

Public Assessment Report Scientific discussion

**Zonnic Mint, lozenge,
1.25 mg, 2.5 mg
Zonnic Pepparmint, oromucosal spray,
1mg/spray
(nicotine)**

SE/H/776/01-03/DC

Applicant: NicoNovum AB

This module reflects the scientific discussion for the approval of Zonnic Mint, lozenge, 1.25 mg, 2.5 mg and Zonnic Pepparmint, oromucosal spray, 1 mg/spray (nicotine). The procedure was finalised at June 26th 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, lozenge, 1.25 mg, 2.5 mg and Zonnic Peppermint, oromucosal spray, 1mg/spray”.

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 lozenges containing 1.25 mg and 2.5 mg of nicotine and oromucosal spray containing 1 mg/spray of nicotine.

The excipients in lozenges 1.25 and 2.5 mg are aspartame (E951), carbomer, microcrystalline cellulose (E460), eucalyptus flavour, isomalt (E953), magnesium stearate (E470b), methacrylic acid-methyl methacrylate copolymer, peppermint flavour and anhydrous sodium carbonate.

The lozenges are packaged in a blister of aluminium/PVC/PVDC containing 20,100 or 200 pieces of lozenges or each lozenge is packaged in an aluminium bag of aluminium/PE and PET containing 20,100 or 200 lozenges.

The excipients in oromucosal spray are anhydrous ethanol, glycerol, mint flavour, potassium dihydrogen phosphate, sodium hydroxide, sucralose and water. Each oromucosal spray is packaged in a glass or in a plastic bottle, each contains 200 sprayings.

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

Zonnic Peppermint, oromucosal spray

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. The proposed limits for related substances and assay are justified. The batch analysis results show that the drug products meet the specifications proposed at release. The proposed shelf life for the oromucosal spray is 2 years when stored in the glass container which also is acceptable. 15 months of shelf life is acceptable for the oromucosal spray in the PET container.

Zonnic Mint lozenges

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. The proposed limits for related substances and assay are justified. The batch analysis results show that the drug products meet the specifications proposed. A shelf life for the lozenges of 9 months when stored below 25°C is accepted.

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 Peppermint and Zonnic Mint. The use of Zonnic Peppermint and Zonnic Mint 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 Pharmacokinetics

The amount of absorbed nicotine from a nicotine lozenge 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 absolute bioavailability of nicotine after sublingual administration is approximately 50 %. The high and rapidly increasing nicotine concentrations that are observed in smokers are rarely reached after a lozenge from the originator.

After smoking, the average plasma concentration is approximately 15 ng/ml.

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.

The clearance of nicotine is reduced by approximately 50 % in patients with severe renal impairment and moderate hepatic impairment. Increased plasma concentrations have been observed in patients on haemodialysis.

The applicant has performed one pharmacokinetic study (Nic PKPD 06/02) where plasma concentrations of Zonnic Mint 2.5 mg and 1.25 mg were compared to Nicorette chewing gum 4 mg and Nicorette 0.5 mg/dose nasal spray. The analytical method was properly validated. The study was performed at Department of Medicine, Section of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden, for which GCP compliance was concluded. Bioequivalence between the 2.5 mg lozenge and the 4 mg chewing gum could not be concluded.

The application of Zonnic Peppermint is based on clinical efficacy data, although plasma nicotine samples were drawn in the NEWS study, where it was shown that similar exposures and maximal concentrations are obtained with 2 squirts as compared to one 2.5 mg lozenge or one 4 mg originator chewing gum. However, the maximal concentrations are reached earlier with the oromucosal spray.

IV.2 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.3 Clinical efficacy

The applicant submitted a clinical efficacy and safety study (Study NEWS) and also an open-label safety and tolerability study (Study TS 2002).

The NEWS study was a Phase III, randomized crossover trial of the withdrawal relief effects of Zonnic 1 mg/dose oromucosal spray and Zonnic 2.5 mg lozenge as compared with standard nicotine chewing gum and placebo lozenge. The study was conducted because bioequivalence of the Zonnic 2.5 mg lozenge to the Nicorette chewing gum could not be shown in Study Nic PKPD 06/02. Forty-seven subjects were enrolled and 44 completed the study. A subgroup of 12 subjects submitted blood samples for assessment of nicotine plasma concentrations. The primary efficacy outcome was change in composite craving score over 60 minutes (measured as AUC), using the Minnesota Nicotine Withdrawal Scale. During the study, the initial dosage of Zonnic 1 mg/dose oromucosal spray was amended from 3 sprays to 2 sprays due to nausea associated with the higher dose.

A treatment effect on nicotine craving from baseline to 60 minutes was shown for the Zonnic 2.5 mg lozenge versus placebo lozenge and for the Zonnic 1 mg/dose oromucosal spray versus placebo lozenge. Similarly, a treatment effect on craving was shown for the Nicorette 4 mg

chewing gum versus placebo lozenge. There was no statistically significant difference between the Zonnic lozenge and the Nicorette chewing gum or between the Zonnic oromucosal spray and the chewing gum. Also, there was no significant difference between the Zonnic treatments. Similar effects were seen on change from baseline to 60 minutes with respect to urge to smoke, irritability, restlessness, and difficulty concentrating. That is, a significant effect versus placebo for both Zonnic products and also for the Nicorette and no significant difference between the active treatments.

It was concluded that efficacy of the Zonnic Mint 2.5 mg lozenge and the Zonnic Peppermint 1 mg/dose oromucosal spray (2 sprays) versus placebo has been shown in this study. With regard to the Zonnic oromucosal spray, comparison to a placebo spray rather than a placebo lozenge would have been a more appropriate choice. However, PK assessments in a subgroup of subjects showed fairly similar exposure data following administration of the lozenge and the spray, with a shorter T_{max} for the spray.

Efficacy comparisons with Nicorette chewing gum should be interpreted with some caution because 53% percent of subjects in the study had previous experience with nicotine chewing gum in earlier quit attempts. This may have affected subject rating of effect for this product. Overall, efficacy for the Zonnic 2.5 mg lozenge and the 1 mg/dose oromucosal spray (2 sprayings) seemed comparable to Nicorette 4 mg chewing gum.

IV.4 Clinical safety

The overall duration of exposure in the NEWS study was limited; patient exposure was 9 hours for each of the 4 products. The overall adverse event profile in this study was similar to the well-known profile with nicotine replacement treatment.

Adverse events with the highest incidence were feeling sick and mouth irritation. The Zonnic 1 mg/dose oromucosal spray showed a higher rate of mouth irritation and also hiccups as compared with the other active treatments. During previous review, it was concluded that the Zonnic 1 mg/dose oromucosal spray should be limited to 1-2 sprays per dosing because subjects in the NEWS study did not tolerate dosing with 3 sprays.

The applicant also submitted an open-label tolerability study (Study TS 2002) that assessed local subjective adverse effects of a nicotine 1 mg/dose oromucosal spray over a 28-day period. However, the composition of the spray was quite different from the to-be-marketed Zonnic oromucosal spray. The study is therefore not considered to be very informative. There were no SAEs in any of the studies.

IV.5 Discussion on the clinical aspects

Despite limited safety evaluation, the overall data supports a positive benefit-risk for the Zonnic lozenges and oromucosal spray. The products are recommended for approval.

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, lozenge 1.25 and 2.5 mg and Zonnic Peppermint, oromucosal spray, 1mg/spray were recommended for approval.

VI. APPROVAL

The Decentralised procedure for “Zonnic Mint, lozenge, 1.25 and 2.5 mg and Zonnic Peppermint oromucosal spray, 1 mg/spray” was successfully finalised on 20080626.

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)