



MHRA UK PUBLIC ASSESSMENT REPORT

Nicobrevin: withdrawn from UK market as risks outweigh benefits

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PLAIN-LANGUAGE SUMMARY

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses an analysis of the risks and benefits of an anti-smoking product called Nicobrevin.

The dangers of smoking are well known. Cigarettes contain over 4 000 different chemicals, of which more than 60 are carcinogenic (cancer-causing). Smoking increases the risk of getting many serious and often fatal diseases, including lung cancer^a, cardiovascular diseases (conditions that affect the heart and blood vessels)^b such as coronary heart disease, and respiratory diseases (which affect breathing) such as asthma and chronic obstructive pulmonary disease (COPD)^c. Smoking also poses health risks to people around the smoker, as well as to the smoker themselves.

Giving up smoking can therefore have major benefits and substantially improve long-term health. There are several effective treatments available to help people give up smoking (known as ‘smoking cessation’ treatments). These include nicotine replacement therapy (NRT) products; and prescription-only, non-nicotine-containing medicines such as bupropion (brand name Zyban) and varenicline (Champix). See our [‘stop smoking webpage’](#) for more details.

However, there are also some less effective products available on the market which may actually do more harm than good. A product called Nicobrevin has been marketed as an ‘anti-smoking preparation’ in the UK since 1964, and was classified as General Sales List^d in 1998. This product comes in the form of liquid-filled capsules for swallowing, which contain the ingredients menthyl valerate, quinine, camphor and eucalyptus. Each of these ingredients is listed as ‘active’ in the product information; ie, it is claimed that they each have an effect in aiding smoking cessation.

For some time there have been doubts regarding the clinical effectiveness of Nicobrevin and its constituent ingredients in helping people to stop smoking. There is a lack of good clinical evidence supporting Nicobrevin’s use as a smoking cessation aid, and the availability of other, more effective and proven smoking cessation products such as NRT products, Zyban, and Champix. There has also been no recommendation of Nicobrevin as a smoking cessation aid by any clinical organisations involved in helping people to stop smoking, because of a lack of good clinical evidence supporting its use. In addition, there have been concerns raised

^a Smoking is responsible for 85–90% of all cases of lung cancer in the UK, and is the leading cause of cancer-related deaths. There are approximately 30 000 deaths in England and Wales each year as a result of lung cancer (see [http://www.nhs.uk/Conditions/Smoking-\(quitting\)/Pages/Risks.aspx](http://www.nhs.uk/Conditions/Smoking-(quitting)/Pages/Risks.aspx) for more detail)

^b Approximately 200 000 people die each year of cardiovascular diseases in the UK

^c COPD is a long-term lung disease which can severely debilitate a person’s daily activities and quality of life. Around 30 000 people die each year in the UK as a result of COPD.

^d Medicines classified as ‘General Sales List’ are approved for sale from a wide range of shops and pharmacies

regarding the safety of Nicobrevin, and the individual safety of its constituent ingredients.

For these reasons, the MHRA performed a review of available scientific data on the effectiveness and safety of Nicobrevin in aiding smoking cessation. The results of the review were presented to the [Commission on Human Medicines](#)^a (CHM) for advice. This report summarises the data and conclusions from the review, and decisions made on the basis of the review.

Results

- There is no evidence available from long-term clinical trials that Nicobrevin can aid smoking cessation.
- There is insufficient evidence to support the effectiveness of any of the ingredients in Nicobrevin as an aid to stopping smoking.
- Based on the evidence, a placebo^b effect remains the most plausible explanation for Nicobrevin's apparent benefits as an anti-smoking preparation
- Recent safety concerns regarding the product's ingredients, particularly quinine, suggest a negative risk-benefit profile for Nicobrevin (ie, the risks of Nicobrevin outweigh the benefits)

Conclusions

There is a lack of data supporting the use of Nicobrevin as a product to help people stop smoking. In addition, there are several safety concerns with this product and its constituent ingredients. On balance, the CHM advised that the risks of Nicobrevin outweigh its benefits. Therefore, Nicobrevin has been withdrawn from the UK market.

Distribution of Nicobrevin in the UK ceased at the end of August 2010, and its license was cancelled on 31st January 2011.

There are many effective medicines and devices available to aid smoking cessation. For details of these and advice on stopping smoking, please see our [stop smoking webpage](#), and [the NHS 'smokefree' webpage](#).

^a An independent committee comprised of health professionals and scientists who give advice to UK government Ministers on the safety, effectiveness and quality of medicines

^b A placebo, as used in research, is an inactive substance given as a control in a clinical trial. The placebo effect is the benefit to health that an inactive substance may have on a patient, due to their positive expectations rather than any real effect of the substance itself.

1. INTRODUCTION

(For an explanation of medical terms, please see the glossary at the end of the report)

The detrimental effects to the individual and to public health associated with smoking tobacco are well-established. Significant steps have been taken to reduce the impact of tobacco smoking on health in the UK, including: increased taxation of tobacco-containing products; the introduction of legislation prohibiting smoking in public areas; influencing younger people via the media not to start smoking; and helping existing smokers to quit. In the case of the latter, one approach to help smokers who want to quit has been to increase the availability of well-established, proven smoking cessation treatments such as nicotine replacement therapy (NRT) products, which are now widely available without prescription. There are also prescription medicines available such as bupropion (Zyban) and varenicline (Champix) which have proved effective.

Although stopping smoking may be difficult, behavioural support and effective pharmacotherapy improve success rates. A considerable body of data exists to support the effective use of NRT in smoking cessation; in well-conducted clinical trials, NRT has been shown to double the chances of success^[1].

However, there are some products on the market intended for smoking cessation purposes that are not as clinically effective as NRT, and may actually cause more harm than good. One such product is Nicobrevin, described as a 'non-nicotine-containing anti-smoking preparation'. Concerns about a lack of robust efficacy data, and gaps in pharmacovigilance^a data led the MHRA to review the risks and benefits of Nicobrevin and present the results to the [Commission on Human Medicines](#)^b (CHM).

The results of the analysis were used by the MHRA and the CHM to determine if Nicobrevin had a role in enabling patients to quit smoking when viewed against other licensed smoking cessation products with regards to efficacy and safety. The following Public Assessment Report presents a summary of the Nicobrevin risk-benefit analysis, and regulatory decisions made on the basis of the analysis.

2. BACKGROUND

Nicobrevin has been available in the UK since 1964, and was reclassified from Pharmacy status to General Sales List^c in 1998. A pack of Nicobrevin contains 48 soft liquid-filled capsules which are taken orally; one pack of 48 capsules is intended to be taken as a 28-day course of treatment. Each capsule contains:

- Menthyl valerate 100 mg;
- Quinine (base) 15 mg;

^a The detection and assessment of any adverse effects of medicines and vaccines

^b An independent committee comprised of health professionals and scientists who give advice to UK government Ministers on the safety, effectiveness and quality of medicines

^c Medicines classified as 'Pharmacy' do not require a prescription, but can only be sold by a trained pharmacist in a pharmacy. Medicines classified as 'General Sales List' are approved for sale from a wide range of shops as well as pharmacies

- Camphor 10 mg;
- Eucalyptus oil 10 mg.

Around 1 million packs of Nicobrevin were sold between 1992–1997 in the UK. This number was reduced markedly to 6 600 packs sold in the period 2003–2008, and just 200 packs were sold from May 2009–December 2010. It is likely that sales of Nicobrevin have diminished significantly for a number of reasons including:

- the wider availability of NRT products;
- the availability of new non-nicotine-containing prescription medicines to help smoking cessation, such as bupropion and varenicline;
- a lack of recommendation of Nicobrevin by any clinical organisations involved in smoking cessation.

There are also concerns regarding the safety of Nicobrevin and its constituent ingredients. Data on the efficacy and safety of Nicobrevin and its ingredients are discussed in the following chapters.

3. EFFICACY DATA CONSIDERED

3.1 Efficacy of Nicobrevin in aiding smoking cessation

In 2006 NICE published a review of the effectiveness of smoking-cessation treatments unavailable on the NHS^[2], which included a review of Nicobrevin. Two studies were cited as having investigated the efficacy of Nicobrevin^[3,4] (discussed in sections 3.1.1 and 3.1.2), but methodological problems were identified with both of these studies, together with a lack of evidence of safety or efficacy on long-term smoking cessation.

An NHS best-practice guidance document published in March 2009 stated that there was no evidence to show a long-term effect on abstinence for Nicobrevin^[5]. The conclusion that there is a lack of evidence indicating efficacy for Nicobrevin is also documented in reports from other, international, smoking cessation organisations such as the Ministry of Health, New Zealand^[6].

There are only two published clinical studies (Schmidt, 1974^[3] and Dankwa, 1988^[4]) which have evaluated the clinical effectiveness of Nicobrevin. These, along with a published Cochrane review which assessed all evidence for the effectiveness of Nicobrevin in assisting long-term smoking cessation, are discussed below.

3.1.1. Schmidt, 1974^[3]

The Schmidt study had a large population of 5000 smoker volunteers. However, the study was limited in a number of ways:

- Only 1824 participants were evaluable (ie, who fitted the inclusion/exclusion criteria).
- Patients had to pay to enter the study, which raises ethical concerns about the study conduct.
- Subjects filled in all questionnaires by post and therefore did not see any of the investigators for the duration of the study. There was no direct medical assessment to confirm key criteria such as pre-existing medical conditions.
- A wide range of products were tested against placebos and Nicobrevin; however, the list of products other than Nicobrevin is given without naming the active ingredients.
- In addition to the products, 'additional advice' was given to the subjects requesting further information. It is not disclosed what advice was given or how this may have influenced non-smoking outcomes.
- Only two placebos were given to match a wide range of actives products. One appears to match another product, Nicortyl, which was described as having a terrible taste. Like Nicobrevin, it is very difficult to manufacture placebos to match products with strong odour/taste and maintain a study blind.
- The placebos appeared to vary with regards to dosing regimen (fixed dose versus flexible dosing).
- There is wide variation in cigarette (and consequently nicotine) consumption;
- Study drugs were obtained from a variety of undisclosed sources.
- The outer packaging for the products was removed in order to rule out any influence the different packaging or origin might cause, but presumably physical appearance, smell taste etc were not blinded, making the active investigational products reasonably easy to identify.

- There is a lack of detail on the study methodology and statistical analysis

Results:

Table 1. Complete abstinence from smoking immediately after smoking-cessation treatment, and 3 months later (adapted from Schmidt, 1974)

Compound	Total no. of participants	No. of non-smokers at end of treatment	% of non-smokers at end of treatment	No. of non-smokers after 3 months	% of non-smokers after 3 months
Placebo ₁	122	40	33%	27	22%
Placebo ₂	117	44	38%	30	26%
Tabex	181	103	57%	68	38%
Ni-Perlen	43	23	54%	18	42%
Atabakko	170	86	51%	50	29%
Citotal	92	46	50%	33	36%
Unilobin	42	20	48%	15	36%
Potassium chloride	169	77	46%	53	31%
Potassium granulate	171	79	46%	52	30%
Potassium citrate	91	40	44%	24	26%
Nicobrevin	168	74	44%	64	38%
Targophagin	91	36	40%	29	32%
Pempidil	42	16	38%	9	21%
Viotil	37	14	38%	11	30%
Lovage root	24	9	38%	7	29%
Raucherstop 5 HT	166	62	37%	45	27%
Nicocortyl	220	74	34%	54	25%

As shown in the results (Table 1), the number of non-smokers at the end of the treatment period was not greatly higher in the Nicobrevin group compared to the placebo group: 44% non-smokers with Nicobrevin compared with 33% or 38% with placebo₁ and placebo₂ respectively.

Three months after the end of the study 38% of patients remained non-smokers with Nicobrevin, compared with 22% or 26% with placebo₁ and placebo₂, respectively.

Table 2 (below) shows the number of participants who reduced their cigarette consumption by at least 50%, both immediately after treatment with Nicobrevin or placebo, and 3 months after the study end. Nicobrevin appears more effective for cigarette reduction than the placebo groups immediately after treatment, but worse than placebo₂ after 3 months. The authors state that a 50% reduction in cigarette smoking does not denote success as previous cigarette consumption will be resumed if the smoker does not achieve complete abstinence. However, the results may indicate a greater relapse rate with Nicobrevin compared to placebo.

Table 2. Reduction by at least 50% of cigarette consumption immediately after smoking-cessation treatment, and 3 months later (adapted from Schmidt, 1974^[3])

Compound	Total no. of participants	No. of participants after treatment who reduced cigarette consumption by $\geq 50\%$	% of participants after treatment who reduced cigarette consumption by $\geq 50\%$	No. of participants 3 months after treatment who reduced cigarette consumption by $\geq 50\%$	% of participants 3 months after treatment who reduced cigarette consumption by $\geq 50\%$
Placebo ₁	122	23	19%	31	25%
Placebo ₂	117	26	22%	33	28%
Nicobrevin	168	41	24%	47	27%

Table 3 shows the side effects reported with Nicobrevin which appear mainly gastrointestinal (GI)-related.

Table 3: Side effects reported with use of smoking cessation products in the study (adapted from Schmidt, 1974^[3])

Compound	placebo	Nicotinyl	Tabex	Atabakko	Nicobrevin	Unilobin	Ni-Perlen	Citobal	Targophagin	Pempidil	Viotil	Potassium chloride	Potassium citrate Giulini	Potassium granulate Dr.	Linden blossom teas	Lovage root tea	Raucherstop 5 HT	Nicotine**
Total evaluations	237	220	181	170	168	42	43	92	91	42	37	169	91	171	29	24	169	216
Unpleasant taste		7									1	2			1		20	
Repulsive taste		14						3								2		
Loss of appetite	10	16	1	3	4			3	7	6	1	5	2	1			5	
Heartburn and satiation		5	4		2		1	1				2	2	5	1		1	1
Nausea	10	29	7	4	8	1	3	7	4	6	2	9	2	11	1	2	13	
Vomiting		11	2	3						4	3						2	
Stomach complaints	4	2	1					5	1		3	8	2	5				3
Stomach pain	3	9	3	8	8				4	5			5	2			9	
Burning tongue	4	16	1		2						2	2	1	1			2	
Dry throat																		
Constipation	1	3	3		5					4	1			2	1		5	4
Diarrhea		5	3	11	1			2						5				1
Vertigo	5	3	3	6	3		1	5		16	14		3	3			2	2
Lowered reaction time	1	1	1							4	7	2		1				
Vision problems (light sensitivity)					1					13	13							
Headaches	3	4	6	2	2				2			3	3				5	3
Insomnia	2		2	2	1							3	1				1	2
Sweating					1		1	2				1						
Itching												2					1	
Pimples			1	2	1								1	1				
Renal pain						1						1	1					
Biliary colic					2							1	1					

Given the limitations of the study, and the reported side effects, the study does not provide any reassuring evidence of the effectiveness of Nicobrevin as an anti-smoking preparation. The paper indicates that Nicobrevin has a similar success rate to placebo at the point of treatment end, and the study falls short of the Russell

Standard^a for outcome assessment in clinical trials of smoking cessation treatments. The follow-up period is too short to be considered a meaningful indicator of continued non-smoking status.

3.1.2 Dankwa, 1988⁽⁴⁾

The Dankwa study is cited by the manufacturer of Nicobrevin in almost all its communications as evidence of Nicobrevin's efficacy as an anti-smoking preparation.

In this study, unlike the Schmidt study, the subjects were examined, there were documented eligibility criteria, and patients were stratified by cigarette consumption. The study also purported to be double-blind and placebo controlled; however Nicobrevin has a very notable smell and taste due to the camphor, methyl valerate and eucalyptus oil, and no details were provided as to how, if at all, these indicators of the active product were masked or matched with the placebo. It may be that any benefits seen with Nicobrevin may themselves be due to a placebo effect promoted by the smell and taste of the capsules.

There was a significant age difference between the Nicobrevin and placebo groups, however, the potential effects of age on motivation to quit smoking were not discussed^b.

The primary endpoint was the number of cigarettes smoked during the 28-day Nicobrevin-treatment period as noted by the trial participants themselves (via self-completed questionnaires), rather than smoking cessation. Recording the number of cigarettes smoked by the participants themselves was noted by the author as an unreliable method of determining consumption.

In addition, baseline carboxyhaemoglobin (COHb) levels were measured and changes at end of the treatment period were noted. COHb levels can be a marker of carbon monoxide levels, and are sometimes used as a proxy marker of cigarette consumption; however, this may not be an accurate measure as there are sources of carbon monoxide other than cigarette smoke, such as vehicle combustion exhaust fumes; wood-burning stoves; and gas appliances. There is also likely to be wide intervariability in COHb levels between individuals caused by the way a cigarette is smoked. Additionally, COHb appears to be a poor correlate to smoking when compared with levels of nicotine, which is unlikely to come from non-tobacco sources (other than NRT products). Despite these concerns the authors suggested that the COHb results provided further evidence of the efficacy of Nicobrevin as an aid to those who want to give up smoking, whereas at best, COHb levels show a greater change in the Nicobrevin group when compared to placebo.

Patients were asked to self-rate treatment efficacy. Despite a greater number of patients rating Nicobrevin 'very effective' ($p < 0.05$) when compared with placebo, it is not possible to determine how many patients rated Nicobrevin 'quite effective' or 'not effective' as all of these results were linked together. Consequently, the appropriate statistical tests were not performed. Details of the questionnaire are not documented in the published paper so it is also unclear if efficacy here means success in quitting

^a Six standard criteria which aid interpretation of results from smoking cessation trials (see [West et al. 2005^{\(7\)}](#))

^b See: '[Age affects motivation for quitting smoking](#)', presented at CHEST 2007; 73rd ACCP meeting. This study found that smokers older than 65 years quit due to physician pressure and stress regarding major health problems, whereas smokers age less than 65 years quit due to costs and tobacco odour.

smoking, or another parameter such as relief of symptoms associated with smoking cessation.

There were suspected side effects reported by the trial participants in both the Nicobrevin and placebo groups. These were mild in severity in both groups, and included sickness and changes in appetite.

The discussion section of the study states that 12 of the 40 patients (30%) who received placebo and who completed the study had stopped smoking during the last week of the study, compared with 25 of the 40 (62.5%) patients in the active (Nicobrevin) group. The authors go on to suggest that the results demonstrate a significantly greater effect for Nicobrevin than placebo and support its use as an anti-smoking aid. However, the data and analyses underlying these figures and conclusions are not present in the paper. These figures are also contradicted in a letter by the same author published at a later date in a New Zealand medical journal^[8]. In this publication, smoking abstinence rates of 46.5% (26 of 42 patients) in the active treatment group, and 21.2% (13 of 47) in the placebo group are quoted. As the origin of the figures in both publications is unclear, they cannot be relied upon to provide evidence of efficacy of Nicobrevin.

3.1.3. Cochrane review, 2006^[9]

A Cochrane review^[9] entitled 'Nicobrevin for smoking cessation' assessed the evidence for the effectiveness of Nicobrevin in assisting long-term smoking cessation. The hypothesis tested was that Nicobrevin was more effective than placebo (or an alternative treatment), in achieving long-term smoking cessation.

The outcome criteria were smoking cessation with at least six months of follow up from the start of treatment – the proposed Russell Standard^[7]. The review assessed studies in which smokers wished to quit, and used the Russell Standard of sustained abstinence in preference to point prevalence (smoking cessation at end of Nicobrevin treatment). Other high benchmarks for cessation were that any participants who could not be followed up for any reason would automatically be regarded as continuing smokers.

No study met all of these criteria, and therefore the only two published studies which use Nicobrevin as an investigational product were discussed^[3,4] (Schmidt, 1974 and Dankwa 1988).

The Cochrane review stated concerns regarding the major limitations of the two published studies: in the Schmidt 1974 study^[3] there was questionable study blinding using non-matching placebo products and for the Dankwa 1988 study^[4], there was no requirement for smokers to quit.

The review concludes that, at best, Nicobrevin has effects on the respiratory and digestive system effects which may relieve some of the symptoms that smokers experience whilst abstaining from cigarettes. However, there is no direct evidence that these effects support the anti-smoking preparation indications of Nicobrevin.

The authors of the review also state that it is possible that relapse rates may be relatively higher in actively treated groups at the end of treatment, so that the net benefit of treatment is eroded. This could have an important safety implication for Nicobrevin if, by using the product, you are more likely to relapse. Furthermore, by using an ineffective product, a patient may be delayed in seeking an effective, sustainable treatment for smoking.

The review dismisses short-term outcomes in smoking cessation, arguing that the benefits of quitting are only likely to come from sustained cessation. Despite the high study entry criteria required by Cochrane, Nicobrevin failed to show any efficacy as an anti-smoking preparation likely to produce sustainable cessation. There remains no evidence to support Nicobrevin as an anti-smoking preparation treatment in long-term smoking cessation, and no quality evidence for its use in short-term cessation.

The efficacy of the individual active constituents, as related to the claims made in Nicobrevin's product information, is discussed below:

3.2 Efficacy of individual ingredients of Nicobrevin in aiding smoking cessation

3.2.1 *Menthyl valerate*

Menthyl valerate (also known as menthyl pentanoate) is contained in Nicobrevin as a 30-35% solution of menthol in menthyl iso-valerate. 100 mg of menthyl valerate is present in each capsule. Menthyl valerate is listed in the Merck Index (2011) as a sedative^[10], and the product information for Nicobrevin refers to the pharmacological action of menthyl valerate as 'counteracting irritability and anxiety. Helping to relieve gastrointestinal disturbances'.

There appears to be some evidence that menthyl valerate has a traditional use as a sedative; however, this use has diminished with the introduction of more potent sedatives, particularly the benzodiazepines. No robust evidence has been found to support the use of menthyl valerate in the treatment of GI symptoms, or how this would support the use of Nicobrevin as an anti-smoking product. The evidence does not point to any specific, discernable mechanism of action for the use of menthyl valerate as a component of an anti-smoking preparation.

3.2.2 *Quinine*

Nicobrevin contains 15mg of quinine (base) in each capsule. Quinine is the principle alkaloid found in the bark of various *Cinchona* species of tree (*Rubiaceae*). The product information for Nicobrevin refers to the pharmacological action of quinine as 'slowing the metabolism of nicotine and reducing the craving to smoke. Helping to curb increased appetite.'

There appears to be no published evidence that quinine affects the metabolism of smoking, or that any alteration of metabolism either directly or indirectly reduces a patients craving to smoke. Literature searches for the use of quinine in smoking cessation only refer to the Nicobrevin product, and no other anti-smoking preparation or non-nicotine-replacement therapy contains quinine. However there is some evidence that cigarette smoking has an effect on quinine pharmacokinetics. A 77% increase in clearance was observed in smokers compared with non-smokers using a single administration of quinine sulphate^[11].

The level of quinine in Nicobrevin is significantly lower than the dose required for the main quinine indication for the treatment and prophylaxis of malaria. The maximum daily dose of quinine taken by a Nicobrevin user is 45mg (3 capsules), whereas the typical anti-malarial daily dose is approximately 1 499 mg quinine (as base).

3.2.3 Camphor

10mg of camphor is present in each capsule of Nicobrevin. Oral camphor has both irritant and carminative properties and has been used as a mild expectorant^[12]. However, there are no formal scientific data to elucidate its precise pharmacological action in Nicobrevin.

3.2.4 Eucalyptus oil

10mg of eucalyptus oil is present in each Nicobrevin capsule. The product information states that eucalyptus oil works by alleviating residual respiratory problems and helping to relieve GI disturbances. Eucalyptus oil has been used as a decongestant, is added to a number of oral catarrh and throat lozenge preparations and may also be applied externally as a rubefacient. However, there does not appear to be any evidence of eucalyptus oil being used for GI conditions. Herbal Medicines (2011) concludes that there is a lack of clinical research assessing the effects of eucalyptus and rigorous randomised controlled clinical trials are required.^[13]

3.3 Overall conclusions with regard to efficacy

There appears to be no clear evidence for Nicobrevin's efficacy in aiding smoking cessation. Most of the efficacy claims made for its constituents are also not substantiated by scientific evidence, and there appears to be confusion about precisely how each of the products' components contributes to the anti-smoking indication. There are only two available clinical studies^[4,5] which investigate the effectiveness of Nicobrevin as an ASP; however, these contain sufficient methodological flaws to refute the claims of efficacy.

Given the lack of evidence that the active ingredients have a pharmacological effect that aids smoking cessation, a placebo effect remains the most plausible explanation for any effect of Nicobrevin as an anti-smoking preparation. One of the efficacy studies also noted that there was a large placebo response with Nicobrevin use^[3].

4. SAFETY DATA CONSIDERED

4.1 Safety of Nicobrevin

Safety information relating to Nicobrevin is limited.

The MHRA received six reports of ADRs in association with Nicobrevin from July 1963 to March 2011 in the UK. One of these reports was a case of pericardial haemorrhage, which had a fatal outcome. The other reports included cases of somnolence, visual problems, bronchospasm, skin irritation, depression, and convulsions. The low level of ADR reporting for Nicobrevin may be due, in part, to the significant decrease in its usage over the years.

4.2 Safety of individual active ingredients in Nicobrevin

4.2.1 Menthyl Valerate

No pharmacokinetic data is available for menthyl valerate, but it is presumed that menthyl valerate undergoes hydrolysis *in vivo* to menthol and valeric acid. Approximately 30–35% of the 100 mg menthyl valerate in a Nicobrevin capsule is free menthol, but the amount of free menthol produced after the remaining menthyl valerate undergoes hydrolysis is unknown. Potentially, 100 mg of menthol per capsule could be bioavailable.

Information on safe limits for menthol is scarce, but fatalities have been reported with 2 g menthol (equivalent to approximately 67 Nicobrevin capsules containing 30 mg menthol per capsule).

There is no data on the metabolism of menthyl valerate in Nicobrevin. A study has, however, determined the pharmacokinetic profile of 100 mg menthol^[13]: around 50% undergoes incomplete glucuronide metabolism and is excreted in the urine, while the remainder is metabolised by hydroxylation. Menthol undergoes extensive enterohepatic recirculation, which may have implications for accumulation, particularly when administered 2–3 times a day as part of the Nicobrevin 28-day treatment course. The study also noted an increase in heart rate with menthol compared to placebo.

The MHRA has received six reports of ADRs suspected to be associated with menthyl valerate (including a fatal outcome from a case of pericardial haemorrhage mentioned in section 4.1).

4.2.2 Quinine

Quinine is highly toxic and deaths have occurred after ingestion of 6 g of quinine sulphate (~4.96g as base) in adults^[14]. Fatalities have been reported with 1 g quinine (equivalent to approximately 67 Nicobrevin capsules) in children.

The maximum daily dose of quinine taken by a Nicobrevin user is just 45 mg. Even if an entire pack of capsules were consumed (720mg quinine), this is unlikely to cause acute overdose effects in an adult. However, in 2006, the medicines regulatory authority in the US (the [Food and Drug Administration](#) [FDA]) ordered manufacturers to stop marketing unapproved drug products containing quinine, citing serious safety concerns, including deaths, associated with quinine-containing products. This

included banning the use of over-the-counter (OTC) quinine as a treatment for nocturnal leg cramps. Nicobrevin could not therefore be marketed as an OTC medicine in the US due to its quinine content. These safety concerns for quinine were reflected in the UK in 2010, when health professionals were advised by the MHRA not to use quinine routinely for nocturnal leg cramps^[15].

One of the safety concerns for quinine has been the reporting of low doses causing thrombocytopenia, at levels normally found in tonic water or bitter lemon^[16]. A small number of deaths linked to thrombocytopenia have been reported in patients taking quinine for the treatment of leg cramps, including two cases in the UK^[15].

There are some reports of hepatotoxicity due to quinine usage and other hypersensitivity reactions (predominantly skin reactions) associated with quinine use. Hepatotoxicity also appears to be causally related to quinidine, a stereoisomer of quinine^[12].

In addition, quinine has a GI irritant effect, and may have contributed to the four reported incidences of loss of appetite in the Schmidt study^[3].

4.2.3 Camphor

Camphor is highly lipid soluble, rapidly absorbed from most body areas, and readily crosses the placenta.

Nicobrevin contains approximately 7% camphor. From 1985–1989, four cases of major toxicity occurred with products containing 6–10% camphor, and a further seven cases with products containing less than 5% camphor. Fatalities have been reported with 1 g camphor (equivalent to 110 Nicobrevin capsules) in adults, and with ingestion of 700mg–1g camphor in children^[17]. External application of camphor liniment is discouraged due to its potential toxicity. In this form, it has been withdrawn from the UK market.

The MHRA has received 43 reports of ADRs with camphor-containing products, including one fatality (for Nicobrevin as mentioned in section 4.1).

4.2.4 Eucalyptus oil

10 mg of eucalyptus oil are present in each capsule. There have been reports of gastrointestinal ADR symptoms such as epigastric burning, nausea and vomiting with eucalyptus ingestion, and central nervous system depression, including coma. Cyanosis, ataxia, miosis, pulmonary damage, delirium and convulsions may also occur^[12]. Fatalities have been reported with 3.2 g eucalyptus oil (equivalent to 320 Nicobrevin capsules).

4.2.5 Safety of Nicobrevin excipients

Nicobrevin contains several excipient ingredients. Two of these ingredients—hydroxybenzoate preservatives and arachis oil—are known to cause hypersensitivity reactions.

4.3 Conclusions with regard to safety

In the clinical study by Dankwa and colleagues^[4] a similar incidence of mild GI effects was reported in both Nicobrevin and placebo groups. Given the relatively low quantities of active substances contained in each Nicobrevin capsule the margin of safety is generally acceptable. However, Nicobrevin's quinine content is a concern. Although it is used in lower amounts when compared to products indicated for malaria, in absolute terms concerns have been raised about quinine's safety.

There are two perspectives to consider regarding the safety of quinine in Nicobrevin. Firstly, although dose-related AEs such as cinchonism and tinnitus (commonly seen in patients treated with quinine for malaria) are less likely to be a significant cause for concern in the normal use of Nicobrevin due to the lower quinine content, dose-dependant reactions cannot be ruled out in children. Although the product information for Nicobrevin states that it is not intended for children, its use is not contraindicated in this age group, and the lower age limit for use is not defined.

Secondly, non-dose related, idiosyncratic AEs, particularly those relating to hypersensitivity such as thrombocytopenia, angioedema and asthma, have been reported with quinine levels as low as those found in tonic water^[16]. Therefore it is unlikely that a lower safe level of quinine can be established, particularly in a product like Nicobrevin, where it has questionable therapeutic benefit in an anti-smoking indication.

Wider safety issues have been raised regarding the use of quinine for non-life threatening indications such as nocturnal leg cramps^[15]. In addition, there is no information given on the potential interactions between quinine and several other medicines including antimalarial medication, cimetidine, anticoagulants, antiarrhythmic medication and flouroquinolone antibiotics. Nicobrevin also contains menthyl valerate, whose metabolism is ill defined, and a level of camphor at which toxicity has been reported.

These safety issues, particularly those associated with quinine, raised concerns about the risk-benefit balance of Nicobrevin.

5. DISCUSSION

There are many innovative and efficacious products authorised for smoking cessation use. Prescription medicines such as Zyban (bupropion) and Champix (varenicline) have a defined pharmacology, and their use as smoking cessation treatments is supported by modern, well-designed clinical studies.

NRT products are also effective in helping people stop smoking, and are widely available in pharmacies and retail outlets. There are a wide range of nicotine products to suit most potential quitters: tablets, gums, lozenges, nasal sprays and inhalator devices which provide nicotine for absorption through either the skin or mucous membranes. Their common aim is to replace the nicotine from tobacco, thus directly reducing the symptoms associated with nicotine withdrawal when quitting smoking.

A Cochrane review^[18] of over 90 studies has found that nicotine replacement does help people to stop smoking, increasing the chances of quitting by one and a half to two times^[1] compared to will-power alone.

Compared with NRT, there is very little evidence that Nicobrevin can aid smoking cessation. To date there have been no clinical trials directly comparing Nicobrevin to NRT. With the advent of newer, non-nicotine-containing prescription medicines to help people stop smoking such as bupropion and varenicline, the need for older and less effective non-nicotine products is questionable. This is partly borne out by the decline in usage of Nicobrevin.

The risks of Nicobrevin's quinine content raise particular concerns. In 2006, the FDA stated that malaria is a life-threatening condition for which it considered the risks of using quinine to be justified. However it did not consider the risks associated with quinine use in the treatment of leg cramps to be justified. These concerns were reflected in the UK in 2010 when doctors were advised by the MHRA not to use quinine routinely for nocturnal leg cramps^[15]. The risks of using Nicobrevin, which contains quinine, cannot be justified, particularly as there is no evidence to support its effectiveness as an anti-smoking preparation and when considering the many alternative products available to aid smoking cessation.

In addition, due to limited study methodologies, neither the Schmidt study^[3], nor the Dankwa study^[4], offer any robust support for Nicobrevin as an anti-smoking preparation. The Cochrane review of Nicobrevin^[9] also confirmed the lack of evidence to support Nicobrevin in long-term smoking cessation.

6. CONCLUSIONS AND ACTIONS

There is a lack of evidence to support the use of Nicobrevin in long-term smoking cessation and little rationale to support the use of any of the ingredients in an antismoking preparation. Furthermore, the product is not supported by any anti-smoking organisation.

The constituent ingredients all have well-established toxicology which contributes to real adverse events. There is a lack of rationale for inclusion of quinine in Nicobrevin, which is of particular concern as it is associated with adverse reactions such as thrombocytopenia.

On the basis of the evidence assessed, the Commission on Human Medicines advised that on balance, the risks of Nicobrevin outweigh its benefits. Because of its negative risk-benefit profile, the MHRA concluded that Nicobrevin should be withdrawn from the UK market, especially in view of the fact that there are many other effective medicines available to aid smoking cessation. Distribution of Nicobrevin in the UK ceased at the end of August 2010, and its license was cancelled on 31st January 2011.

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8. GLOSSARY

Acetylcholine

A **neurotransmitter** found in the body and brain, which activates muscles and sustains attention. It is also found in the nerves of the body known as 'parasympathetic'

Alkaloid

A family of chemical compounds found in plants, many of which are **pharmacologically** active

Allergic reaction

The body's response to sensing a foreign substance, which can consist of symptoms such as a rash, itchy skin or breathing difficulties

Angioedema

An **allergic reaction** consisting of swelling beneath the skin

Antiarrhythmic medication

Medicine that treats an abnormality in the heart rhythm or rate (that occurs because of an abnormality in the electrical activity of the heart)

Anticoagulant

A medicine that prevents the clotting of blood

Anti-smoking preparation

A product designed to help people to stop smoking

Arachis oil

Peanut oil

Ataxia

Loss of voluntary muscle control, which results in lack of balance and coordination

Benzodiazepines

A class of drugs used to treat anxiety and **insomnia**

Biliary colic

Severe abdominal pain caused by a spasm or distention in (usually) the intestines

Bupropion (brand name Zyban)

A prescription medicine given to help people stop smoking

Camphor

An active ingredient in Nicobrevin

Carbon monoxide

A poisonous gas that is contained in cigarette smoke and is found in increased quantities in smokers, compared to non-smokers

Carboxyhaemoglobin

A complex formed when the poisonous gas **carbon monoxide** binds to the protein haemoglobin in red blood cells, displacing oxygen. Large quantities of this complex lead to oxygen deprivation, causing dizziness, unconsciousness and death

Carminative

A drug that induces the expulsion of gas from the stomach or intestines

Champix (scientific name: varenicline)

A prescription medicine which helps people to stop smoking

Cimetidine

A drug that inhibits the production of gas in the stomach and is mainly used for the treatment of heartburn

Cinchonism

A complex syndrome of adverse reactions in the body caused by an overdose of **quinine**. The symptoms include flushed and sweaty skin, **tinnitus**, blurred vision, impaired hearing and confusion

Clinical trial

A research study that tests the effectiveness and safety of medicines in humans

Cochrane review

A series of systematic reviews of primary research in human health care and health policies

Contraindicated

Any factor or medical condition that makes it unwise to give a particular medicine to a patient

Cyanosis

A bluish discolouration of the skin and mucous membranes, which is due to insufficient oxygen in the blood

Decongestant

A drug that helps to clear a blocked nose

Double blind study

A **clinical trial** in which the identity of the test medicine is hidden from both the volunteers and the study investigators (to remove any possible bias from the results)

Efficacy

The effectiveness of a drug measured under laboratory conditions or in clinical trials

Enterohepatic recirculation

Where drugs and metabolites are reabsorbed in the intestine after excretion in the biliary system

Epigastric burning

A pain or burning sensation in the upper middle part of the abdomen

Eucalyptus

An active ingredient in **Nicobrevin**

Excipient

An inactive substance that is combined with an active drug so that it is in a form that is suitable for a patient to take; ie, capsules or tablets

Expectorant

A medicine that helps bring up mucus and other materials from the respiratory tract (lungs and trachea). It is sometimes used in treatments for conditions that are characterised by excess mucus, such as the common cold

Fluoroquinolone

A group of antibacterial medicines (or antibiotics)

Glucuronide metabolism

Metabolism of certain drugs and medicines in the body, such as menthyl valerate, using a substance called glucuronic acid

Hepatotoxicity

Where a substance has toxic effects on the liver

Hydrolysis

Decomposition of a chemical compound by reaction with water

Hydroxybenzoate preservatives (also known as ‘parabens’)

Preservatives added to cosmetics and pharmaceutical drugs to prolong their ‘shelf-life’. They can cause allergic reactions in a small percentage of the general population

Hydroxylation

A chemical process that helps to break down certain compounds

Hypersensitivity reactions

Abnormal **allergic** responses

Insomnia

Inability to fall asleep or remain asleep for an adequate length of time

Malaria

A serious, often fatal, infectious disease caused by a parasite transmitted in the bite of infected mosquitos. The disease is characterised by cycles of chills, fever and sweating.

Menthol

A substance produced when **menthyl valerate** is chemically broken down by the body

Menthyl valerate

An active ingredient in **Nicobrevin**

Metabolism

The chemical processes or changes that occur in the body in order to maintain life. This involves either breaking down substances or making new ones

Miosis

Constriction (narrowing) of the pupil of the eye, as a normal response to light or resulting from the use of certain drugs

Nausea

Feeling of sickness or an urge to vomit

Nicotine

An addictive drug found in tobacco that acts on nicotinic **acetylcholine receptors**, causing an increase in blood pressure and heart rate

Nicotine replacement therapy (NRT)

A method to help people quit smoking, which contains the substance **nicotine**

Nocturnal leg cramps

Sudden painful contractions of the lower leg and foot muscles which occur at night during rest

Pericardial haemorrhage

Serious or fatal bleeding in the membranous sac surrounding the heart

Pharmacological

Related to the science of drugs and their effect on the body

Placebo

Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

Quinine

An active ingredient in **Nicobrevin**

Receptor

An area on the surface of a cell to which specific substances bind. This causes a change in the cell, which in turn affects the body

Renal pain

Pain in the kidney

Respiratory system

The bodily organs that enable breathing and oxygen absorption to occur

Rubefacient

A substance that irritates the skin, causing it to redden

Satiation

A state where appetite has been satisfied

Sedative

Drugs that induce a state of reduced excitement or activity

Smoking cessation therapies/treatment

Drugs that are used to enable people to stop smoking

Study blind

A component of some clinical studies where participants do not know what treatment they are receiving – these studies are referred to as 'single blind'. If neither the participants nor the researchers know which participant is receiving which treatment, this type of study is referred to as 'double blind'

Thrombocytopenia

An abnormal drop in the number of blood cells involved in forming blood clots

Tinnitus

Noises in the ear that originate from within the ear or head

Toxicology

The study of the adverse effects caused by chemical, physical or biological agents on living organisms

Varenicline (brand name Champix)

A prescription medicine which helps people to stop smoking

Vertigo

A medical condition that leads to a sensation of dizziness and disorientation

Zyban (scientific name bupropion)

A prescription medicine which helps people to stop smoking