IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Niquitin mini 4mg mint lozenges
Nicotine
PA1186/018/012

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/287/015-016/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 12th February 2019 under procedure number IE/H/0939/001-002/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/018/011-012
Marketing Authorisation Holder: Chefaro Ireland DAC

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data on quality, safety and efficacy, Czech Republic, Estonia, Finland, Hungary, Ireland, the Slovak Republic and the UK considered that the applications for Nicabate CQ Mini 1.5 and 4mg Lozenges could be approved. The products are available on General Sales Licences (GSL) for the treatment of tobacco dependence by relief of nicotine withdrawal symptoms, including cravings, during a quit attempt. Permanent cessation of tobacco use is the eventual objective. Nicabate CQ Mini 1.5 and 4mg Lozenges should preferably be used in conjunction with a behavioural support programme.

These are applications made under Article 8.3 of 2001/83 EC, as amended, for a known active substance (nicotine resinate). Nicotine resinate belongs to the pharmacotherapeutic group "drugs used in nicotine dependence" (N07BA).

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

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 cotine and nicotine-N-oxide. Nicotine and its metabolites are excreted in the urine.

No new preclinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. Clinical studies on Nicabate CQ Mini
1.5 and 4.5mg Compressed Lozenges were carried out in accordance with Good Clinical
Practice (GCP).

For manufacturing sites outside the community, the RMS has accepted copies of current
GMP Certificates or 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.

ABOUT THE PRODUCT

Name of the product in the Reference Member State	Nicabate CQ Mini 1.5mg Lozenges Nicabate CQ Mini 4mg Lozenges
Name(s) of the active substance(s) (INN)	Nicotine (as nicotine resinate)
Pharmacotherapeutic classification (ATC code)	Drugs used in nicotine dependence" (N07BA)
Pharmaceutical form and strength(s)	1.5 and 4mg lozenges
Reference numbers for the Decentralised Procedure	UK/H/0287/0015-6/DC
Reference Member State	United Kingdom
Member States concerned	Czech Republic, Estonia, Finland, Hungary, Ireland and the Slovak Republic
Marketing Authorisation Number(s)	PL 00079/0614-5
Name and address of the authorisation holder	Beecham Group plc, 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom, T/A GlaxoSmithKline Consumer Healthcare, Brentford TW8 9GS,

	UK.

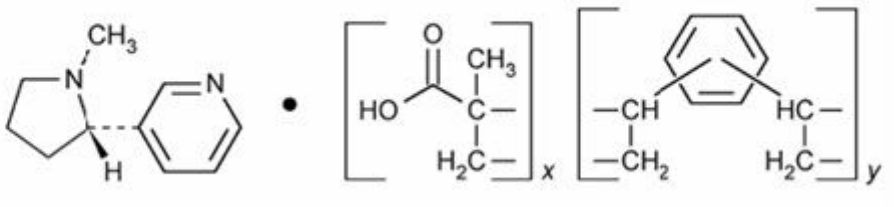
II. QUALITY ASPECTS

S. Active substance
INN/Ph.Eur name: Nicotine (as nicotine resinate)

Chemical name: 2-propenoic acid, 2-methyl, polymer with diethenylbenzene, complex with 1-methyl-2-(3-pyridyl)pyrrolidine.

Methacrylic acid polymer with divinylbenzene, complex with nicotine- S-3-(1-methyl-2-pyrrolidinyl) pyridine.

Structural formula:



Molecular formula: C10H14N2 (C4H6O2)x (C10H10)y

Appearance: White to faintly yellow powder, practically insoluble in water and insoluble to slightly soluble in most solvents

Molecular weight: 162 + 86(x) + 130(y)

Chirality: The only chiral centre is at the pyrrole carbon attached to the pyridine. Nicotine is the subject of a European Pharmacopoeia monograph.
Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

The active substance is packaged in low-density polyethylene bags, which are placed in high- density polyethylene drums and sealed. Specifications for all packaging have been provided. The primary packaging has been shown to comply with current legislation concerning materials in contact with food.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting the proposed retest period of 1 year.

P. Medicinal Product
Other Ingredients
Other ingredients consist of pharmaceutical excipients potassium bicarbonate, sodium alginate, mannitol, calcium polycarbophil, sodium carbonate anhydrous, xanthan gum, magnesium stearate, peppermint flavour, taste masking flavour, menthol flavour and acesulfame potassium.

All excipients comply with their European Pharmacopoeia monograph, with the exception of peppermint flavour, taste masking flavour and menthol flavour (which are controlled to a suitable in-house specification) and calcium polycarcophil (USP).

None of the excipients contains materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate new lozenge products (at strengths appropriate to light and heavy smokers) that dissolve faster, are smaller in size and better tasting than the current lozenge products.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
Both strengths of tablets are packaged in child-resistant polypropylene tablet container and cap, incorporating a molecular sieve desiccant (sodium aluminosilicate). Each container contains 20 lozenges. Packs may contain one or three tablet containers.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding use of materials in contact with food.

Stability of the product
Stability studies were performed on batches of all strengths of finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with the storage conditions "Do not store above 30°C" and "Store in the original package in order to protect the product from moisture".

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

The marketing authorisation holder has stated that they do not wish to market the product in the UK at the current time, but have committed to submitting mock-ups of the PIL and packaging before marketing either product.

User testing results have been submitted for a typical PIL for these products. The results indicate that the PIL 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.

MAA forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
The grant of marketing authorisations is recommended.

III. NON-CLINICAL ASPECTS

1. INTRODUCTION
1.1 Type of application and aspects on development

These are decentralised applications for Nicabate CQ Mini 1.5 mg and 4 mg Lozenges containing nicotine as the complex nicotine polacrilex (1.5mg and 4mg strengths contain equivalent to 8.333 and 22.222mg nicotine polacrilex, respectively).

The applicant is seeking a line extension to replace nicotine with nicotine polacrilex (with the same therapeutic moiety), to add a new pharmaceutical form, new strength and new route of administration to their currently marketed NiQuitin CQ transdermal patch, which is available in three strengths namely 7, 14 and 21 mg (UK/H/287/01-03; PL 00079/0345-0347). These applications are complete application submitted under Article 8.3 of Directive 2001/83/EC as amended by 2004/27/EC.

The active ingredient in both the originator product and the current application is identical. The compressed lozenges provide similar plasma concentrations of nicotine to the transdermal patch, albeit via different pharmaceutical forms and by different routes of administration. Therefore the applicant has not conducted any further specific pharmaco- toxicological studies. The applicant asks that, given that substantial toxicological data on nicotine and its metabolites exist, the reviewer be referred to the NiQuitin CQ patch application for an in depth review and critical assessment of the safety of nicotine. This is acceptable. Since the non-clinical data submitted in support of the application for the originator product has been assessed previously, they will not be reassessed here. In the proposed product, nicotine is formulated as its polacrilex (NPA) salt, because NPA is more stable and easier to formulate than nicotine.

In addition the applicant has provided a review of more recent published toxicological data that have become available in the scientific literature since the submission of the original application. Doses or plasma levels of nicotine presented in the published data have been compared to nicotine exposures or plasma levels resulting from use of the lozenges at the recommended dosage. Additionally, a summary of the excipients and a review of the identified degradation products and residual solvents are also presented.

The proposed indication is similar to that approved for the transdermal patch.

The proposed maximum recommended daily dose is 15 lozenges; 22.5mg for the 1.5mg strength or 60mg for the 4mg strength of nicotine. The maximum daily dose approved for the originator product is 21mg of nicotine.

The main non-clinical concerns are whether oromucosal administration of NPA increases systemic exposure (hence toxicity) or causes local irritation or retention of dose in the oromucusal cavity.

1.2 GLP aspects

No new non-clinical studies were submitted in support of this application. Reference is made to published data in the Non-Clinical Overview but the GLP status of these published reports cannot be verified.

2. PHARMACOLOGY

Nicotine is an agonist at both peripheral and central nervous system receptors with a well- established pharmacology, including adrenergic and cholinergic autonomic effects. The pharmacodynamic effects of nicotine have been well-documented in published literature. No new studies of the pharmacodynamic effects of nicotine have been published since submission of the NiQuitin CQ transdermal patch application. It is considered that human data have largely superseded those of animals in relation to the pharmacology of nicotine.
Based on the available data and established clinical experience with similar nicotine replacement therapy products, the pharmacological, profile of nicotine, when used in a controlled manner is well characterized and hence no further studies have been submitted nor are required.

3. PHARMACOKINETICS

No new non-clinical pharmacokinetic (PK) studies with the proposed lozenge formulations have been performed. Absence of non-clinical PK data with the mini lozenges is considered acceptable; as such data would be superseded by clinical PK data.

Published data indicate that nicotine is rapidly absorbed across the buccal mucosa and GI tract, the amount of nicotine absorbed increases with the increase in pH (pKa=8). The proposed formulations include bicarbonate to increase the pH. Once swallowed, nicotine is poorly absorbed in the acidic gastric environment, and undergoes extensive first pass metabolism. It is reported that after oromucusal administration to humans, the lozenges completely dissolve in the oral cavity within 20-30min. The dissolved nicotine is then absorbed either through the buccal mucosa or ingested and absorbed from the GI mucosa. Apparently, a peak plasma concentration of 9.09 ng/ml nicotine is achieved following a single use of the 4 mg Nicotine CQ Mini Lozenge. When used once every 60 minutes, a peak steady state plasma concentration of 18.4 ng/ml nicotine is achieved with the 1.5 mg Nicotine CQ Mini Lozenge. In comparison, the peak steady state plasma concentrations of nicotine achieved from use of the NiQuitin CQ 14 and 21 mg patch are 16.8 and 23.5 ng/ml, respectively, while the mean steady state concentrations of nicotine are 11.8 and 17.1 ng/ml, respectively. In contrast, half-hourly smoking of cigarettes produces

average plasma concentrations of approximately 44 ng/ml (NiQuitin CQ Part IV, Original Clinical Documentation, 1991, Section 3.11.1, Summary of Product Characteristics).

No new scientific literature regarding the absorption, distribution or excretion of nicotine has been reported since submission of the original application. Since similar plasma concentrations are achieved following administration of the mini lozenges in comparison to the original product it is acceptable to cross refer to the pharmaco-toxicological data previously assessed for the NiQuitin CQ Transdermal Patch.

Several new studies on the metabolism of nicotine have been reviewed by the applicant since submission of the original application. These studies investigate the potential of nicotine to activate cytochrome p450 2E1 (CYP2E1), an isoenzyme known to bioactivate tobacco smoke components and other pre-carcinogens. Conclusions drawn from studies are conflicting. In one study, nicotine increased CYP2E1 levels in rats, even at low doses; in another study nicotine was shown to inhibited CYP2E1 activity, with respect to its ability to convert p−nitrophenol to 4-nitrocatechol. Another recent study revealed that CYP2A13-catalyzed
4−(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK - a nicotine-derived carcinogen) metabolism was inhibited competitively by nicotine suggesting that nicotine is a substrate of CYP2A13.

Given the conflicting nature of these findings, The applicant concludes that, along with the fact that the metabolic pathway for nicotine varies with animal species and the fact that the *in vivo* induction of CYP2E1 by nicotine has not been demonstrated to date in humans, the newly reported findings are considered to be of limited relevance to the use of Nicabate CQ Mini 1.5mg and 4mg Lozenges. While the reported results indicate that CYP2A13 can efficiently activate the metabolism of nicotine, the observed *in vitro* results cannot be directly correlated to reactions that occur *in vivo*. Even if CYP2A13 does activate the metabolism of nicotine *in vivo*, CYP2A13 is predominantly expressed in the human respiratory tract and not in the liver, which is the primary site for the metabolism of nicotine. As such, the low level of CYP2A13 expression in the human liver would play an insignificant role in the clearance of nicotine from the human body.

From a non-clinical point of view the SPC sections 5.1 and 5.2 are satisfactory.

4. TOXICOLOGY

No new preclinical studies using the proposed formulation are submitted. The applicant briefly summarises the toxicity of nicotine in experimental animals.

4.1 Single dose toxicity

Acute doses of nicotine administered by various routes (iv, sc, oral etc) are relatively toxic with LD50 of generally <100mg/kg in rodents, dogs and rabbits. In mice, rats, rabbits and dogs major toxicological effects of sub-acute and chronic doses of nicotine appear to be cardiovascular and metabolic effects which reflect exaggerated pharmacological activity of nicotine.

Data published in 2000 revealed LD50 values of 57.6 mg/kg for nicotine and 62.1 mg/kg for a tobacco extract containing nicotine following acute administration to male mice.

4.2 Repeat-dose toxicity

Several non-clinical repeat dose toxicity studies have been reported in the literature since the assessment of the non-clinical package for the originator product.

Data published in 1999 indicate that chronic parenteral administration of nicotine (3.0 or 4.5 mg/kg/day) to female rats for 3 months adversely affected bone formation and reduced body storage of vitamin D. A second publication indicates that the mechanism of acute and chronic effects of nicotine on T-lymphocytes appears to be distinct, in that chronic administration of nicotine causes T cell anergy whereas acute effects are mediated via activation of the hypothalamus-pituitary-adrenal axis. The cardiovascular effects of nicotine in female rats were further investigated in 2001; following subcutaneous administration of 4.5 mg/kg/day of nicotine for 15 to 22 days, there was an effect on nitric oxide's down-regulation of calcium channels and up-regulation of calcium-activated potassium channels, which is required for full vasorelaxation. The same year it was reported that, in rats, nicotine caused a dose-dependent degeneration of axons in the brain (neurotoxicity) following subcutaneous administration of nicotine tartrate over 5 days by continuous infusion or by injection at doses up to 43.1 mg/kg/day and 11.32 mg/kg/day respectively.

In 2003 it was reported that Nicotine caused a reduction in heart weight, heart length and overall blood volume in a dose-related manner following subcutaneous administration of up to 12 mg/kg/day for 14 days. In 2004 the effects of nicotine on lung morphology were investigated in Wistar rats. Following a single intraperitoneal dose of 1 mg/kg for 8 days, an increase in volume fraction of alveolar parenchyma, a reduction of volume and surface fraction of septal elastic fibers, and an increase

of the numerical fraction of microvasculature vessels were noted. This indicates progressive morphological damage to lungs caused by nicotine, even after a recovery period.

These studies do not reveal any further toxicity issues than those previously assessed for the originator product and hence do not adversely alter the safety profile of previously approved nicotine replacement therapy products nor highlight further concerns relating to the safety profile of the current proposed products.

4.3 Genotoxicity

No new data are submitted as a range of nicotine concentrations have been previously assessed (NiQuitin CG Transdermal Patch submission) using the standard battery of *invitro* and *in vivo*genotoxicity tests to reveal that nicotine is not mutagenic in the appropriate assays. However, two additional *invitro* studies have recently been published in the scientific literature which has revealed potential mutagenic and genotoxic effects of nicotine. In one of these studies exposure to nicotine for 60 minutes at 0.125, 0.25,0.5, 1, 2, and 4 mM nicotine induced a statistically significant dose-dependent increase of DNA migration up to 3.8-fold and 3.2-fold in DNA sourced from human lymphatic cells of palatine tonsils and human lymphocytes, respectively. DNA migration is used as a measure of possible single strand brakes, alkali labile sites and incomplete repair sites. The lowest observed effect level was 0.5 mM. In the second study, using the *invitro*cytokinesis-block micronucleus test, the effects of nicotine on DNA damage induction and apoptosis in human fibroblasts was reported. 1µM of nicotine caused a statistically significant increase in micronucleus frequency, attenuated staurosporine induced apoptosis, and an increase in reactive oxygen species. In contrast, a recent *in vivo* mouse bone marrow assay reported no increase in micronucleus frequency in polychromatic erythrocytes, following single oral doses of 1 or 2 mg/kg.

Assessor'scomment

The recent genotoxic effects revealed in the *in vitro* human assays do not support effects seen in the recent *in vivo* micronucleus test nor the previous findings assessed for the originator product. Since the originator product and the proposed product exhibit comparable similar systemic exposure, it can be assumed that the genotoxic potential of the mini lozenges will also be similar.

4.4 Carcinogenicity

Review of literature in the Niquitin CQ patch applications suggests that nicotine, cotinine and nicotine N-oxides are not carcinogenic, but some studies have reported a co-carcinogenic effect for nicotine and nicotine N-oxides. Repeat application of nicotine (for 12 weeks) in combination with 7,12-dimethylbenzanthracene (DMBA) to the cheek pouch mucosa of hamsters increased the incidence of tumours induced by DMBA, while no tumours were seen when nicotine alone was applied. In addition, nicotine also enhanced the carcinogenic effects of N-nitrosonornicotine (NNN) and 4-(N-methyl-N-nitrosamine)-1-(3-pyridyl)-1-butanone (NNK) following repeated application to the cheek pouch mucosa of hamsters. These co- carcinogenic effects of nicotine are not considered relevant because under normal circumstances patients taking the mini lozenges would not be exposed to such potential carcinogens.

Other components of tobacco smoke such as nitrosamines and polycyclic aromatic hydrocarbons are potentially carcinogenic. The use of nicotine-containing lozenges would provide a lower risk in comparison with smoking, given the absence of carcinogenic components of tobacco smoke.

4.4.1 Tumourigenic Potential

A potential link between nicotine exposure and enhanced tumour growth was first reported in 2001 following *in vitro* studies using human endothelial cells and *in vivo* studies in mice. Results revealed increased growth of the human cells, increase in the formation of cellular networks and decreased apoptosis under hypoxic conditions. In mice, nicotine increased capillary formation and vascularization, accelerated atherosclerotic lesion growth and enhanced tumour growth, but not tumour proliferation. Enhanced tumour neovascularization and growth has been reported in mice administered 20 mg/kg/day nicotine for 5 days followed by subcutaneous administration of synergic colon cancer cells. Is has also been reported that bone marrow derived cells can contribute to tumour neovascularization in nicotine treated mice. A further experiment revealed that nicotine stimulated vascular endothelial cell growth factor production by the CMT93 (carcinoma cells) but did not stimulate the proliferation of this cell line *invitro*. In 2004 a study was reported that showing that, *in vitro*, a human adenocarcinoma cell line incubated with 10, 100 or 1000 nM of nicotine exhibited increased cell proliferation in a dose dependent manner. EGFR tyrosine kinase inhibitor (AG1478) and c-Src inhibitor (PP2) phosphorylation and 5-LIPOX protein expression levels were also increased. AG1478 and PP2 alleviated the actions of nicotine on cell proliferation and 5-LIPOX protein expression, and the combination of both agents produced an additive effect. Following the incubation of these cells with nicotine for 5 hours they were injected into the skin of female BALB/c nu/nu mice, a nude mouse xenograft model. Enhanced tumour growth and vascularization was observed in treated mice. Mitogen- activated protein kinase inhibitors were shown to inhibit the nicotine-induced tumour growth and neovascularization seen in nude mice (with gastric cancer cells implanted into the gastric wall) treated with 0, 50, or 200 µg/ml nicotine.

4.4.2 Tobacco-Specific Nitrosamines (TNSA)
An alternate metabolic pathway involving the 2'-hydroxylation of nicotine that results in the *in vitro* formation of a tobacco-specific lung carcinogen precursor has been the subject of a number of scientific studies. In contrast, *in vivo* one study has demonstrated no evidence for the endogenous formation of TNSAs in human subjects who did or did not use 15 mg nicotine patch therapy for 6 weeks following smoking cessation.

Assessor'scomment
As summarised above; the clinical relevance of this data on the tumuorigenic potential of nicotine in humans is unknown; however, it has to be born in mind that nicotine replacement therapy is preferable to tobacco smoke.

The ability of nicotine to facilitate the formation of TNSAs is inconclusive as the *in vitro* formation of TNSAs was not seen *invivo*. Any non-clinical findings would be superceded by the findings in the human study, which did not reveal the presence of endogenous TNSAs following treatment with nicotine alone.

4.5 Reproductive and developmental toxicity
The applicant cross-refers to data submitted in the Niquitin CQ patch dossiers. Literature published since the Niquitin CQ Patch applications report the following findings:
In male rats, nicotine (4mg/kg, oral or ip) reduced epididymis and vas deferens weights and sperm count and produced abnormal sperm morphology.
In female rats, nicotine (3mg/kg, oral or ip) decreased ovarian and uterine weights.
Perinatal exposure to nicotine (sc, 6mg/kg/day) impaired ability of new-born rats to autoresuscitate from primary apnoea during repeated exposure to hypoxia.
In female mice, nicotine (5, 7.5 or 10mg/kg) did not significantly perturb the rate of oocyte maturation or increase the frequency of aneuploidy.
In female rats, nicotine (6.0 mg/kg/day (day 4 – 20 of gestation)) increased the density of serotonin transporter binding sites in the forebrain of their offspring, which could adversely affect physiological / behavioural development.
In rats, nicotine (9.0 mg/kg/day - 23 days from day 4 of gestation) increased the binding of [125I]epibatidine, which labels α4β2 nicotinic receptors, in layer 1 of the visual cerebral cortex and layer 1 of the somatosensory cerebral cortex of their offspring. Again resultant adverse behavioural development could be expected
Prenatal exposure to nicotine (2.0 mg/kg/day - throughout gestation) caused a decrease in cell size, cell layer thickness, and cell packing density of neurons in the hippocampus and dentate gyrus in rats offspring. Indicative of abnormal neuronal maturation leading to alteration in the structure of key brain regions responsible for learning, memory and cognition.
Prenatal exposure to nicotine (3.0 to 5.0 mg/kg/day nicotine from day 7 of gestation to postnatal day 32) significantly retarded development and decreased the maximum density of presynaptic high affinity-choline transport sites and selectively reduced postsynaptic muscarinic receptor density in the cerebral cortex of, suggesting
inhibition in the development of cholinergic pathways both pre- and post-synaptically.

An abstract published in 1998 reported that sc administration of nicotine (0.35, 1.1 or
3.5mg/kg/day) alone or in combination with mecamylamine to rats (GD 6-15) and rabbits (GD 6-18) caused maternal toxicity in both species and developmental effects (lower foetal weights and retarded ossification) in rats only.

Pre- and postnatal exposure to nicotine has been shown to adversely affect the development of the gas exchange region in lungs. Observations include suppression of alveolarisation, reduction in internal lung surface area and lower radial alveolar counts and number of capillaries in the septa in rat offspring. A range of studies report findings that indicate prenatal nicotine exposure impairs protective responses that may sustain life during exposure to hypoxia in an age-dependent manner.

Adverse behavioural affects (hyperactivity) have been revealed following sc administration of nicotine (0.75 – 3.0 mg/kg/day) to rats from day 4 of gestation through to postnatal day 16.

Studies in juvenile animals indicate that nicotine causes hypoactivity at 4 months in mice previously administered nicotine on postnatal days 10 to 14. These findings indicate a time- response / time0dependent effect.

The applicant considers these effects of nicotine to be of little relevance to the intended use of nicotine lozenges, considering the doses and routes of administration used (effects mainly
seen following ip. administration) and that fact that similar findings have been previously presented in the NiQuitin CQ transdermal patch application.

4.6 Local tolerance

No preclinical local tolerance studies with the Nicabate CQ Mini Lozenges have been performed and the applicant asks that the reviewer be referred to the pharmaco-toxicological documentation summary assessed for the NiQuitin CQ transdermal patch application. Immortalised hamster cheek pouch cells *in vitro* and hamster cheek pouch tissue *in vivo* was subjected to incubation/treatment with nicotine and other smokeless tobacco extracts. In vitro nicotine induced DNA strand breaks and a dose-dependent decrease in viability of the cheek pouch cells; *in vivo* nicotine induced mild epithelial dysplasia following 10 months of treatment (three times a week). Alterations in ligand-binding kinetics of nicotinic acetylcholine receptors (which can affect oral tissues) was observed in rats and mice following oral administration of nicotine for 3 weeks. However, it has been reported that nicotine 2mg sublingual tablets (up to 20-40 tablets daily, for up to 6 months) caused no adverse long-term effects on the oral mucosa of humans and any lesions that did occur were transient and reversible. Similar findings are reported in a preclinical *in vivo* study, whereby hamster oromucosa treated with nicotine for 12 weeks exhibited no adverse effects.

Assessor'scomment
Adverse effects were reported *in vitro*, however, distinctly different findings are reported *in vivo* and in the clinic. It is anticipated that the proposed lozenges will not cause any local irritation at the MRD of 15 lozenges per day. Extensive clinical use with Nicotine Replacement Therapy (NRT) Lozenges supports this.

4.7 Other toxicity studies

4.7.1 Components of Lozenges

Inactive ingredients of these lozenges include polacrilex resin to which nicotine is bound, mannitol, sodium alginate, xantham gum, potassium bicarbonate, calcium polycarbophil, sodium carbonate, acesulfame-K, magnesium stearate, and the mint powder flavouring. With the exception of the flavours, all of the inactive ingredients are approved pharmaceutical grade materials (European Pharmacopoeia, United States Pharmacopoeia and/or United States National Formulary) and hence no preclinical data has been submitted in support of their use.

The proposed maximum daily intake (MDI) of mannitol is 2.5g. An acceptable daily intake(ADI) of mannitol has not been specified by the WHO since the amount consumed as a sweetening agent was not considered to represent a hazard to health . however, it has been reported that laxative effects may occur if orally consumed in large quantities (approximately 20g daily). The proposed MDI of calcium polycarbophil is 76mg. Again an acceptable daily intake for calcium polycarbophil has not been specified by the WHO. However it has been reported that daily dosages of up to 4 to 5 g in adults appears to be quite safe and non-toxic. The proposed MDI of sodium (as sodium carbonate and sodium alginate) is approximately 279mg. In the UK, dietary reference values have been published that recommend sodium intake be limited to 1.6g daily. The WHO has specified an ADI of 15mg/kg for acesulfame-K and the proposed MDI is 0.45mg/kg for a 50kg person.

Magnesium stearate is a widely used non-toxic component of solid dosage formulations between 0.25% and 5.0% w/w. potassium bicarbonate acts as the buffering agent

The components of the flavouring agents are designated as substances that are generally recognised as safe (GRAS). Additionally, each of these flavours complies with the provisions of EEC Directive 88/388/EEC. Exposure to each of these inactive ingredients from use of Nicotine/Nicabate CQ 1.5 mg and 4 mg Mini Lozenges is comparable to exposures from similar products that are currently marketed.

There are no apparent safety concerns with respect to the proposed components of the mini lozenges as all comply with the published acceptable daily intake levels, where applicable, or appropriate guidance.

4.7.2 Degradation Products

Potential degradation products/impurities of nicotine polacrilex are cotinine, nicotine N- oxides, [(1'R,2'S)-nicotine-1'-N-oxide and (1'S,2'S)-nicotine-1'-N-oxide, myosmine, a complex of nornicotine and anatabine, and pseudooxynicotine.

These impurities are controlled according to USP. Given the proposed MDI of 60mg nicotine; ICH Q3B(R2) - *Impurities in New Drug Products;* specifies that the reporting, identification and qualification thresholds are 0.1%, 0.2% and 0.5% (or 200µg total daily intake, which ever is lower) respectively. The FPS limits proposed for named impurities are, therefore, above the lower ICH threshold for qualification. However, the proposed limits for cotinine and the N-oxides are considered acceptable given that are potential metabolites of nicotine. The set limit for myosmine is also deemed acceptable since it is a naturally occurring alkaloid less toxic and less pharmacologically potent than nicotine.

The limits set for Pseudooxynicotine and the Nornicotine/ Anatabine complex could result in a total daily intake of 300µg. Results of stability analyses have revealed that Nornicotine/ Anatabine complex consists of 78.9 to 87.8% nornicotine and 12.2 to 21.1% anatabine. Therefore each component of the complex can be calculated to be up to 263.4 µg/day (5.3 µg/kg/day; 0.439%) nornicotine and up to 63.3 µg/day (1.3 µg/kg/day; 0.106%) anatabine. To justify the limits of nornicotine and Pseudooxynicotine, the applicant has reviewed and presented relevant toxicological publications in scientific literature.

Nornicotine has been revealed as a metabolite of nicotine in several animal species and humans, with and LD50 value approximately 566-fold more than the proposed MDI, and minor mutagenic potential at high concentrations (2.5mg/ml).

Pseudooxynicotine has been identified as a mixture of four molecular species in equilibrium, consisting of 2'−hydroxynicotine, nicotine-1',2'-iminium ion, N−methylmyosmine and pseudooxynicotine (aminoketone). A structure-activity relationship (SAR) analysis was performed for each of the four molecular species that comprise the pseudooxynicotine complex using DEREK (Deductive Estimation of Risk from Existing Knowledge) version 6.0.0. DEREK is a rule based application, which compares the compound of interest with the substructural features contained within its knowledgebase that are indicators for mutagenicity, carcinogenicity, sensitization, irritation and other toxicological endpoints, including developmental toxicity, teratogenicity, nephrotoxicity, hepatotoxicity, neurotoxicity, pulmonary toxicity and estrogenicity. This evaluation resulted in no alerts for 2'−hydroxynicotine, nicotine-1',2'-iminium ion, or N−methylmyosmine. However, an alert resulted for pseudooxynicotine, because as an aminoketone it is a secondary amine and under the appropriate conditions has the potential to be nitrosated to form nitrosamine, 4- (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Once activated, NNK is said to be a significant initiator of lung cancer, since it induces benign and malignant lung tumours in rodents. Human lung tissue can activate NNK. NNK has been shown to produce pancreatic cancer in rats and metaplasia in human pancreatic explants. Its carcinogenic potential has also been demonstrated in the nasal cavity and liver of rodents.

The applicant concludes that since alternate metabolic pathways exist for secondary amines, that the nitrosation of this amine in the stomach requires optimal chemical conditions, and that there is a lack of a concomitant source of nitrate or nitrite in the proposed product, nitrosation of the minimal amount of pseudooxynicotine to form the nitrosamine NNK is considered highly unlikely. The applicant continues with the predication that use of Nicotine CQ 1.5 mg and 4 mg Mini Lozenges for a prescribed period of around 6 weeks, depending on the patient, would result in a significantly lower exposure to pseudooxynicotine than exposures associated with chronic smoking. Exposure to tobacco-specific nitrosamines, including NNK, has also been definitively shown to occur from cigarette smoking, while to date the endogenous formation of tobacco-specific nitrosamines has not been demonstrated to occur *invivo* from use of nicotine replacement therapies.

In view of the above justifications, and the fact that the, the proposed limits for Pseudooxynicotine and the Nornicotine/ Anatabine complex have previously been approved for products already marketed in Europe (NiQuitin CQ 2mg, 4mg Mint Lozenges – PL00079/0373-4– approved in UK 2002; UK/H/287/11-12), the proposed finished product shelf life specification limits for the impurities are acceptable.

The limits proposed for residual solvents, namely cyclohexane, dichloromethane, 2-propanol and acetic acid, comply with ICH Q3C(R3) *Impurities: Residual Solvents*.

4.8 Ecotoxicity/environmental risk assessment

This is an application for a line extension product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.

4.9 Assessor's overall conclusions on toxicology

No new preclinical data were supplied with this application, which is justified by the fact that exposure to the active ingredient (nicotine) is not likely to be significantly greater following administration of the proposed formulation compared to the originator product. Therefore, clinical experience with nicotine overrides the need for further preclinical data. The nonclinical overview provides a satisfactory review of the relevant preclinical pharmacological and toxicological literature published since approval of the originator product. The degradation products are considered toxicologically qualified or meet ICH guidelines. There are no new safety concerns associated with the proposed products.

IV. CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

To support the application, the applicant has submitted four bioequivalence studies.

2.1 Biowaiver

Not applicable.

2.2 Pharmacokinetic studies

To support the application, the applicant has submitted four bioequivalence studies: three single-centre, three-period, single-dose crossover trials; and a single-centre, single-blind, multiple-dose, crossover design trial.

Study 1: S2300319

Randomised, three-period, single dose, cross-over, bioequivalence study comparing two formulations of test 2mg nicotine polacrilex lozenges versus reference nicotine polacrilex gum.

Study protocol

20 healthy >5/day smokers, 15 male and 5 female, aged 19-55 years, were included in this study. Three subjects discontinued prematurely. Each subject received a 2mg nicotine dose of one of three nicotine formulations. A randomisation scheme was included in the report. The following formulations were administered:

Treatment A: 2mg Nicotine Polacrilex (mannitol based) mini lozenge (GSK.Batch No.: GSK5339B011)

Treatment B: 2mg Nicotine Polacrilex (master mannitol granulation based) mini lozenge (GSK. Batch No.: GSK5337B011)
Reference C: 2mg Nicotine Polacrilex Gum (Nicorette UK. Batch No.: FF085A) The reference product is registered in UK. The formulations were given following a controlled period of fasting and exclusion from any nicotine intake from 24 hours pre dose. Subjects were free to drink water from 1-hour post dose and eat standard meals from 2 hours. Blood samples were taken at pre-dose and at 5, 10, 15, 20, 30, 45, 50 minutes and at 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after administration of the products. There then followed a 48-hour washout period before crossover and repeat.

The plasma nicotine concentrations were measured by LC/MS/MS. The LLOQ for nicotine was 1ng/ml. AUC(0-t.), AUC(0-inf), Cmax, tmax and t½ were calculated according normal standard procedures.

Statistical evaluation was performed for AUC(0-t), AUCinf and Cmax with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated with the results as follows:

	Mean ± SD (N)			
Study Treatment	**2mg Nicotine Polacrilex (mannitol-based) Mini Lozenge**	**2mg Nicotine Polacrilex Gum**	**Mean Ratio #**	**90% CI #**
C_{max} (ng/mL)	4.46 ± 1.34(18)	3.67 ± 0.96(19)	121.1	(107.8, 136.0)
$AUC_{(0-t)}$ (ng*hr/mL)	12.13 ± 4.23(18)	8.102 ± 2.57(19)	155.0	(136.0, 176.6)
$AUC_{(0-inf)}$ (ng*hr/mL)	16.42 ± 4.90(16)	12.04 ± 2.98 (16)	137.9	(123.9, 153.4)
	2mg Nicotine Polacrilex (MMG-based) Mini Lozenge	**2mg Nicotine Polacrilex Gum**	**Mean Ratio #**	**90% CI #**
C_{max} (ng/mL)	4.96 ± 1.70(17)	3.67 ± 0.96(19)	134.9	(119.7, 152.1)
$AUC_{(0-t)}$ (ng*hr/mL)	13.63 ± 5.52 (17)	8.102 ± 2.57(19)	172.7	(150.9, 197.5)
$AUC_{(0-inf)}$ (ng*hr/mL)	17.68 ± 6.33 (15)	12.04 ± 2.98(16)	143.1	(127.9, 160.1)

SD= standard deviation
CI = confidence interval
# = Based on the least square means
Source: Tables 9.2.2.1, 9.2.2.2, 9.2.2.3, 9.2.3.1, and 9.2.3.2

Three subjects discontinued prematurely and were excluded from analysis. Two subjects discontinued for personal reasons, and one for non-compliance. There were no serious adverse events recorded.

Study 2 S2300320
Randomised, two-period, single-dose, crossover, bioequivalence study comparing the test 4mg nicotine polacrilex lozenges versus reference 4mg nicotine polacrilex gum.

Study protocol
30 healthy >15/day smokers, 21 male and 9 female, aged 19-55 years, were included in this study. Five subjects discontinued prematurely. Each subject received a 4mg nicotine dose of one of two nicotine formulations. The following formulations were administered:

Treatment A: 4mg Nicotine Polacrilex (master mannitol granulation based) mini lozenge (GSK. Batch No.: GSK5336B011)
Reference B: 4mg Nicotine Polacrilex Gum (Nicorette UK. Batch No.: FF022A) The reference is registered in UK. The formulations were given following a controlled period of fasting and exclusion from any nicotine intake from 24 hours pre dose. Subjects were free to drink water from 1-hour post-dose and eat standard meals from 2 hours. Blood samples were taken at pre-dose and at 5, 10, 15, 20, 30, 45, 50 minutes and at 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after administration of the products. There then followed a 48 hour washout period before crossover and repeat.

The method of plasma analysis was LC-MS/MS. The LLOQ for nicotine was 1ng/ml. AUC(0-t.), AUC(0-inf), Cmax, tmax and t½ were calculated according normal standard procedures.

Statistical evaluation was performed for AUC(0-t), AUCinf and Cmax with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

	Mean ± SD (N)			
Parameter	4mg Nicotine Polacrilex Mini Lozenge	4mg Nicotine Polacrilex Gum	% Mean Ratio#	90% CI #
C_{max} (ng/mL)	9.09 ± 2.83 (29)	7.46 ± 2.33 (26)	--	--
$AUC_{(0-t)}$ (ng.hr/mL)	33.79 ± 16.54 (29)	23.91 ± 12.54 (26)	--	--
$AUC_{(0-inf)}$ (ng.hr/mL)	39.65 ± 19.39 (28)	28.69 ± 13.58 (25)	--	--
$ln(C_{max})$	2.163 ± 0.300 (29)	1.961 ± 0.326 (26)	123.4	(112.2, 135.6)
$ln[AUC_{(0-t)}]$	3.430 ± 0.413 (29)	3.057 ± 0.489 (26)	149.8	(135.9, 165.1)
$ln[AUC_{(0-inf)}]$	3.598 ± 0.385 (28)	3.264 ± 0.428 (25)	143.5	(132.6, 155.2)

= Based on the LSMEAN values
Source: Tables 9.2.2.1, 9.2.2.2 and 9.2.3.1

Five subjects discontinued and were excluded from analysis. Two discontinued for personal reasons, one failed drug/alcohol screening, one took prescription medication and one failed to return for period 2. There were no serious adverse events recorded.

Study 3 S2300339
Randomised, two-period, multiple-dose, crossover, bioequivalence study comparing the test 1.5mg nicotine polacrilex lozenges versus reference 2mg nicotine polacrilex gum.

Study protocol
40 healthy >5/day smokers, 30 male and 14 female, aged 19-55 years, were included in this study. Six subjects discontinued prematurely. Each subject received a nicotine dose of one of two nicotine formulations. Each subject received one dose every hour for 13 hours. The following formulations were administered:

Treatment A: 1.5mg Nicotine Polacrilex (master mannitol granulation based) mini lozenge (GSK. Batch No.: GSK5336B013)

Reference B: 2mg Nicotine Polacrilex Gum (Nicorette UK. Batch No.: FF085A)

The reference is registered in UK. The formulations were given following a controlled period of fasting and exclusion from any nicotine intake from 24 hours pre dose. Blood samples were taken at pre-dose and immediately before the 11th, 12th, and 13th doses and following the 13th dose every 10 minutes for 60 minutes. There then followed a 48-hour washout period before cross over and repeat.

The method of plasma analysis was LC-MS/MS and the LLOQ for nicotine was 1ng/ml. A validation report is provided. AUC(0-t.), AUC(0-inf), Cmax, tmax and t½ were calculated according normal standard procedures.

Statistical evaluation was performed for AUC(0-t), AUCinf and Cmax with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

	Mean ± SD (N)			
Variables	1.5mg Nicotine Polacrilex Mini Lozenge	2mg Nicotine Polacrilex Gum	Mean Ratio #	90% CI #
$AUC_{(0-t)}$ (ng*hr/mL)	16.65 ± 6.28 (41)	13.71 ± 3.14 (40)	116.9	(106.7 - 128.1)
C_{max} (ng/mL)	18.40 ± 6.81 (42)	15.33 ± 4.23 (40)	118.5	(107.2 - 131.0)
C_{min} (ng/mL)	15.03 ± 5.55 (42)	12.76 ± 3.10 (38)	114.1	(104.7 - 124.4)
Fluctuation	0.196 ± 0.134 (41)	0.195 ± 0.165 (38)		

SD= standard deviation
CI = confidence interval
# = Based on the least square means
Source: Tables 9.2.2.1 , 9.2.2.2 and 9.2.3.1

The following subjects were discontinued from the study:

Reason for Discontinuation	Subject	Treatment Sequence	Party Initiating Discontinuation	Period of Withdrawal
Failed Drug/Alcohol Screen[1]	1010	BA	Investigator	Day 1, Period 2
Personal Reason	1017	AB	Subject	Day -1, Period 2
Other[2]	1025	BA	Subject	Day 2, Period 1
Other[2]	1030	AB	Subject	Day 2, Period 1
Noncompliance	1032	AB	Investigator	Day 1, Period 2
Personal Reason	1044	AB	Subject	Day -1, Period 2

[1]Subject 1010 tested positive for amphetamines
Treatment A = 1.5 mg nicotine polacrilex mini lozenge
Treatment B = 2 mg nicotine polacrilex gum
[2]Withdrew Consent
Source: Data Listing 2.9.2 and Table 9.1.1

There were no serious adverse events recorded.

Given the suprabioavailability of proposed lozenges, it is considered likely that they will display no less efficacy in the requested indications than that of the reference medicinal product. There would not appear to be any additional safety signals raised from the new 4mg strength.

Additional Information as of Day 160:

Further to the data contained within the original file, the applicant also provides a 4th bioavailability study comparing the proposed 4mg lozenge with their existing 4mg lozenge:

Study 4 S3010466

Randomised, two-period, multiple-dose, crossover, bioequivalence study comparing the test 4mg nicotine mini lozenges versus reference 4mg nicotine lozenge.

Study protocol

28 healthy smokers (defined as requiring a cigarette within 30 minutes of waking), 19 male and 9 female, aged 20-51 years, were included in this study. 27 completed at least one study treatment and 24 completed both. Four subjects withdrew consent from the study. Each subject received a single dose of one of the two nicotine formulations. The following formulations were administered:

Treatment A: 4mg Nicotine mini lozenge (GSK. Batch No.: GSK5526B011) Reference B: 4mg Nicotine Polacrilex Lozenge (GSK. Batch No.: GSK5498B021) The reference is registered in UK. The formulations were given following a controlled period of fasting and exclusion from any nicotine intake from 24 hours pre dose. Blood samples were taken at pre-dose and at 5, 10, 15, 20, 30, 40, 50 minutes and at 1, 1.5, 2, 3, 4, 6, 8, 9, 10 and 12 hours following dose administration. There then followed a 48 hour washout period before cross over and repeat.

The method of plasma analysis was LC-MS/MS and the LLOQ for nicotine was 1ng/ml. A validation report is provided. AUC(0-t.), AUC(0-inf), Cmax, tmax and t½ were calculated according normal standard procedures.

Statistical evaluation was performed for AUC(0-t), AUCinf and Cmax with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

Table 1: Summary of Baseline-Adjusted Nicotine Pharmacokinetic Variables

	Means*		Ratio: Mini/Standard	
Parameter	Mini	Standard	Estimate	90% CI
C_{max} (ng/mL)	7.23	7.61	95.0%	[87.4%,103.3%]
$AUC_{(0-t)}$ (ng*hr/mL)	24.39	25.63	95.2%	[89.8%,100.9%]

*Geometric adjusted means calculated by exponentiating adjusted mean log

There were no serious adverse events recorded.

The 4mg test and reference lozenges can be considered bioequivalent.

The findings of this study can be extrapolated to lower dose formulations given that the product fulfils the criteria for dose proportionality for immediate release oral dosage forms identified in Section 5.4 of the relevant EU guidelines [CPMP/EWP/QWP/1401/98]:

- The pharmaceutical products are manufactured by the same manufacturer and process.
- The drug input is linear over the therapeutic dose range.
- The qualitative composition of the two strengths is the same.
- The ratio between amounts of excipients is similar for the two strengths.
- The dissolution profiles are similar for both strengths of lozenge.

It is normally considered that the highest dose strength is the most discriminatory for the purposes of bioequivalence testing, which is the strength which has been tested here. The confidence intervals for the bioequivalence parameters of the presented studies are within the required limits by a substantial margin. The results of study S3010466 with the 4mg formulation can be extrapolated to other strength 1.5mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98, section 5.4.)

The SPC wording is considered to be acceptable in order to address the potential confusion for patients in altering NRT dosage forms.

3. Post marketing experience

Nicotine has a well-recognised efficacy and an acceptable level of safety in the indications approved for Nicabate CQ Mini Lozenges, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

4. Benefit-Risk assessment
The benefit–risk assessment for this product is considered to be positive.

5. Conclusions
The grant of a marketing authorisation for Nicabate CQ Mini 1.5 and 4mg Lozenges is recommended from a clinical viewpoint.

V. OVERALL CONCLUSIONS

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY
The important quality characteristics of Nicabate CQ Mini 1.5 and 4mg Compressed Lozenges 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 this type.

EFFICACY
The four comparative biopharmaceutical studies comparing the proposed product versus gum have confirmed that the test products are more bioavailable than the reference gum.

The bioequivalence study comparing the proposed test 4mg lozenge versus an already licensed 4mg lozenge showed that these products can be considered bioequivalent. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg lozenge can be extrapolated to the 1.5mg lozenge.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for other similar products.

RISK-BENEFIT 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 risk benefit is, therefore, considered to be positive.

VI. REVISION DATE

October 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/287/015-016/ DC to IE/H/939/001-002/ DC	N/A	N/A	N/A	Approved 12/02/2019