LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nico Frukt
Nico Mint

(nicotine resinate)

SE/H/1198/01-04/DC

This module reflects the scientific discussion for the approval of Nico. The procedure was finalised at 2012-06-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Apotex Europe B.V. has applied for a marketing authorisation for Nico medicated chewing-gum, 2 mg and 4 mg fruit, 2 mg and 4 mg mint. 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-gum authorised in Sweden since 1981, with McNeil Sweden AB as marketing authorisation holder. The product contains nicotine resinate as active substance.The reference product used in the bioequivalence study is Nicorette Mint, 4mg, medicated chewing-gum from UK with McNeil Products Limited, UK, as marketing authorisation holder.

For approved indications see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Nico medicated chewing-gum, 2 mg and 4 mg fruit, 2 mg and 4 mg mint is presented in the form of medicated chewing-gums containing 14.9 mg or 29.9 mg of nicotine resinate, which corresponds to 2 mg and 4 mg of nicotine, respectively. The excipients are gum base (containing butylated hydroxytoluene (E321)), calcium carbonate, sorbitol (E420), sodium carbonate anhydrous, sodium hydrogen carbonate, saccharin (E954), acesulfame potassium (E950), talc, maltitol (E965), acacia, titanium dioxide (E171) and carnauba wax. The medicated chewing-gums also contain the following flavouring agents:
- Mint flavoured medicated chewing-gums: mint liquid flavour, peppermint liquid flavour, lemon liquid flavour and menthol powder flavour.
- Fruit flavoured medicated chewing-gums: levomenthol, lemon liquid flavour no. 2, mango liquid flavour and lemon powder flavour.
The medicated chewing-gums are packed in/filled in PVC/PVdC/aluminium blister.

II.2 Drug Substance

Nicotine resinate has a monograph in the Ph Eur.

Nicotine resinate is a white or slightly yellowish powder which is practically insoluble in water. The structure of nicotine resinate has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Nico medicated chewing-gum, 2 mg and 4 mg fruit, 2 mg and 4 mg mint is formulated using excipients described in the current Ph Eur, except for the gum base and flavours which are controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin/has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

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

The amount of released nicotine absorbed from a nicotine chewing gum depends on the amount of nicotine released in the oral cavity and the amount that is swallowed. The main part of nicotine released is absorbed through the buccal mucosa. The systemic bioavailability of swallowed nicotine is lower due to first- passage elimination. Maximal blood concentration is achieved after 30 minutes of chewing.

Nicotine is metabolised mainly in the liver and plasma clearance is in average about 70 l/ hour. Nicotine is also metabolised in the kidneys and lungs. More than 20 metabolites are identified whereof all are believed to be less active than nicotine. The primary metabolite of nicotine is cotinine which has a half-life of 15-20 hours and which gives plasma concentrations approximately 10-fold higher than nicotine. The terminal half-life for nicotine is 2 hours.

There is a tendency at higher doses to decreased absorption with oral nicotine formulations (lozenges, sublingual tablets and chewing gum) because of higher percentage swallowed at

higher doses and therefore a higher first pass effect.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 38 healthy smoking male volunteers, comparing Nicotine 4 mg gum with Nicorette 4 mg gum under fasting conditions. The study was conducted between 01 March 2011 and 15 April 2011. Blood samples were collected pre-dose and up to 10 hours post-dose. The study design is considered acceptable. Plasma concentrations of nicotine were determined with an adequately validated LC/MS/MS method. 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 results of study 104799 with Nicotine 4 mg gum can be extrapolated to the 2 mg strength, according to the conditions in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

Based on the submitted bioequivalence study, Nico is considered bioequivalent with Nicorette.

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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 regarding the PIL content to Zonnic Mint medicated chewing-gum, assessed and accepted in procedure SE/H/713/01-03/DC.

Reference regarding layout was made to Valsartan Apotex 40 mg, 80 mg, 160 mg and 320 mg, film-coated tablets (procedure NL/H/1914/001-004/DC) and Latanoprost 0.005% W/V Eye Drops, solution (procedure UK/H/2236/001/DC).

The bridging reports submitted by the applicant have been found acceptable.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

The risk/benefit ratio is considered positive and the applications for Nico medicated chewing-gum, 2 mg and 4 mg fruit and 2 mg and 4 mg mint are recommended for approval.

VI. APPROVAL

The Decentralised procedure for Nico was successfully finalised 2012-06-27.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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