Public Assessment Report
Scientific discussion

Zonnic Mint, medicated chewing gum, 
1.5 mg, 3 mg 
Zonnic Mint, oromucosal powder in pouch, 4 mg 
(nicotine)

SE/H/713/01-03/DC

Applicant: NicoNovum AB

This module reflects the scientific discussion for the approval of Zonnic Mint, medicated chewing gum, 1.5 mg, 3 mg and Zonnic Mint, oromucosal powder in pouch, 4 mg (nicotine). The procedure was finalised at May 23rd 2008. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

NicoNovum AB has applied for a marketing authorisation for “Zonnic Mint, medicated chewing gum, 1.5 mg, 3 mg and Zonnic Mint, oromucosal powder in pouch, 4 mg”. The active substance is nicotine. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Zonnic Mint is presented in the form of medicated chewing gums containing 1.5 mg and 3 mg of nicotine and oromucosal powder in pouch containing 4 mg of nicotine.

The excipients in medicated chewing gums are gum base, maltitol (E 965), isomalt (E 953), mint flavourings, talc, magnesium stearate, anhydrous silicon dioxide colloidal, microcrystalline cellulose, ascorbyl palmitate (E 304), acesulfame potassium (E 950), aspartame (E 951), acacia, titanium dioxide (E 171) and macrogol.

The medicated chewing gums are packaged in blister of aluminium/PVC/PVDC containing 10 pieces of chewing-gum or each chewing-gum is packaged in an aluminium bag of polyester, aluminium and polyethylene. 20 pieces of the individually packaged chewing-gums are thereafter packaged in a zip-lock aluminium bag.

The excipients in oromucosal powder in pouch are microcrystalline cellulose, mint flavourings, ascorbyl palmitate (E 304), trisodium phosphate, acesulfame potassium (E 950) and aspartame (E 951).

Each oromucosal powder in pouch is packaged in an aluminium bag of polyester, aluminium and polyethylene. 20 pieces of the individually packaged pouches are thereafter packaged in a zip-lock aluminium bag.

II.2 Drug Substance

Nicotine has a monograph in the Ph Eur.

Nicotine is a colourless or brownish viscous volatile liquid which is soluble in water. The structure of nicotine 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
**Medicated chewing gums:**
Zonnic Mint medicated chewing gums are formulated using excipients described in the current Ph Eur, except for gum powder and the mint flavours which are controlled according to acceptable in house specifications respectively. None of the raw materials used in the product are of animal or human origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as release and stability of the drug 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 and storage conditions claimed in the SPC.

**Oromucosal powder in pouch:**
Zonnic Mint oromucosal powder in pouch are formulated using excipients described in the current Ph Eur, except for anhydrous trisodium phosphate and the peppermint flavour which are controlled according to NF or acceptable in house specifications respectively. None of the raw materials used in the product are of animal or human origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as release and stability of the drug 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 and storage conditions claimed in the SPC.

### III. NON-CLINICAL ASPECTS

#### III.1 Pharmacology, Pharmacokinetics and Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of nicotine are well known. As nicotine is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

#### III.2 Ecotoxicity/environmental risk assessment

An ERA was submitted for Zonnic Mint, medicated chewing gum and oromucosal powder in pouch. The use of Zonnic Mint (for these pharmaceutical forms) is not considered to increase the risk to the environment beyond or above that which may be caused by other previously approved nicotine-containing products.
IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics
The amount of absorbed nicotine from a nicotine chewing gum depends on the amount released in the oral cavity and the amount that disappears from swallowing. The majority of the amount released is absorbed through the buccal mucosa. The systemic bioavailability of swallowed nicotine is lower because of first pass metabolism. The high and rapidly increasing nicotine concentrations that are observed in smokers are rarely reached after a chewing gum.

Normally, approximately 1.4 mg nicotine is released from a 2 mg chewing gum and approximately 3.4 mg from a 4 mg chewing gum. The maximal plasma concentration is reached after 30 minutes of chewing, comparable to the nicotine concentrations seen 20-30 minutes after smoking a medium strength cigarette.

The volume of distribution following i.v. administration of nicotine is about 2 to 3 L/kg. Plasma protein binding of nicotine is less than 5%.

The major eliminating organ is the liver, and average plasma clearance is about 70 L/hour and the half-life is approximately 2 hours. The kidney and lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound. The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxy-cotinine (45% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% of nicotine may be excreted unchanged in the urine with high flow rates and acidification of the urine below pH 5.

NicoNovum has provided two bioequivalence studies. The study evaluating bioequivalence of Zonnic Coolmint 1.5 mg versus Nicorette 2 mg was performed at Department of Clinical Pharmacology, University Hospital, Lund, Sweden. The other study was performed at Department of Medicine, Section of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden, evaluating bioequivalence between Zonnic Coolmint medicated chewing gum 3 mg and Zonnic Freshmint pouch 4 mg and Nicorette medicated chewing gum 4 mg. A few questions were raised in the procedure that was satisfactorily answered. Bioequivalence of Zonnic Mint oromucosal powder, pouch 4 mg could not be concluded upon, therefore the pharmacokinetic data for the pouch was complemented with clinical efficacy data.

IV.3 Pharmacodynamics
The pharmacodynamics of nicotine is well known. The applicant has provided an updated list of literature references up to year 2007 which is considered acceptable.

IV.4 Clinical efficacy
In the NEWS study, efficacy of Zonnic oromucosal powder, pouch 4 mg versus placebo has been shown.
Due to the non-blinding, the efficacy versus Nicorette chewing gum should be interpreted with caution. Even though the plasma levels observed in the PK study suggest lower absorption (approximately 30% lower) from the pouch than from the chewing gum Nicorette 4 mg, nicotine replacement products have a very wide therapeutic window and the risk of lack of effect is low with a self-titration with one pouch administered every 1-2 hours (up to 24 pouches daily).

IV.5 Clinical safety
The duration of exposure was very limited in the efficacy study why the safety was not fully investigated. However, given the excipients used in the products, new safety issues besides those already observed for other nicotine replacement products are unlikely to occur. Mouth and throat irritation were the adverse events with the highest prevalence.

IV.6 Discussion on the clinical aspects
Although limited safety evaluation, the overall data supports a positive benefit-risk for the Zonnic pouch and chewing-gums.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

SPC, PL and labelling are acceptable.
User testing of the package leaflet has been performed.

The risk/benefit ratio is considered positive and Zonnic Mint, medicated chewing gum 1.5 and 3 mg and Zonnic Mint, oromucosal powder in pouch was recommended for approval.

VI. APPROVAL

The Decentralised procedure for “Zonnic Mint, medicated chewing gum, 1.5 and 3 mg and Zonnic Mint oromucosal powder in pouch 4 mg”, was successfully finalised on 20080523.
Public Assessment Report – Update

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