigarettes as much as possible. Behavioural therapy, advice and support is recommended for users making a quit attempt.

Cost analysis

There is no price currently available for e-Voke. There are a large number of comparable products (i.e. rechargeable devices with replaceable nicotine cartridges) already on the market; with rather variable prices. These devices are sold as consumer products with no medicinal claims. Table 3 below shows some examples.

Cost of e-cigarette use depends on degree of use as well as acquisition cost. As with cigarettes users will have different levels of consumption, which may vary with daily activities such as social and occupational commitments.

Table 3: Example "cig-a-like" e-cigarettes currently on the market.

| Brand | Product | Cigarette equivalent | Price |
|---------------------------|---|----------------------|--------|
| Puritane ¹⁸ | Rechargeable e-cigarette starter kit (includes 2 cartridges) | Up to 70 | £22.99 |
| Puritane ¹⁸ | Refills x 2 (0 to 16 mg nicotine) | Up to 70 | £8.99 |
| Vapourlites ¹⁹ | Electronic rechargeable cigarette (includes 1 cartridge) | Not specified | £9.99 |
| Vapourlites ¹⁹ | Refills x 5 (6 to 20 mg nicotine) | Not specified | £9.99 |
| Nicolites ²⁰ | Rechargeable Electronic Cigarette Starter Kit (includes 2 cartridges) | Up to 40 | £11.99 |
| Nicolites ²⁰ | Refills x 3 (0 to 16 mg nicotine) | Up to 60 | £5.39 |

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