LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Nicorama Mint/Nicorama Fruktmint (nicotine resinate)

SE/H/2016/01-04/MR

This module reflects the scientific discussion for the approval of Nicorama Mint/Nicorama Fruktmint. The procedure was finalised on 2019-08-02. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Nicorama Mint/Nicorama Fruktmint, 2 mg and 4 mg, medicated chewing gums, are generic applications made according to Article 10(1) of Directive 2001/83/EC. The applicant, Enorama Pharma AB applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Nicorette, 2 mg and 4 mg, medicated chewing gums, authorised in SE since 1981, with McNeil Sweden AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Nicorette Classic, 4 mg, medicated chewing-gum from DK with McNeil Denmark ApS as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted 2 bioequivalence studies comparing Nicorama with the reference product Nicorette.

Pharmacokinetic properties of the active substance
The amount of nicotine extracted from one chewing gum depends on how vigorously and for how long it is chewed. The amount of nicotine absorbed depends on the amount extracted and the loss from the oral cavity due to swallowing or expectoration. The bioavailability is approximately 55 %. Maximal plasma concentration occurs after approximately 30 minutes of chewing.

The pharmacokinetics of nicotine is affected by food and drinks and therefore the user should not eat or drink while using the chewing-gum. Drinks that lower the pH in the mouth, e.g. coffee, fruit juice or sodas, may reduce the absorption of nicotine from the oral cavity. To achieve the maximum absorption of nicotine, these drinks should be avoided up to 15 minutes prior to using the chewing-gum

There is a tendency of higher doses showing decreased absorption because of higher percentage swallowed at higher doses and therefore a higher first pass effect.

The terminal half-life is 2 hours.

Study Nicorama Fruktmint (C17476)
Methods
This was a single-dose, two-way crossover study conducted in 34 healthy, smoking volunteers, comparing Nicorama Fruktmint, 4 mg, medicated chewing gum with Nicorette, 4 mg, medicated chewing gum under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of nicotine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2018-02-08 and 2018-03-14.

Results
The results from the pharmacokinetic and statistical analysis are presented in

below.

IV.1.1.1.1.1 **Table 1. Pharmacokinetic parameters (non-transformed values; mean ± SD, tmax median,range) for nicotine, n=30.**

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**40.04 ±15.91**	**8.83±2.74**	**1.25 (0.17-2.0)**
Reference	**40.87±14.82**	**9.79 ±3.29**	**0.83 (0.33-3.29)**
***Ratio (90% CI)**	**97.7 (91.25-104.58)**	**90.5 (82.5-99.22)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 2 mg.

Study Nicorama Mint (C16404)

Methods

This was a single-dose, two-way crossover study conducted in 34 healthy, smoking volunteers, comparing Nicorama Mint, 4 mg, medicated chewing gum with Nicorette, 4 mg, medicated chewing gum under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of nicotine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2017-09-22 and 2017-11-03.

Results

The results from the pharmacokinetic and statistical analysis are presented in below.

Table 1. Pharmacokinetic parameters (non-transformed values; mean ± SD, t_{max} median, range) for nicotine, n=30.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**86.66±111.22**	**13.09±4.85**	**1.13 (0.17-36.00)**
Reference	**79.59±91.18**	**13.93 ±4.85**	**0.83 (0.33-36.00)**
***Ratio (90% CI)**	**111.3 (99.50-124.50)**	**94.8 (85.51-105.10)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 2 mg.

Discussion and overall conclusion

The bioequivalence studies and its statistical evaluation were generally in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

However, for the Mint product the PK data for subjects 2, 18, 25, 26 and 30 are not understood, and gives rise to doubts regarding absence of nicotine intake during the study. The Applicant has performed an investigation to find out the possible root cause for the raise of nicotine concentrations during the elimination phase for certain subjects. No deviations from SOPs were found and all restrictions were followed as per protocol. Based upon the investigation done there was no evidence found to support nicotine in-take throughout the study.

A sensitivity analysis where subjects 2, 18, 25, 26 and 30 in study C16404 were excluded from the statistical BE analysis was performed and is summarized in table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; mean ± SD, tmax median,range) for nicotine, n=29.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**55.95±25.60**	**12.44±4.27**	**0.83 (0.17-2.00)**
Reference	**49.25±17.95**	**13.15 ±4.59**	**0.50 (0.33-2.00)**
***Ratio (90% CI)**	**113.1 (103.63-123.44)**	**96.0 (86.08-107.11)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The AUC values are doubled in study C16404 (mint) compared to study C17476 (Fruktmint). However, it is noted that the AUC values for subjects 2, 25 and 26 in particular are very high compared to the other subjects, and that this may have contributed to the increase in AUC compared to the other study. In the sensitivity analysis summarized above, these three subjects (as well as two more subjects) have been excluded which led to a marked reduction in AUC.

The results of study C17476 (Fruktmint) and C16404 (Mint) with 4 mg formulation CAN be extrapolated to other strength 2 mg (Fruktmint and Mint respectively), according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Nicorama Mint/Nicorama Fruktmint (Nicobright Mint/Nicobright Fruktmint)

Safety specification
The MAH has submitted the version 0.1 RMP dated 25/09/2018 and proposed the following summary safety concerns:

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

The Applicant has proposed no safety concerns which is accepted. The NRT products have an established safety and tolerability profile. Given the fact the NRT products are well characterized, have been on the market for more than 30 years and are approved for OTC use, it is acceptable to have no remaining important risks.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 25/09/2018 is considered acceptable.

An updated RMP should be submitted:
- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Nicovel Mint/Nicovel Frukt, SE/H/1195/01-04/DC and Nicorette Cools Lozenge 2mg/4mg, PL 15513/0374-5. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Nicorama Mint/Nicorama Fruktmint, 2 mg and 4 mg, medicated chewing gums are recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Nicorama Mint/Nicorama Fruktmint, 2 mg and 4 mg, medicated chewing gums were approved in the national procedure on 2019-08-02.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/2016/01-04/MR	Initial Mutual Recognition Procedure	Yes	2020-05-27	Approval	N/A

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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