Safeguarding public health

Public Assessment Report

Decentralised Procedure

Nicabate Mint 2.5 mg Orodispersible Film

PL 00079/0640

UK/H/0287/17/DC

Beecham Group plc

Medicines and Healthcare products Regulatory Agency

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Beecham Group plc a Marketing Authorisation (licence) for the medicinal product Nicabate Mint 2.5 mg Orodispersible Film (product licence number: PL 00079/0640) on 13 May 2011. This medicine can be bought from pharmacies and other outlets without a prescription.

Nicabate Film is used to help people stop smoking. This type of treatment is called nicotine replacement therapy. It is the nicotine in cigarettes that can make smokers physically addicted to them. Nicabate Film replaces the nicotine that smokers get from cigarettes. This nicotine relieves some of the unpleasant symptoms that smokers may have when they try to give up. These include feeling ill or irritable. The nicotine can also relieve cravings for a cigarette and curb the urge to smoke. Nicabate Film does not have the health dangers of tobacco because it does not contain the tar, carbon monoxide or other toxins that are found in cigarette smoke.

The data submitted in support of this application for Nicabate Film raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about Decentralised Procedure

Name of the product in the Reference Member State	Nicabate Mint 2.5 mg Orodispersible Film
Type of application	Article 8.3 (known active substance)
Name of the active substance (INN)	Nicotine
Pharmacotherapeutic classification (ATC code)	Drugs used in nicotine dependence (NO7B A01)
Pharmaceutical form and strength	Orodispersible film, 2.5 mg
Reference number for the Decentralised Procedure	UK/H/0287/17/DC
Reference Member State	United Kingdom
Member States concerned	AT, PT, BE, LU, SE, CZ, HU, SK, DE, IE, NL, DK, IT and PL
Start of Decentralised Procedure	10 May 2010
End date of Decentralised Procedure	4 May 2011
Marketing Authorisation number	PL 00079/0640
Name and address of the authorisation holder	Beecham Group plc 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicabate Mint 2.5 mg Orodispersible Film

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Orodispersible Film contains 2.5 mg nicotine
Contains ethanol, not more than 3.9 mg per film

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orodispersible Film
Transparent film approximately 20 mm by 30 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nicabate Films are to be used for the treatment of tobacco dependence by relief of nicotine withdrawal symptoms, including cravings, during a quit attempt (See section 5.1). Permanent cessation of tobacco use is the eventual objective.

Nicabate Films should preferably be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

Posology
Nicabate Films are suitable for smokers who have their first cigarette of the day more than 30 minutes after waking up.

Users should not eat or drink while a nicotine film is in the mouth.

Behavioural therapy, advice and support will normally improve the success rate.

Adults (18 years and over)

Users should make every effort to stop smoking completely during treatment with Nicabate Films.

Recommended treatment schedule:

Step 1 Weeks 1 to 6	Step 2 Weeks 7 to 9	Step 3 Weeks 10 to 12
Initial treatment period	Step down treatment period	Step down treatment period
1 nicotine film every 1 to 2 hours	1 nicotine film every 2 to 4 hours	1 nicotine film every 4 to 8 hours

During weeks 1 to 6 it is recommended that users take a minimum of 9 nicotine films per day. Users should not exceed 15 nicotine films per day.

To help stay smoke free beyond 12 weeks, users may take 1-2 nicotine films per day only on occasions when they are strongly tempted to smoke.

Those who use the nicotine films beyond 9 months are recommended to seek additional help and advice from a healthcare professional.

Paediatric population

Nicabate Films should only be used by adolescents (12-17 years inclusive) with advice from a physician.

Nicotine films are contraindicated for use in children under 12 years of age due to the lack of data on safety and efficacy. See section 4.3. There is no experience in treating adolescents under the age of 18 with Nicabate films.

Method of administration

Place one nicotine film on the tongue. Close the mouth and press the tongue gently to the roof of the mouth until the nicotine film dissolves (approximately 3 minutes). The nicotine film should not be chewed or swallowed whole. Do not use if nicotine film is damaged.

4.3 Contraindications

- people with hypersensitivity to nicotine or any of the excipients
- children under the age of 12 years
- non-smokers

4.4 Special warnings and precautions for use

The risks associated with the use of NRT are substantially outweighed in virtually all circumstances by the well established dangers of continued smoking.

Dependent smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal's angina, severe cardiac arrhythmias, uncontrolled hypertensions or recent cerebrovascular accident should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Nicabate Films may be considered but as data on safety in this patient group are limited, initiation should only be under close medical supervision.

Diabetes Mellitus: Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when NRT is initiated.

Allergic reactions: Susceptibility to angioedema and urticaria.

A risk-benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

- *Renal and hepatic impairment*: Use with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.
- *Phaeochromocytoma and uncontrolled hyperthyroidism*: Use with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma as nicotine causes release of catecholamines.
- *Gastrointestinal Disease***:** Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers and oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

Danger in small children: Doses of nicotine tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal. Products containing nicotine should not be left where they may be misused, handled or ingested by children.

Stopping smoking: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs.

Transferred dependence: Transferred dependence is rare and is both less harmful and easier to break than smoking dependence**.**

Ethanol (alcohol): This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per nicotine film.

4.5 Interaction with other medicinal products and other forms of interaction

Adults and paediatric (12-17 years inclusive) population

No clinically relevant interactions between nicotine replacement therapy and other medicinal products have definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

4.6 Pregnancy and lactation

Pregnancy

Smoking during pregnancy is associated with risks such as intra-uterine growth retardation, premature birth or stillbirth. Stopping smoking is the single most effective intervention for improving the health of both pregnant smoker and her baby. The earlier abstinence is achieved the better.

Ideally smoking cessation during pregnancy should be achieved without NRT. However for women unable to quit on their own, NRT may be recommended by a healthcare professional to assist a quit attempt. The risk of using NRT to the fetus is lower than that expected with tobacco smoking, due to lower maximal plasma nicotine concentration and no additional exposure to polycyclic hydrocarbons and carbon monoxide.

However, as nicotine passes to the fetus affecting breathing movements and has a dose dependent effect on placental/fetal circulation, the decision to use NRT should be made as early on in the pregnancy as possible. The aim should be to use NRT for only 2-3 months.

Intermittent dosing products may be preferable as these usually provide a lower daily dose of nicotine than patches. However patches may be preferred if the woman is suffering from nausea during pregnancy.

Breastfeeding
Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to from NRT is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to.

Ideally smoking cessation during breastfeeding should be achieved without NRT. However for women unable to quit on their own, NRT may be recommended by a healthcare professional to assist a quit attempt.

Using intermittent dose NRT preparations, compared with patches, may minimise the amount of nicotine in the breast milk as the time between administrations of NRT and feeding can be made as long as possible. Women should try to breastfeed just before they use the nicotine films.

Fertility
There are no relevant data available.
See section 5.3

4.7 Effects on ability to drive and use machines

There are no known effects of Nicabate Films on the ability to drive and use machines. However, users of nicotine replacement products should be aware that smoking cessation can cause behavioural changes.

4.8 Undesirable effects

Adults

Nicotine films can cause adverse reactions similar to those associated with nicotine from tobacco. Many of the observed adverse reactions are consistent with the pharmacological effects of nicotine, which are dose dependent.
The following undesirable effects detailed in Table 1 are nicotine related adverse events for all oral dosage forms.

Events were identified from

- a double-blind, randomised, placebo controlled lozenge clinical study involving 1818 patients. Adverse events reported in this study have

been considered for inclusion, where the incidence in the 2 mg or 4 mg nicotine arm was higher than the corresponding placebo arm. Frequencies are calculated from the study safety data.

- post-marketing experience of oral nicotine products. Frequencies for these events cannot be estimated for oral nicotine dosage forms from the available data.

Table 1

Cardiac Disorders	
Frequency: Unknown	palpitations, tachycardia
Gastrointestinal Disorders	
Very common ≥ 1/10	nausea
Common ≥1/100 to<1/10	vomiting, dyspepsia, abdominal pain upper, diarrhoea, dry mouth, constipation, hiccups, stomatitis, flatulence, oral discomfort
Frequency: Unknown	dysphagia, eructation, salivary hypersecretion
General Disorders and Administration Site Conditions	
Frequency: Unknown	asthenia*, fatigue*, malaise*, influenza type illness*
Immune System Disorders	
Frequency: Unknown	hypersensitivity, angioedema, urticaria, ulcerative stomatitis, and very rare anaphylactic reactions
Nervous System Disorders	
Common ≥1/100 to <1/10	headache*, dizziness*
Frequency: Unknown	tremor
Psychiatric Disorders	
Common ≥1/100 to <1/10	insomnia*
Frequency: Unknown	nervousness*
Respiratory, Thoracic and Mediastinal Disorders	
Common ≥1/100 to <1/10	pharyngitis, cough*, pharyngolaryngeal pain
Frequency: Unknown	dyspnoea

***** These events may also be due to withdrawal symptoms following smoking cessation

Paediatric population (12 - 17 years inclusive)

There are no specific adverse event data for this population. However, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as adults, based upon a pharmacokinetic study demonstrating a similar pharmacokinetic profile in the adolescent age group compared to adults.

4.9 Overdose

Adults and paediatric (12 - 17 years inclusive) population

Symptoms: The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Even small quantities of nicotine may be dangerous in children and may prove fatal. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately. Symptoms of acute nicotine poisoning include nausea, salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and marked weakness. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse and terminal convulsions.

***Management of an overdose*:** All nicotine intake should stop immediately and the patient should be treated symptomatically. Artificial respiration with oxygen should be instituted if necessary. Activated charcoal reduces the gastro-intestinal absorption of nicotine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in nicotine dependence
ATC Code: N07BA01

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. When consumed in tobacco products, it has been shown to be addictive and abstinence is linked to craving and withdrawal symptoms. These craving and withdrawal symptoms include urge to smoke, depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty in concentrating, restlessness and increased appetite or weight gain. Cravings and other symptoms of nicotine withdrawal are at their most intense during the first few weeks of a quit attempt, diminishing thereafter. The nicotine films replace some of the nicotine provided by tobacco. Clinical studies for the bioequivalent 2 mg lozenge have shown a reduction in intensity of cravings.

5.2 Pharmacokinetic properties

Nicotine films completely dissolve in the oral cavity, and the entire amount of nicotine contained in the nicotine film becomes available for buccal absorption or ingestion (swallowing). The complete dissolution of a nicotine film is typically achieved in approximately 3 minutes. The peak plasma concentrations of nicotine achieved after a single dose are approximately 4.13 ng/ml.

As the plasma protein binding of nicotine is low (4.9% - 20%), the volume of distribution of nicotine is large (2.5 l/kg). The distribution of nicotine to tissue is pH dependent, with the highest concentrations of nicotine found in the brain, stomach, kidney and liver.

Nicotine is extensively metabolised to a number of metabolites, all of which are less active than the parent compound. The metabolism of nicotine

primarily occurs in the liver, but also in the lung and kidney. Nicotine is metabolised primarily to cotinine but is also metabolised to nicotine N′-oxide. Cotinine has a half-life of 15-20 hours and its blood levels are 10 times higher than nicotine. Cotinine is further oxidised to *trans*-3′-hydroxycotinine, which is the most abundant metabolite of nicotine in the urine. Both nicotine and cotinine undergo glucuronidation.

The elimination half-life of nicotine is approximately 2 hours (range 1 - 4 hours). Total clearance for nicotine ranges from approximately 62 to 89 l/hr. Non-renal clearance for nicotine is estimated to be about 75% of total clearance. Nicotine and its metabolites are excreted almost exclusively in the urine. The renal excretion of unchanged nicotine is highly dependent on urinary pH, with greater excretion occurring at acidic pH.

5.3 Preclinical safety data

The general toxicity of nicotine is well known and taken into account in the recommended posology. Nicotine was not mutagenic in appropriate assays. The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine. In studies in pregnant animals, nicotine showed maternal toxicity, and mild fetal toxicity. Additional effects included pre- and postnatal growth retardation and delays and changes in postnatal CNS development.

Effects were only noted following exposure to nicotine at levels in excess of those which will result from recommended use of nicotine films. Effects on fertility have not been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), Type A

Triethyl Citrate (E1505)

Peppermint Flavour TAK - 032230

Sucralose (E955)

Sodium Hydrogen Carbonate (E500 ii)

Ethanol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package to protect from light and moisture

6.5 Nature and contents of container

Each nicotine film is contained in a polyethyleneterephthalate (PET)/aluminium/polyacrylnitrile (PAN) laminate sachet.
Each pack contains 10, 15, 30 or 60 sachets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Beecham Group plc
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom
T/A GlaxoSmithKline Consumer Healthcare
Brentford TW8 9GS, UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00079/0640

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/05/2011

10 DATE OF REVISION OF THE TEXT

13/05/2011

Module 3

Product Information Leaflet

The following text is the approved Product Information Leaflet (PIL) text. No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nicabate Mint 2.5 mg Orodispersible Film
Nicotine

Please read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to use Nicabate Mint 2.5 mg Orodispersible Films carefully to get the best results from them.

- Keep this leaflet. You may need to read it again.
- Ask a healthcare professional e.g. doctor, nurse, smoking cessation adviser or pharmacist if you need more information or advice.
- If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell a healthcare professional.
- Throughout this leaflet Nicabate Mint 2.5 mg Orodispersible Films are referred to as Nicabate Films or nicotine films.

In this leaflet:

1. What Nicabate Films are and what they are used for
2. Before you use Nicabate Films
3. How to use Nicabate Films
4. Possible side effects
5. How to store Nicabate Films
6. Further information

1. WHAT NICABATE FILMS ARE AND WHAT THEY ARE USED FOR?

Nicabate Films are used to help people stop smoking. This type of treatment is called Nicotine Replacement Therapy or NRT.

It is the nicotine in cigarettes that can make you physically addicted to them.

- Nicabate Films help you to give up smoking by replacing some of the nicotine you get from cigarettes.
- This nicotine relieves some of the unpleasant symptoms that smokers may have when they try to give up. These include feeling ill or irritable.
- The nicotine can also relieve your cravings for a cigarette and help you to resist the urge to smoke.

Nicabate Films do not have the health dangers of tobacco. This is because they do not contain the tar, carbon monoxide or other toxins in cigarette smoke. Some people worry that after stopping smoking, they may become dependent on Nicabate Films instead. This is very rare, and if it did happen, it is less harmful than continuing to smoke. It also an easier habit to break.

Your chances of stopping smoking will be improved if you take part in a support programme. These "stop smoking programmes" are known as behavioural support. For information on stop smoking programmes please talk to a healthcare professional.

2. BEFORE YOU USE NICABATE FILMS

Do not use Nicabate Films if:

- you are allergic (hypersensitive) to nicotine or any of the other ingredients in the film (See section 6: Further information)
- you are a non-smoker or under the age of 12 years

There are no health benefits to smoking. It is always better to give up smoking. Using Nicotine Replacement Therapy (NRT), like Nicabate Films, can help. In general, any possible side effects associated with NRT are far outweighed by the well known dangers of continuing to smoke.

Take special care with Nicabate Films:

- If you have had a recent heart attack or stroke, or you suffer from severe heart rhythm problems, unstable or worsening angina (chest pain) or resting angina or uncontrolled high blood pressure you should try to quit smoking without using any NRT products unless your doctor tells you to use them.
- If you have diabetes you should monitor your blood sugar levels more often than usual when you start using Nicabate Films. Your insulin or medicine requirements may change.
- If you have ever had allergic reactions that involve swelling of the lips, face and throat (angioedema) or itchy skin rash (urticaria). Using NRT can sometimes trigger this type of reaction.
- If you have children under 12 years:A normal dose for adults could cause a severe poisoning in children which can cause death. It is therefore very important to always keep Nicabate Films out of the reach and sight of children

If you are pregnant or breastfeeding it is best if you can give up smoking without the use of NRT. However, it is better to stop smoking using NRT than to continue smoking. (See the section on pregnancy and breastfeeding below for more information.)

Get help and advice from a healthcare professional if you have:

- Serious liver or kidney problems because you may be more likely to get side effects.
- Uncontrolled overactive thyroid gland or phaeochromocytoma (a tumour of the adrenal gland that can affect blood pressure) - your doctor will have told you this - because nicotine may make your symptoms worse.
- Stomach or duodenal ulcers or an inflamed oesophagus or gullet (the passage between the mouth and stomach) because swallowing nicotine can make your symptoms worse. It may also cause mouth ulcers. If your symptoms do get worse you should talk to your doctor. You might want to use a non-oral form of NRT instead, such as patches.

Taking other medicines

Please tell your healthcare professional if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Nicabate Films with food and drink

You should not eat or drink while a Nicabate Film is in the mouth.

Pregnancy or breastfeeding

Smoking during pregnancy has risks for the baby. These include poor growth before birth, premature birth or stillbirth. Stopping smoking is the best way to improve both your health and that of your baby. The earlier you stop smoking the better.

Ideally, if you are pregnant, you should stop smoking without using NRT. However, if you have tried and this has not worked, NRT may be recommended by a healthcare professional to help you stop smoking. This is because it is better for your developing baby than if you carry on smoking. The decision to use NRT should be made as early on as possible in your pregnancy. You should aim to use it for only 2-3 months. Remember, the most important thing is to stop smoking. Products such as Nicabate Films may be preferable to nicotine patches. This is because with Nicabate Films, you do not get the nicotine all the time. However, patches may be preferred if you have nausea or sickness.

If you are breastfeeding tobacco smoke causes breathing difficulties and other problems in babies and children. Ideally you should stop smoking without using NRT. However, if you have tried and this has not worked, NRT may be recommended by a healthcare professional. If you need to use NRT to help you quit, the amount of nicotine your baby may get is small. It is much less harmful than breathing in second hand smoke. It is best to use NRT products that are taken at certain times of the day (such as a Nicabate Film, rather than patches). It is also better to breastfeed just before you use the product. This helps your baby to get the smallest amount of nicotine possible.

Driving and using machines

There are no known effects of Nicabate Films on your ability to drive or use machines. However, you should be aware that giving up smoking can cause behavioural changes that could affect your ability to drive or use machines.

Important information about some of the ingredients of Nicabate Films

This medicine contains small amounts of ethanol (alcohol), less than 100 mg per Nicabate Film.

3. HOW TO USE NICABATE FILMS

Always use Nicabate Films exactly as stated in this package leaflet. You should check with your healthcare professional if you are not sure.

During any attempt to give up smoking using Nicabate Films it is important that you make every effort to stop smoking completely. However, if you do smoke a cigarette while you are using NRT, you should continue your quit attempt. If you continue to have difficulty stopping smoking talking to your doctor, nurse, smoking cessation advisor or pharmacist may help.

Instructions for opening the sachet are on the outside of the sachet.

Do not use if nicotine film is damaged.

You should use Nicabate Films by putting one film on your tongue, close your mouth and press the tongue gently to the roof of the mouth until the Nicotine Film dissolves (approximately 3 minutes). Do not chew the film or swallow it whole. You should not eat or drink while a Nicabate Film is in your mouth as this may reduce the absorption of the nicotine. Do not use more that 15 Nicabate Films a day. If you feel the need to use Nicabate Films for longer than 9 months in total, you should ask a healthcare professional for advice.

Adults (18 years and over)
The table below shows how many nicotine films to use during the first 12 weeks of treatment.

- For the first 6 weeks use at least 9 nicotine films a day

STEP 1 Weeks 1 to 6	STEP 2 Weeks 7 to 9	STEP 3 Weeks 10 to 12
Initial treatment period 1 nicotine film every 1 to 2 hours	Step down treatment period 1 nicotine film every 2 to 4 hours	Step down treatment period 1 nicotine film every 4 to 8 hours

- To help you stay smoke free over the next 12 weeks, you can use 1-2 nicotine films per day in situations where you are strongly tempted to smoke.
- Once you are using only 1-2 nicotine films a day, stop using them altogether.

Young people (12-17 years inclusive)

You should only use Nicabate Films following advice from a doctor.

Do not exceed the stated dose. Follow the instructions carefully and do not use more than 15 nicotine films in one day (24 hours).

Children under 12 years of age should not use nicotine films.

This product is for oromucosal use. This means that the nicotine in the nicotine films is released slowly into the mouth from where it is absorbed into the body.

If you are tempted to start smoking again

If you are:
- worried that you may start smoking again
- finding it difficult to stop using the nicotine films completely

talk to a healthcare professional.

If you do start to smoke again, they can advise you on how to get the best results from further courses of Nicotine Replacement Therapy (NRT).

If you use more nicotine films than you should

If you use too many nicotine films you may start to feel sick, dizzy and unwell. Stop using the nicotine films and get advice straightaway from a doctor or hospital casualty department. If possible, show them the packet or this leaflet.

The nicotine films are not suitable for children under 12 or non-smokers. If the nicotine films are used by children or non-smokers they may show signs of nicotine overdose. These include headache, sickness, stomach pains and diarrhoea. If a child has used or eaten any of the nicotine films, contact your doctor or nearest hospital casualty department straightaway. If possible show them the packet or this leaflet.

If you have any further questions on the use of this product, ask your healthcare professional.

If you forget to use Nicabate Films

You should carry on using the medicine as recommended.

If you stop using Nicabate Films

If you stop using the medicine before the recommended time you may feel the urge to smoke again.

4. POSSIBLE SIDE EFFECTS

Like all medicines Nicabate Films can cause side effects, although not everybody gets them.

Stopping smoking itself can cause symptoms such as headache, dizziness, increased coughing or a cold. Symptoms such as weakness, tiredness, feeling unwell, nervousness and insomnia may also be related to giving up smoking.

Other side effects are listed below - they are based on the likelihood with which they can occur:

Very common (affects *more than* 1 in 10 people)

- feeling sick.

Common (affects *between* 1 in 10 and 1 in 100 people)

- being sick
- indigestion/heartburn
- stomach discomfort
- diarrhoea
- dry mouth
- constipation
- hiccups
- sore or swollen throat
- flatulence
- slight soreness or irritation of mouth or tongue
- headache
- dizziness
- insomnia
- cough

Other side effects which have been reported are:

- an increase in your heart rate or awareness of your heart beat
- difficulty swallowing, belching, increased saliva
- feeling weak, lack of energy, flu-like symptoms, feeling unwell
- allergic reaction including itchy bumpy rashes, mouth irritation and ulcers
- tremor
- nervousness
- shortness of breath

It is not known how frequently these effects occur.

Very rare (affects *less than* 1 in 10,000 people)

- serious allergic reaction causing swelling of the face, tongue, or throat which may cause difficulty in swallowing or breathing

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell a healthcare professional.

5. HOW TO STORE NICABATE FILMS

Keep all medicines out of the reach and sight of children.

- Do not use the nicotine films after the expiry date which is stated on the sachet and carton. The expiry date refers to the last day of that month.
- Do not store above 30ºC.
- Store in the original package to protect from light and moisture.
- Dispose of the pack responsibly. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Nicabate Films contain

The active substance is nicotine 2.5 mg per orodispersible film.

The other ingredients are Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), Type A, Triethyl Citrate (E1505), Peppermint Flavour TAK - 032230, Sucralose (E955), Sodium Hydrogen Carbonate (E500 ii), Ethanol.

What Nicabate Films look like and contents of the pack

Nicabate Films are transparent films approximately 20 mm by 30 mm.
Each film comes in its own sachet. Each pack contains 10, 15, 30 or 60 sachets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder to be completed nationally

Manufacturer: LTS Lohmann Therapie- Systeme AG, Lohmannstr. 2, D- 56626 Andernach, Germany

This leaflet was last revised in {MM/YYYY}.

Module 4

Labelling

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nicabate Mint 2.5 mg Orodispersible Film
Nicotine

2. STATEMENT OF ACTIVE SUBSTANCE

Each nicotine film contains 2.5 mg nicotine

3. LIST OF EXCIPIENTS

Ingredients

Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), Type A, Triethyl Citrate (E1505), Peppermint Flavour TAK - 032230, Sucralose (E955), Sodium Hydrogen Carbonate (E500 ii), Ethanol.
This medicinal product contains small amounts of ethanol (alcohol).

4. PHARMACEUTICAL FORM AND CONTENTS

Contains 10 orodispersible films
Contains 15 orodispersible films
Contains 30 orodispersible films
Contains 60 orodispersible films

5. METHOD AND ROUTE OF ADMINISTRATION

Oromucosal use
Read the package leaflet before use
Instructions for opening the sachet are on the outside of the sachet.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Storage Precautions

Do not store above 30ºC. Store in the original package to protect from light and moisture.

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

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

To be completed nationally.

12. MARKETING AUTHORISATION NUMBER

To be completed nationally.

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS FOR USE

Stop smoking aid
Nicotine films are used to help people stop smoking
How to use
For smokers who smoke their first cigarette more than 30 minutes after waking up

STEP 1 Weeks 1 to 6	STEP 2 Weeks 7 to 9	STEP 3 Weeks 10 to 12
Initial treatment period 1 nicotine film every 1 to 2 hours	Step down treatment period 1 nicotine film every 2 to 4 hours	Step down treatment period 1 nicotine film every 4 to 8 hours

- do not eat, drink or chew while a nicotine film is in the mouth
- do not swallow the nicotine film whole.
- do not use more than 15 nicotine films per day.
- dissolve 1 nicotine film fully in the mouth (approximately 3 minutes) by placing one nicotine film on the tongue. Close the mouth and press the tongue gently over the roof of the mouth until the nicotine film dissolves.
- if you need to use the nicotine films for longer than 9 months seek advice from a healthcare professional.
- young people (12-17 years inclusive) should only use nicotine films following advice from adoctor.
- do not use if nicotine film is damaged.

Do not use
- if you are allergic to any of the ingredients listed.
- if you are a non-smoker or under the age of 12 years.

Consult a healthcare professional
- if you have or recently had heart problems.
- if you have serious liver or kidney disease, uncontrolled overactive thyroid gland or phaeochromocytoma stomach ulcers or other problems with your stomach or throat.
- before use if you are pregnant or breastfeeding.

16. INFORMATION ON BRAILLE

To be completed nationally

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Nicabate Mint 2.5 mg Orodispersible Film
Nicotine
Oromucosal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Dissolve 1 nicotine film fully in mouth (approximately 3 minutes)

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contains 1 orodispersible film

6. OTHER

Keep out of the reach and sight of children

Instructions for opening – to be agreed nationally on translation.

Module 5

Scientific Discussion

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Nicabate Mint 2.5 mg Orodispersible Film in the treatment of tobacco dependence by relief of nicotine withdrawal symptoms, including cravings, during a quit attempt could be approved.

EXECUTIVE SUMMARY

Problem statement

This application was submitted according to Article 8.3 of Directive 2001/83/EC, for a new product with a known active substance (with the addition of a new strength and a new pharmaceutical form). The application is a line extension to the Marketing Authorisations for Nicabate 7 mg/24 hrs, 14 mg/24 hrs and 21 mg/24 hrs transdermal patches, which were approved through Mutual Recognition Procedures UK/H/287/01, UK/H/287/02 and UK/H/287/03, respectively.

With the UK acting as RMS in this DCP, Beecham Group plc sought Marketing Authorisation for Nicabate Mint 2.5 mg Orodispersible Film in Austria, Portugal, Belgium, Luxembourg, Sweden, Czech Republic, Hungary, The Slovak Republic, Germany, Ireland, the Netherlands, Denmark, Italy and Poland.

About the product

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

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

General comments on the submitted dossier

The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossier regarding the quality, preclinical and clinical parts have been submitted.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GLP

No new preclinical studies were submitted with this application. The GLP status of the literature data referenced in the preclinical section of the dossier cannot be verified.

GCP

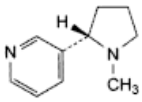
Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practices (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

rINN: Nicotine
Chemical name: 3-[(2S)-1-Methylpyrrolidin-2-yl]pyridine
CAS number: 54-11-5
Structural formula:



Molecular formula: $C_{10}H_{14}N_2$
Molecular weight: 162.2
General properties: Colourless or brownish viscous liquid, volatile, hygroscopic, soluble in water, miscible with anhydrous ethanol

Nicotine is a well-known active substance described in the Ph Eur. All aspects of the manufacture and control of nicotine are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of nicotine for inclusion in this medicinal product.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the proposed packaging.

Drug product
The drug product is a transparent orodispersible film (approximately 20 mm by 30 mm) containing 2.5 mg nicotine and the excipients methacrylic acid (ethyl acrylate copolymer (1:1), Type A), triethyl citrate (E1505), peppermint flavour TAK (032230), sucralose (E955), sodium hydrogen carbonate (E500 ii) and ethanol.

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of sucralose, which is controlled to NF standards, and peppermint flavour TAK, which is controlled by a suitable in-house specification; in the absence of European Pharmacopoeial monographs for these excipients, this is acceptable.

Satisfactory certificates of analysis have been provided for all excipients. Suitable declarations issued by suppliers of the excipients confirming compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided.

Pharmaceutical development
A satisfactory account of the pharmaceutical development of the product has been provided.

Product manufacture
A satisfactory account of the manufacturing process has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted

Finished product specification
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-closure system
Each nicotine film is contained in a polyethyleneterephthalate (PET)/aluminium/ polyacrylnitrile (PAN) laminate sachet. Each pack contains 10, 15, 30 or 60 sachets, although not all pack sizes may be marketed.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

Stability of the product
Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for this product when the storage precautions ‘Do not store above 30°C’ and ‘Store in the original package to protect from light and moisture’ are applied.

Product literature
The SmPC, PIL and labels 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.

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

Quality conclusion
There are no objections to the approval of Nicabate Film from a quality point of view.

Preclinical aspects

Preclinical overview
The pharmacodynamic, pharmacokinetic and toxicological properties of nicotine are well known. As nicotine is a widely used, well-known active substance, no further studies are required and the applicant has not provided any. An overview based on a literature review is, thus, appropriate; the application also cross refers to the toxicology data for Nicabate transdermal patches.

The preclinical overview was written by an appropriately qualified toxicologist. It lists one hundred and twenty-two references up to 2009 and is dated the 28 January 2010. It includes both a review of the literature and a discussion of specific aspects relating to the components of the product. There was no information found that would change the risk: benefit balance for nicotine as an aid to stopping smoking. The preclinical overview is generally satisfactory.

Environmental Risk Assessment
The absence of a formal Environmental Risk Assessment (ERA) was justified on the grounds that the film will be used as a substitute for existing smoking materials and the excipients and packaging are all widely used for pharmaceutical and food products. The SmPC specifies that unused films or waste packaging material should not be disposed of in the environment.

Product literature
The product literature is acceptable from a preclinical point of view.

Preclinical conclusion
There are no objections to the approval of Nicabate Film from a preclinical point of view.

Clinical aspects

Clinical studies

In support of their Marketing Authorisation application the applicant has conducted one comparative bioavailability study and one safety/ tolerability study in healthy volunteers.

Study 1

The first study was a comparative bioavailability study: an open label, randomised, four-way, cross-over study comparing the systemic exposure of nicotine following single doses of nicotine mint 2 mg and 2.5 mg mouth films, nicotine lozenge 2 mg and nicotine gum 2 mg.

Study protocol

70 healthy, >5/day smokers, 41 male and 29 female, aged 19-54 years, were included in this study. 50 subjects completed all four periods.

Subjects received a single oral dose of the four treatments during each study period, in accordance with the randomization schedule: 2 mg nicotine mouth strip, 2.5 mg nicotine mouth strip, 2 mg nicotine polacrilex lozenge and 2 mg nicotine polacrilex gum. Subjects were to refrain from smoking during the study periods and were subjected to expired carbon monoxide measurement to confirm abstinence. The products were given following a controlled period of ≥8 hours fasting. Blood samples were taken at pre-dose and up to 12 hours following dosing. There followed a 48 hour washout period before crossover and repeat. A randomisation scheme was included in the report.

An intra-individual comparison, as described, is considered appropriate for comparative bioavailability trials. The sampling points are deemed acceptable to achieve relevant pharmacokinetic parameters. Considering the reported t1/2, the wash-out period is sufficient.

Nicotine mouth strip

The investigator placed a single mouth strip on the subject's tongue to be dissolved. The subject was instructed to close his or her mouth and press the tongue gently to the roof of the mouth until the strip dissolved. The mouth strip dose, initial dose time, and complete dissolution time were captured.

Nicotine lozenge

The investigator or designee placed a single lozenge in the subject's mouth to be dissolved. The subject was instructed to move the lozenge from one side of the mouth to the other periodically and not to swallow or chew the lozenge. The lozenge dose, initial dose time, and complete dissolution time were captured.

Nicotine gum

The investigator or designee placed a single piece of nicotine gum in the subject's mouth and instructed him or her to chew the gum once every four seconds, as guided by a metronome that emitted a sound every four seconds. Additionally, the investigator or designee verbally prompted the subject to move the gum from one side of the mouth to the other and to swallow accumulated saliva every 30 seconds. The

investigator or designee repeated chewing instructions for any subject who was non-compliant.

The nicotine gum remained in the subject's mouth for 30 minutes after which it was collected and stored in an appropriately sized individually-labelled container. The container was placed in a freezer at -20°C within 30 minutes of collection and was stored separately from plasma PK samples for analysis of residual nicotine content at a later date, as necessary.

Plasma samples were analysed for nicotine by LC-MS/MS. $AUC_{(0\text{-}t.)}$, $AUC_{(0\text{-}inf)}$, C_{max}, t_{max} and $t_{½}$ were calculated according normal standard procedures.

Statistical evaluation was performed for $AUC_{(0\text{-}t)}$, AUC_{inf} and C_{max} with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated:

2 mg Film vs. 2 mg Gum

Parameter	Mean (N)		*Ratio: 2mg strip vs. 2 mg gum	
	2 mg strip	2 mg gum (Standard)	Estimate	90% CI
C_{max}(ng/ml)	3.27 (60)	3.93 (59)	80.24%	[73.60%, 87.47%]
$AUC_{(0\text{-}t)}$ (ng-hr/ml)	12.24 (60)	12.79 (59)	92.90%	[87.07%, 99.12%]
$AUC_{(0\text{-}\infty)}$ (ng-hr/ml)	13.80 (59)	14.20 (56)	94.26%	[88.62%, 100.26%]

2.5 mg Film vs 2 mg Gum

Parameter	Mean (N)		*Ratio: 2.5mg strip vs. 2 mg gum	
	2.5 mg strip	2 mg gum (Standard)	Estimate	90% CI
C_{max}(ng/ml)	4.13 (62)	3.93 (59)	99.15%	[91.00%, 108.02%]
$AUC_{(0\text{-}t)}$ (ng-hr/ml)	15.65 (62)	12.79 (59)	115.09%	[107.91%, 122.74%]
$AUC_{(0\text{-}\infty)}$ (ng-hr/ml)	18.13 (55)	14.20 (56)	118.43%	[111.17%, 126.17%]

2.5 mg Film vs 2 mg Lozenge

Parameter	Mean (N)		*Ratio: 2.5mg strip vs. 2 mg lozenge	
	2.5 mg strip	2 mg lozenge (Standard)	Estimate	90% CI
C_{max}(ng/ml)	4.13 (62)	4.48 (62)	88.99%	[81.82%, 96.78%]
$AUC_{(0-t)}$ (ng-hr/ml)	15.65 (62)	16.19 (62)	92.89%	[87.22%, 98.93%]
$AUC_{(0-\infty)}$ (ng-hr/ml)	18.13 (55)	18.16 (60)	94.68%	[89.06%, 100.65%]

No deaths, serious adverse events (AEs) or other significant events occurred during the study.

The aim of this study was to provide comparative bioavailability data for the proposed product and the chosen references, Nicotine 2 mg Gum and Lozenge, which have an established efficacy and safety profile.

These data would appear to show that the proposed product is supra-available to the reference gum, in terms of $AUC_{(0\text{-}inf),}$ and entirely bioequivalent with the lozenge.

The clinical data for the approved Nicotine 2 mg Lozenge are directly applicable to the Nicotine Film as regards efficacy, and this line extension is accepted. The proposed posology is identical to that for the approved 2 mg lozenges and this is also supported.

Study 2

The second study was a single centre, open-label, randomized, two-arm and parallel design study designed to assess the overall incidence and intensity of oral soft tissue related AEs with a 2.5 mg nicotine mouth film and a 2 mg nicotine lozenge occurring during the treatment period.

Study protocol

The purpose of this study was to assess the overall incidence and intensity of oral soft tissue related AEs with a 2.5 mg nicotine mouth strip and a 2 mg nicotine lozenge occurring during the treatment period. This tolerance study was single center, open-label, randomized, two-arm and parallel in design. The dosing period was 12 weeks. As two different dosage forms were utilized, the subjects and study staff were open to the treatment but the examiner (investigator) conducting the oral soft tissue exams was blinded.

Subjects were instructed to place the 2.5 mg mouth strip on the tongue. The subjects were then instructed to close the mouth and press the tongue gently to the roof of the mouth until the 2.5 mg mouth strip dissolved.

For the first dose administered on-site, study personnel placed the 2.5 mg mouth strip on top of the subject's tongue. The time taken to complete dissolution of the 2.5 mg mouth strips was recorded.

With the lozenge, subjects were instructed to place it in the mouth until it dissolved. The subjects were instructed to periodically move the lozenge from one side of the mouth to the other and were instructed to repeat the process until the lozenge completely dissolved. Subjects were instructed not to chew or swallow the lozenge.

Subjects were instructed to use the 2.5 mg mouth strip or 2 mg lozenge whenever there was an urge to smoke in order to maintain complete abstinence from smoking.

Subjects were instructed to use one mouth strip or lozenge every one to two hours, up to a maximum of 15 per day. It was recommended that subjects use a minimum of nine mouth strips or lozenges per day. Subjects used the investigational treatments up to 12 weeks to break the habit of smoking and were instructed to use no more than one mouth strip or lozenge within one hour.

No efficacy measurements were taken in this study. At the baseline visit, subjects received an oral soft tissue (OST) exam, had oral images taken, had their breath assessed by an odour judge and were randomized to a treatment, according to the randomization schedule. They received behavioural counselling and were then administered their first dose of nicotine replacement therapy. They also completed a sensory questionnaire.

Subjects visited the study site weekly for four consecutive weeks and biweekly thereafter. During these visits, continuing eligibility was checked, adverse events and concomitant medications were recorded, and the subject diary card was reviewed for compliance. Smoking status was confirmed by measuring expired CO levels. Subjects received an OST exam, oral imaging, a breath assessment and behavioural counselling. Unused study medication was collected and a new supply dispensed, unless the subject self-discontinued from the trial due to self-discontinuation of the product or from an AE. At the final visit, all remaining study medication was collected.

Two weeks after study medication use was completed, subjects returned to the site one last time and received an OST exam. Adverse events and concomitant medications were recorded and smoking status was confirmed by expired CO level.

A total of 200 subjects who smoked between 5-20 cigarettes per day for the previous 12 months were randomly assigned to treatment. The group consisted of 75 (37.5%) males and 125 (62.5%) females. 144 subjects completed the study. Twenty five (25.0%) subjects in the 2.5 mg mouth strip group did not complete the study. Of these, 12 subjects withdrew consent, eight subjects were lost to follow-up, and five subjects discontinued due to an adverse event. Thirty one subjects (31%) in the 2 mg lozenge group did not complete the study. Of these, 19 subjects withdrew consent, seven subjects withdrew due to an adverse event, and five subjects were lost to follow-up.

In all, there were 12 discontinuations due to AEs (five in the 2.5 mg mouth strip group and seven in the lozenge group).

Results

A total of 81 subjects in the 2.5 mg mouth strip group and 91 subjects in the 2 mg lozenge group used their respective test products for greater than three weeks. Subjects used an average number of 9.60 mouth strips per day and 9.86 lozenges per day. Forty-one percent (41%) of the subjects used between 801- 1200 mouth strips and 42% of the subjects used between 801-1200 lozenges throughout the course of the study. Two subjects in each treatment group used greater than 1200 doses throughout the course of the study. In addition, a total of 83 subjects in the 2.5 mg mouth strip group and 86 subjects in the 2 mg lozenge group reported at least one episode of concurrent cigarette smoking during study.

A total of 69 subjects (69%) receiving the 2.5 mg mouth strip reported at least one treatment emergent AE. In comparison, a total of 75 subjects (75%) receiving the 2 mg lozenge reported at least one treatment emergent AE. There was no statistically significant difference in the number of subjects reporting at least one AE between the two treatment groups.

A total of 37 incidences of oral disorder AEs were reported by 27 subjects randomized to the 2.5 mg mouth strip. In comparison, 74 oral disorder AEs were reported by 44 subjects in the 2 mg lozenge group. The most commonly reported oral disorders were throat irritation and mouth injury. Five incidences of throat irritation were reported by four subjects in the mouth strip group and 15 incidences of throat irritation were reported by 13 subjects in the lozenge group. Five incidences of mouth injury were reported by five subjects in the mouth strip group and eight incidences of mouth injury were reported by six subjects in the lozenge group. All reported incidences of throat irritation were related to product use. Conversely, none of the incidences of mouth injury (primarily cheek bites or traumatic abrasions) were related to product use. Most (95%) of the treatment emergent/treatment related throat irritation AEs were mild in intensity.

There was, therefore, a similarity between the tolerability profiles of the 2.5 mg mouth strip and the 2 mg lozenge. The similarity in tolerability profiles between the investigational products was consistent across a range of subgroups, including, but not limited to, age, gender, product exposure, and cigarette use.

In summary, the 2.5 mg mouth strip was well tolerated and the incidence and pattern of AEs were very similar to the marketed 2 mg lozenge and in accord with the known safety profile.

There was a similar frequency of adverse events between treatment groups. Of note, there were no differences between groups in regards to oral tolerability.

Conclusion of studies 1 and 2
These studies support the claim that the proposed product is bioequivalent to the approved Nicotine 2 mg Lozenge and that the product is well tolerated with no difference in the incidence of adverse events to the already approved lozenge.

Pharmacokinetics
No new data

Pharmacodynamics

The pharmacodynamic characteristics of nicotine have been well-studied in the past. There would be no particular concerns for this medicinal product. No new data have been submitted and none are required.

Clinical efficacy and safety
No new data are presented and none are required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of nicotine.

Pharmacovigilance system
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan
Nicotine is a well established substance and there are many years of experience to enable safety monitoring via routine risk minimisation. Therefore, in line with CHMP/96268/2005, no risk management plan has been provided. This is satisfactory.

Periodic Safety Update Report (PSUR)
The applicant has applied for a PSUR submission scheme of 3 years upon approval as nicotine is a well known active substance which has been marketed for many years throughout the EU. The suggestion is acceptable

Expert report
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, summary of the clinical part of the dossier.

Product literature
All product literature (SmPC, PIL and labelling) is medically satisfactory.

Clinical conclusion
There are no objections to the approval of Nicabate Film from a clinical point of view.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Nicabate Film 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of these type.

EFFICACY

The use of nicotine replacement therapy to help people stop smoking is well established. New efficacy data is, therefore, not needed.

SAFETY

No new or unexpected safety concerns arise from this application. The tolerability study conducted in support of this application showed that the product is well tolerated with no difference in the incidence of adverse events to the already approved lozenge.

The SmPCs and PIL are satisfactory and consistent with those of the reference product. Satisfactory labelling has also been submitted.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with nicotine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be acceptable. A Marketing Authorisation should be granted.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that has (have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	**Application type**	**Scope**	**Outcome**
07 May 2012	Type 1B	To update Sections 2 (Qualitative and quantitative composition), 4.3 (Contraindications), 4.6 (Fertility, pregnancy and lactation), 4.7 (Effects on ability to drive and use machines), 5.2 (Pharmacokinetic properties) and 6.6 (Special precautions for disposal) of the Summary of Product Characteristics (SmPC) and relevant label and leaflet text in line with the Quality Review of Documents (QRD) template.	Approved 30 July 2012

Annex 1

Reference: PL 00079/0640, Application 0004
Product: Nicabate Mint 2.5 mg Orodispersible Film
Marketing Authorisation Holder: Beecham Group plc
Active Ingredient(s): Nicotine
EU Procedure Number: UK/H/0287/017/IB/092

Reason
To update Sections 2 (Qualitative and quantitative composition), 4.3 (Contraindications), 4.6 (Fertility, pregnancy and lactation), 4.7 (Effects on ability to drive and use machines), 5.2 (Pharmacokinetic properties) and 6.6 (Special precautions for disposal) of the Summary of Product Characteristics (SmPC) and relevant label and Patient Information Leaflet (PIL) text in line with the Quality Review of Documents (QRD) template.

Supporting Evidence
Revised SmPC, labelling and PIL text have been provided.

Evaluation
Proposed changes are in line with the latest CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human) QRD template.

The updated SmPC sections, label and leaflet texts are satisfactory.

Conclusion
The amendments to the SmPC fragments, labelling and leaflet can be approved.

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website. The amended labelling text is presented below.

Amended labelling text:

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nicabate Mint 2.5 mg Orodispersible Film
Nicotine

2. STATEMENT OF ACTIVE SUBSTANCE

Each nicotine film contains 2.5 mg nicotine

3. LIST OF EXCIPIENTS

Ingredients

Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), Type A, Triethyl Citrate (E1505), Peppermint Flavour TAK - 032230, Sucralose (E955), Sodium Hydrogen Carbonate (E500 ii), Ethanol.
This medicinal product contains small amounts of ethanol (alcohol).

4. PHARMACEUTICAL FORM AND CONTENTS

Contains 10 orodispersible films
Contains 15 orodispersible films
Contains 30 orodispersible films
Contains 60 orodispersible films

5. METHOD AND ROUTE OF ADMINISTRATION

Oromucosal use
Read the package leaflet before use
Instructions for opening the sachet are on the outside of the sachet.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Storage Precautions

Do not store above 30°C. Store in the original package to protect from light and moisture.

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

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

To be completed nationally.

12. MARKETING AUTHORISATION NUMBER

To be completed nationally.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

To be completed nationally.

15. INSTRUCTIONS FOR USE

Stop smoking aid
Nicotine films are used to help people stop smoking
How to use
For smokers who smoke their first cigarette more than 30 minutes after waking up

STEP 1 Weeks 1 to 6	STEP 2 Weeks 7 to 9	STEP 3 Weeks 10 to 12
Initial treatment period 1 nicotine film every 1 to 2 hours	Step down treatment period 1 nicotine film every 2 to 4 hours	Step down treatment period 1 nicotine film every 4 to 8 hours

- do not eat, drink or chew while a nicotine film is in the mouth
- do not swallow the nicotine film whole.
- do not use more than 15 nicotine films per day.
- dissolve 1 nicotine film fully in the mouth (approximately 3 minutes) by placing one nicotine film on the tongue. Close the mouth and press the tongue gently over the roof of the mouth until the nicotine film dissolves.
- if you need to use the nicotine films for longer than 9 months seek advice from a healthcare professional.
- young people (12-17 years inclusive) should only use nicotine films following advice from adoctor.
- do not use if nicotine film is damaged.

Do not use
- if you are allergic to any of the ingredients listed.
- if you are a non-smoker or under the age of 12 years.

Consult a healthcare professional
- if you have or recently had heart problems.
- if you have serious liver or kidney disease, uncontrolled overactive thyroid gland or phaeochromocytoma stomach ulcers or other problems with your stomach or throat.
- before use if you are pregnant or breastfeeding.

16. INFORMATION ON BRAILLE

To be completed nationally

Decision: Approved (30/07/2012).