LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nicorette Pepparmint
(nicotine)

SE/H/904/01/DC

This module reflects the scientific discussion for the approval of Nicorette Pepparmint. The procedure was finalised at 2010-10-06. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

McNeil AB has applied for a marketing authorisation for Nicorette Pepparmint (Nicorette QuickMist in the CMS), 1 mg/spray, oromucosal spray. The active substance nicotine is also the active substance (in the form of nicotine resinate) in Nicorette, 2 and 4 mg, medicated chewing-gum, marketed by McNeil AB since 1981. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Nicorette Pepparmint is presented in the form of an oromucosal spray containing 1 mg/spray of nicotine. The excipients are propylene glycol, anhydrous ethanol, trometamol, poloxamer 405, glycerol, sodium hydrogen carbonate, levomenthol, mint flavour, cooling flavour, sucralose, acesulfame potassium, hydrochloric acid and purified water. The oromucosal spray is filled in a PET bottle placed in a dispenser with a mechanical spray pump.

II.2 Drug Substance

Nicotine has a monograph in the Ph Eur.

Nicotine is a colourless or brownish viscous liquid, volatile, hygroscopic which is soluble in water and miscible with anhydrous ethanol. 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

Nicorette Pepparmint, 1 mg/spray, oromucosal spray is formulated using excipients described in the current Ph Eur, except for the mint and cooling flavour which are controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin.

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, when stored below 25°C.

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of nicotine are considered well known. Impurities in the drug substance, degradants in the drug product and excipients are qualified.

The applicant has submitted an environmental risk assessment based on published data. It is agreed that the use of the product does not represent a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

A new formulation has been developed, nicotine oromucosal spray. The pharmacokinetics of this formulation has been compared with chewing gums and lozenges.

IV.2 Pharmacokinetics

Two pivotal pharmacokinetic studies have been performed with the new oromucosal spray. In the single dose study, bioequivalence is shown with respect to AUC but not to Cmax when comparing 4 mg oromucosal spray with two different reference products, Nicorette chewing gum 4 mg and NiQuitin lozenge 4 mg. A difference in the pharmacokinetic profile is shown for the first 10 minutes. However, the contribution of the first 10 minutes to the total AUC is limited. See also the pharmacodynamic section regarding the relevance of this difference. Cmax of the oromucosal spray 4 mg is approximately 20 % higher versus Nicorette 4 mg chewing gum and 34 % higher than NiQuitin 4 mg lozenge. The applicant has justified the higher Cmax by comparison to levels of nicotine obtained after administration of a nasal spray and smoking itself that is considered acceptable.
In the multiple dose study, the formulation seems to be able to deliver the same dose and approximately half the exposure is obtained with dosing 2 mg/30 minutes compared to 4 mg/h for the two reference products when measuring exposure during a dosing interval. There is no apparent difference in the pharmacokinetics between self-administration and staff-administration.

Some issues were raised in the product information with respect to pharmacokinetic data/interactions. The applicant´s response was considered acceptable (Section 4.2, harmonisation of section 4.5, and the absorption section of 5.2.

IV.3 Pharmacodynamics

The pharmacological actions of nicotine are well known. The applicant submitted urge to-smoke data obtained in a nonpivotal pharmacokinetic study aimed to compare the pharmacokinetics of 1 mg/spray to a reference product (Nicorette gum 2 mg). The study had

an open-label randomized, single-dose, 4-way crossover design and included 31 healthy smokers. The craving relief findings from this study indicated that most subjects obtained craving relief within the first 10 minutes after administration of the oromucosal spray, with approximately 50% of the subjects obtaining relief within 2 minutes and approximately 70% within 5 minutes.

Whether the properties of the spray could result in improved rates of nicotine reduction or quitting as compared with other nicotine products was not studied. Accordingly, some issues were raised regarding possible acceptable language pertaining to 'onset of craving relief' in the SPC and the applicant has agreed to include the language that was proposed by RMS.

IV.4 Clinical efficacy

The applicant submitted a supportive Phase 2 pilot low intervention study. This was a randomized, open-label, multiple-dose study to evaluate subject use patterns of nicotine mouth spray over a 3-week treatment period. The study enrolled healthy male and female smokers motivated to quit smoking. The enrolled subjects were randomized into 2 groups that received either fixed or flexible dosage use directions for the mouth spray. A total of 258 subjects were enrolled and analyzed (129 in each dosage group).

Overall, the usage of the mouth spray was actually lower than recommended in both groups. No significant differences were observed regarding relief of craving or other withdrawal symptoms between the fixed-dosage and flexible-dosage regimens. There was no difference in product use, AE profile, or quit rate between the fixed and the flexible dosing regimen of the mouth spray.

The dosing schedule that is proposed by the applicant consists of 3 steps, which includes full dosing for the first 6 weeks, followed by tapering. During the procedure, the applicant was requested to further justify this proposed schedule, bearing in mind the relatively short duration of treatment compared with other approved nicotine replacement products (in most cases 12 weeks). The applicant provided an acceptable response including literature review that supported the proposed dosing recommendations. It is also considered that other approved nicotine replacement products (such as NiQuitin lozenges) have a similar recommended period of full dosing of 6 weeks.

IV.5 Clinical safety

The overall exposure to the oromucosal spray included 140 subjects in the 4 PK studies and the 258 subjects in the 3-week low intervention study.

In the low intervention study, patients were treated for up to 3 weeks. No longer-term safety data are available. However, the overall adverse event profile of the oromucosal spray appeared similar to other nicotine replacement products. Certain AEs such as hiccups appear to occur more frequently with nicotine spray formulations compared with nicotine gum or lozenges. However, no active comparator clinical studies were submitted. Based on the available data from the PK studies and the Phase 2 study, no significant new safety issues were identified.

The applicant was requested to further discuss the local (*in casu* oral) safety and tolerability profile of the oromucosal spray in comparison to other nicotine replacement products. Since this is a liquid formulation, the duration of mucosal exposure is likely shorter when compared to other oral formulations such as gum or lozenges, and this should reduce the effects or

exposure to the oral mucosa. The applicant also estimated that the overall nicotine exposure from a period of full dosing (using the maximum recommendations) with the spray is lower compared with full dosing with 4 mg of nicotine gum.
All excipients are approved for oral use and overall, it seems reasonable to extrapolate the safety experience from other nicotine product for this oromucosal administration.

Regarding pharmacovigilance, no safety concerns were identified, which would warrant activities beyond routine surveillance.

Thus, overall, it is viewed that sufficient documentation has been provided by the applicant to conclude that treatment with Nicorette Pepparmint will be safe and efficacious and that there is no potential serious risk to public health.

IV.6 Discussion on the clinical aspects

Nicotine products are used therapeutically as an adjunct to facilitate smoking cessation and a variety of different pharmaceutical formulations for nicotine administration are available.

Nicorette Pepparmint is developed as a nicotine replacement product. An oromucosal nicotine spray (ONS) was chosen as the delivery system. The applied indication is as follows:

“For the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit.
Advice and support normally improve the success rate.”

In the pharmacokinetic studies, bioequivalence was shown with respect to AUC but not to Cmax when comparing 4 mg oromucosal spray with two different reference products. The applicant has justified the higher Cmax by comparison to levels of nicotine obtained after administration of a nasal spray and smoking itself, which is considered acceptable.

The pharmacological actions of nicotine are well known. A submitted pharmacodynamic study and a Phase 2 pilot intervention study indicated that the efficacy and safety of Nicorette Pepparmint can be expected to be similar to other nicotine replacement products for oral use. The proposed dosing schedule is considered acceptable and the applicant has accepted required modifications to the SPC.

Thus, overall, the clinical risk/benefit balance is considered positive and similar to other nicotine replacement products for oral use.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bioequivalence is shown with respect to AUC in the single dose pivotal pharmacokinetic study but not to Cmax when comparing 4 mg oromucosal spray with two different reference products, Nicorette chewing gum 4 mg and NiQuitin lozenge 4 mg. A difference in the pharmacokinetic profile is shown for the first 10 minutes. However, the contribution of the first 10 minutes to the total AUC is limited. Cmax of the oromucosal spray 4 mg is approximately 20 % higher versus Nicorette 4 mg chewing gum and 34 % higher than NiQuitin 4 mg lozenge. The Applicant has justified the higher Cmax by comparison to levels of nicotine obtained after administration of a nasal spray and smoking itself that is considered acceptable.

No clinical efficacy studies were submitted except for an exploratory Phase 2 pilot study that showed no difference in product use, AE profile, or quit rate between a fixed and a flexible dosing regimen of the mouth spray. The overall adverse event profile of the oromucosal spray appears similar to other nicotine replacement products for oral use.

The proposed dosing schedule in the SPC is also acceptable. The RMS requested additional modifications to the SPC. These were adequately addressed and the SPC is now considered acceptable.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. 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.

In conclusion, the risk/benefit ratio is considered positive and similar to other nicotine replacement products for oral use. Thus, Nicorette Pepparmint, 1 mg/spray, oromucosal spray, is recommended for approval.

VI. APPROVAL

The decentralised procedure for Nicorette Pepparmint, 1 mg/spray, oromucosal spray, was successfully finalised on 2010-10-06.

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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/904/01/II/27	The applicant proposes to revise Section 4.1 (Therapeutic Indications) of the SmPC to include gradual smoking cessation as an indication to allow smokers to utilise Oromucosal Spray to reduce smoking prior to quitting. As a result, Section 4.2 (Posology) of the SmPC has been updated to include the posology for this indication. Gradual smoking cessation is already indicated in a number of EU markets for the oromucosal spray, lozenge and gum.	Yes	2020-06-25	Approval	The applicant has provided responses to list of questions raised by the RMS and CMS and the benefit risk balance for Nicorette Pepparmint 1mg/spray, Oromucosal spray, solution remains positive. The variation is considered acceptable.

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

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