LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

NiQuitin

(nicotine resinate)

SE/H/2006/01/DC
2019-0915

This module reflects the scientific discussion for the approval of NiQuitin. The procedure was finalised on 2021-02-25. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for NiQuitin 2 mg, compressed lozenge, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Perrigo Sverige AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, CZ, EE, ES, HU, IE, LU, NL, PL, PT and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Niquitin Menthe Douce, 2 mg, lozenge, authorised in FR since 2001, with Laboratoires Omega Pharma France as marketing authorisation holder.

The reference product used in the bioequivalence studies is Niquitin Menthe Douce, 2 mg lozenge, with Laboratoires Omega Pharma France as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS CZ, EE, ES, HU, IE, LU, PL, PT and SK (i.e. all except for BE and NL): Niquitin Mint, 2 mg, lozenge, authorised in SE since 2002, with Perrigo Sverige AB as marketing authorisation holder.

The justification to use this product is based on information received from CZ, EE, ES, HU, IE, LU, PL, PT and SK, and on RMS's own files.

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 a bioequivalence study comparing NiQuitin (Nicotine mini mint Lozenge) with the reference product NiQuitin Lozenge.

Pharmacokinetic properties of the active substance

Absorption

NiQuitin dissolve completely in the oral cavity, and the entire amount of nicotine contained in the lozenge becomes available for buccal absorption or ingestion (swallowing).

Distribution

As the plasma protein binding of nicotine is low (4.9%), 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.

Biotransformation

Nicotine is extensively metabolized 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 metabolized primarily to cotinine but is also metabolized 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 oxidized to *trans*-3'-hydroxycotinine, which is the most abundant metabolite of nicotine in the urine. Both nicotine and cotinine undergo glucuronidation.

Elimination

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.

Method of administration

One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved (approximately 10 minutes). The lozenge should not be chewed or swallowed whole. Users should not eat or drink while a lozenge is in the mouth.

Study 18-06-139 (2 mg)

Methods

This was a single-dose, two-way crossover study conducted in 30 healthy adult human light smoker subjects, comparing Nicotine mini mint 2 mg Lozenge with NiQuitin 2 mg Lozenge under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 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 clinical part of the study was conducted between 08 October 2018 and 25 October 2018.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for nicotine, n=16.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**30.55 ± 6.61**	**7.53 ± 1.59**	**1.00 (0.33-2.00)**
Reference	**30.65 ± 7.64**	**7.41 ± 1.70**	**1.00 (0.33-1.50)**
***Ratio (90% CI)**	**99.84 (89.12-111.87)**	**102.27 (93.03-112.43)**	**-**

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*

Fourteen subjects were excluded from the final PK and statistical analysis as pre-dose concentrations of these subjects were greater than 5% of C_{max}.

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%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were 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.

Based on the submitted bioequivalence study, NiQuitin is considered bioequivalent with NiQuitin Lozenge.

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 NiQuitin 2 mg compressed lozenge.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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 1.2 for France and 1.2.1 for UK / SE signed 07 June 2019 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- 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 the Public AR for NiQuitin Minis Mint 4 mg lozenges, MA number PL 02855/0249. The bridging report submitted by the applicant has been found acceptable.

In addition, the package leaflet has been evaluated via a user consultation study, including combination therapy with lozenges, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The combination therapy section of the PIL, also user tested and accepted, was carried out for the procedure IE/H/0939/II/193/G. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of NiQuitin 2 mg, is found adequate. There are no objections to approval of NiQuitin 2 mg from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The benefit/risk ratio is considered positive and NiQuitin 2 mg compressed lozenges is therefore 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

The decentralised procedure for NiQuitin 2 mg compressed lozenge was positively finalised on 2021-02-25.

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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

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

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