COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nicotinell Mondspray Mint 1 mg/spray, oromucosal spray, solution (nicotine)

NL/H/5607/001/DC

Date: 18 June 2024

This module reflects the scientific discussion for the approval of Nicotinell Mondspray Mint 1 mg/spray, oromucosal spray, solution. The procedure was finalised on 26 June 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CoA	Certificate of Analysis
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
HPLC	High-performance Liquid Chromatography
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PP	Polypropylene
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nicotinell Mondspray Mint 1 mg/spray, oromucosal spray, solution, from Pharos Pharmaceutical Oriented Services Ltd.

The product is indicated for: the treatment of tobacco dependence in adults by relief of nicotine withdrawal symptoms, including cravings, during a quit attempt or to cut down smoking before stopping completely. Permanent cessation of tobacco use is the final objective. Nicotinell Mondspray Mint should preferably be used in conjunction with a behavioural support program.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Nicorette Pepparmint 1 mg/spray, oromucosal spray, solution (NL RVG 111210) which has been registered in Sweden by McNeil Sweden AB since 2010 (original product). In the Netherlands, Nicorette Pepparmint has been registered since 2012 by the procedure SE/H/0904/001.

The concerned member states (CMS) involved in this procedure were Belgium, Denmark, Finland, France, Ireland, Iceland, Luxembourg, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Nicotinell Mondspray Mint is an oromucosal spray solution. It is a clear colourless to brownish solution with a spicy mint flavour.

One spray delivers 1 mg nicotine in 0.07 mL solution. 1 mL solution contains 13.6 mg nicotine.

The excipients are: propylene glycol (E1520), glycerol (E422), anhydrous ethanol, poloxamer 407, glycine (E640), sodium hydrogen carbonate (E500 (ii)), levomenthol, mint flavour (contains benzyl alcohol, propylene glycol (E1520), pulegone), cooling agent (contains menthol, menthol carboxamide, essential oil, propylene glycol (E1520)), sucralose (E955), acesulfame potassium (E950), sodium hydroxide (E524) and purified water.

The spray solution is packaged in 15 mL blue painted amber glass bottles (Type III) with a mechanical spray pump with a dip tube and an overcap. The visible parts of the spray pump are the following: polypropylene (PP) actuator, PP housingcap, low density polyethylene/

polypropylene (LDPE/PP) compound diptube. Each bottle contains 13.2 mL of solution which provides 150 sprays.

II.2 Drug Substance

The active substance is nicotine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a colourless or brownish viscous liquid which is volatile and hygroscopic. Nicotine if freely soluble in water, easily soluble in ethanol, ether and chloroform. Nicotine possesses one chiral centre. The polymorphic form and particle size distribution are not considered critical parameters as the drug substance is completely dissolved in the drug product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the Ph. Eur. monograph for nicotine, the CEP and the Ph. Eur. requirements for microbiological quality of non-sterile products. An additional test for nitrosamine impurity is included. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

The active substance is stable for four years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients and their functions have been explained. The quantities of excipients have been briefly justified. The composition has been compared with the reference product and differences are explained. Information on droplet size distribution and reproducibility of doses throughout the whole container life (actuations taken at beginning, middle and end of a container life) has been provided. The development of the manufacturing process has been adequately performed and any scalability issues have been

investigated. Pump performance and usability are tested and compared with the reference product.

Manufacturing process

The manufacturing process involves dispensing, compounding, filling, stoppering and labelling. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines. The claimed bulk hold time of 3 months is adequately supported by the bulk hold time study.

Control of excipients

All excipients used in the drug product are mentioned in Ph. Eur. monographs, except the flavouring agent and cooling agent which comply with EC 1334/2008. Statement of compliance with EC 1334/2008 for mint flavour are included in 3.2.P.4. For the specifications and analytical methods of the compendial excipients, reference is made to Ph. Eur. monograph. Specifications are provided for the flavouring agent and cooling agent, which are acceptable.

All the excipients are kept similar to the reference formulation apart from two excipients. One excipient is replaced by glycine in the buffering system and another excipient by sodium hydroxide used for the pH adjustment.

A compatibility study with the active substance and the proposed excipients was performed
The samples were analysed for related substances (impurity C, impurity E, maximum individual unknown impurity and total impurities). Based on the results, the applicant concludes that the samples are within the acceptance criteria of the drug product specification. Furthermore, the compatibility of these excipients with the active substance was verified through the stability studies conducted for the prototype batches in the final container closure system at 40°C/75%RH conditions for a period of 6 months. There is no incompatibility between the selected excipients and the active substance.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity of nicotine and of alcohol, alcohol content, pH, viscosity, assay, related substances, uniformity of dosage, uniformity of mass, deliverable volume, and microbiological quality. Release and shelf-life specifications are identical except for the limits for the alcohol content and known and total impurities. The microbiological quality specifications are in line with Ph. Eur. 5.1.4 for non-sterile dosage forms for oromucosal use, which is acceptable. A justification has been provided for the skip testing of the microbiological quality. The drug product specification is acceptable. The stability indicating nature of the High-performance liquid chromatography (HPLC) methods for assay and related substances has been demonstrated by forced degradation studies. Appropriate tests for nitrosamine presence are performed on the final product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three validation batches stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The photostability study indicates that upon direct exposure the product is not sensitive to light, so no special storage conditions with respect to light are required for the drug product. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability data have been provided demonstrating that the product remains stable for 6 months following first opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Nicotinell Mondspray Mint has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Nicotinell Mondspray Mint is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Nicorette Pepparmint which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology,

pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Nicotine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Nicotinell Mondspray Mint 1 mg/spray oromucosal spray, solution (Pharos Pharmaceutical Oriented Services Ltd, Greece) was compared with the pharmacokinetic profile of the reference product Nicorette Pepparmint 1 mg/spray, oromucosal spray, solution (McNeil AB, Sweden).

The oromucosal solution was manufactured according to the formula and process described. The CoAs of both products are presented, and show a difference in assay value of less than 5% (101.7% for test product and 101.2% for reference product). The applicant concludes that bioequivalence was demonstrated between the test and reference product when administered in healthy male volunteers under fasted conditions.

Bioequivalence studies

Design

A single-dose, single center, randomized two-period, , two-sequence, crossover, blinded bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 18 - 60 years. Each subject received a single dose (2 sprays, equivalent to 2 mg) of one of the two nicotine formulations after an overnight fasting period of at least 10 hours. Delivered dose was controlled by weighing the bottle after priming and before administration. Subjects were asked to swallow immediately before drug administration to remove excess saliva from mouth. Subjects were asked not to inhale (to prevent inhaling spray) and to not swallow for at least 10 seconds after spraying. Fasting continued for at least 4 hours following drug administration, after which a standardized lunch was served. There were two dosing periods, separated by a washout period of 48 hours.

Blood samples were collected pre-dose and at 0.033, 0.067, 0.1, 0.133, 0.167, 0.2, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours after administration of the products.

The design of the study is acceptable. A single dose using the highest recommended dose per dosing episode, i.e. 2 mg test or reference mouth spray, under fasting conditions is submitted to support the application. Dosing under fasting conditions is justified as the spray formulation

should be taken without food or drinks. A submission with the highest recommended dose per dosing episode is considered adequate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
54 subjects enrolled in the study. 4 subjects were withdrawn from the study after dosing of period 1 due to protocol removal criteria. 1 subject was withdrawn from the study prior to dosing of period 2 due to protocol removal criteria. 10 subjects were excluded from pharmacokinetic and statistical analysis due to protocol removal criteria related to dosing and difficulties with blood collection. 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nicotine, 2 mg under fasted conditions.

Treatment N=39	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	17.88 ± 9.39	19.49 ± 10.99	5.0 ± 2.03	0.50 (0.07 – 2.5)
Reference	17.87 ± 10.40	19.44 ± 12.25	5.0 ± 2.44	0.75 (0.1 – 2)
***Ratio (90% CI)**	0.96 (0.92 – 1.01)	-	0.99 (0.90 – 1.09)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nicotinell Mondspray Mint is considered bioequivalent with Nicorette Pepparmint.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and

interventions designed to identify, characterise, prevent or minimise risks relating to Nicotinell Mondspray Mint.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nicorette Pepparmint. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a multiple bridging report making reference to Nicorette Pepparmint 1 mg/spray oromucosal spray, solution, SE/H/904/01/DC, and Felocord 5 mg and 7.5 mg film-coated tablets, HU/H/0448/001-002/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified the key safety messages (Nicorette Pepparmint) and design and layout (Felocord) of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nicotinell Mondspray Mint 1 mg/spray, oromucosal spray, solution has a proven chemical-pharmaceutical quality and is a generic form of Nicorette Pepparmint 1 mg/spray oromucosal spray, solution. Nicorette Pepparmint is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nicotinell Mondspray Mint with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 June 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5607/001-2/IA/001	**Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))** • *Change that does not affect the product information*	No	04-03-2024	Approved	N/A