LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nicorette Fruktmint
(nicotine)

SE/H/904/02/DC

This module reflects the scientific discussion for the approval of Nicorette Fruktmint. The procedure was finalised on 2017-01-19. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

McNeil Sweden AB has applied for a marketing authorisation for Nicorette Fruktmint, 1 mg/spray, Oromucosal spray, solution. The active substance is nicotine. The difference between the previously approved oromucosal nicotine spray and the newly developed is restricted to the flavouring, a minor part of the formulation.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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 Pharmacology/pharmacokinetics/toxicology

No new pharmacology, pharmacokinetic or toxicology data have been submitted. Based on the well-known profile of nicotine this is considered acceptable.

The composition of the product is the same as the one of the already approved Nicorette Pepparmint (SE/H/904/01/DC) with the exception of the additional flavor Red fruit flavor 911441, half the amount of levomenthol, and the exclusion of the mint flavour. The Applicant has declared the qualitative composition of the Red fruit flavor 911441 and it is agreed that the source materials included, comply with the conditions of Regulation (EC) 1334/2008 and are (US) FEMA GRAS.

There are no toxicological concerns in relation to the degradation products and the excipients.

III.2 Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): Nicotine					
CAS-number (if available): 54-11-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential log K_{ow}	Literature reference	log K_{OW} = 1.17			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{OW}	log K_{OW} = 1.17			B (No)
	BCF	Not tested			B (No)
Persistence	Ready biodegradability	Readily biodegradable in sludge			P (Yes)
Toxicity	NOEC (Daphnia)	70µg/L			T (No)
PBT-statement :	The compound is not considered to be an PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC_{SW} , default or refined	Default Fpen: 0.01 DOSEai = 65mg	0.32µg/L			> 0.01 µg/L (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 OPPTS 835.1110	$K_{d\ sludge}$ *: unknown* $K_{oc\ sludge}$ *: unknown*			Koc > 10000 L/kg triggers a Phase IIB
Ready Biodegradability Test	OECD 301B	Ultimate biodegradation 82.1 - 84.5%			Ready biodegradation
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = *unknown* $DT_{50,\ sediment}$ = *unknown* % AR in sediment at day 14 = *unknown*			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC EC_{50}, growth EC_{50}, biomass	10 000 56 000 88 300	µg/L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OPPTS 850.1300	$NOEC_{body\ length}$ $NOEC_{replication}$	70 120	µg/L	*Daphnia pulex* 16d study
Fish, Early Life Stage Toxicity Test/*Species*	Post-hatch+60d bioassay	NOEC	2 600	µg/L	*Oncorhyncus mykiss* (no embryogenesis exposure)
Activated Sludge, Respiration Inhibition Test		EC_{10} EC_{50}	*Unknown* *Unknown*	µg/L	Not tested

The ERA is based on literature reports and only values that come with provided reference literature has been used (with the exception of log K_{OW}). While the ERA guideline strongly recommends that log K_{OW} values should be determined experimentally (EMA/CHMP/SWP/44609/2010), nicotine is historically very well-characterized as an

agricultural chemical. The provided log K_{OW} value of 1.17 and log D = 0.17 (Seckar et al, 2008) are therefore acceptable in this particular case. Based on this information, nicotine triggers Phase IIA assessment (PEC_{SW} = 0.32µg/L > 0.01µg/L) but does not require a PBT classification.

Nicotine is readily biodegradable in sludge (Seckar et al, 2008), supporting the conclusion that it is not a PBT substance and mitigating the need for OECD TG308 information (EMA/CHMP/SWP/44609/2010) and any OECD TG308 dependent studies (e.g. the sediment-dweller-toxicity test). The ERA does not include information of the adsorption/desorption properties of nicotine (provided by OECD TG106 or OPTTS 835.1110 tests), making a full phase IIA assessment impossible. No recommended sludge microorganism toxicity test data has been included (e.g. OECD TG209), also making a full Phase IIA assessment problematic.

The aquatic toxicity of nicotine has been fully evaluated in green algae (*Raphidocelis subcapitata*) and crustaceans (*Daphnia pulex*) and partially in fish (*Oncorhyncus mykiss*). The algae chronic toxicity values was based on a OECD TG201 study (96h algae growth inhibition test; reported by Seckar et al, 2008), giving a nicotine NOEC of 10mg/L. Full life cycle aquatic crustacean chronic toxicity according to OPPTS 850.1300 was reported for *Daphnia pulex* (Savino and Tanabe, 1989), giving a NOEC of 70µg/L. The ERA provides a NOEC of 2.9 mg/L from a rainbow trout 60d chronic toxicity test (Passino-Reader et al, 1995). The Passino-Reader (1995) study did not include the likely most sensitive life–stage - the embryogenesis period - within the exposure period (embryonic exposure is also recommended in OECD TG210). The fish toxicity values can therefore only be seen as indicative of nicotine's aquatic toxicity potential but not fully conclusive.

Nicotine containing pesticides and non-consumed discarded nicotine products/waste (e.g. cigarette butts, incorrectly handled nicotine waste such as nicotine patches and non-depleted spray bottles) are likely far more of an environmental issue than NRT-consumed nicotine. Overall, and considering that the European Union harmonized classification and labelling (CLP) system has classified Nicotine as being toxic to aquatic life (ECHA 200-193-3; Aquatic Chronic 2, H411, toxic to aquatic life with long lasting effects), the available data does not allow one to conclude definitively on the potential environmental risk of oromucosal nicotine spray product-derived nicotine.

IV. CLINICAL ASPECTS

IV.1 Introduction

Since the difference between the approved oromucosal nicotine spray and the newly developed is restricted to the flavoring, it is deemed highly unlikely that the relatively minor changes in the formulation will have any impact on bioavailability, safety or efficacy.

IV.2 Pharmacokinetics

Two pivotal pharmacokinetic studies have been performed with the oromucosal nicotine spray 1 mg/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. 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 seem 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.

IV.3 Pharmacodynamics

One randomized, three-way crossover study compared the effect of ONS 2 mg with that of Nicotine lozenge 2 mg and 4 mg, respectively. Urges to smoke were measured using a 100 mm visual analogue scale (VAS) before and repeatedly after treatment administration.
Over the first 1, 3, 5 and 10 minutes after administration statistically significantly lower urges to smoke scores for two sprays of ONS 1 mg/spray than for Nicotine lozenge 2 mg and Nicotine lozenge 4 mg, respectively, were observed. This study showed that also the onset of relief of urges to smoke is fast compared with other oral NRT products.

IV.4 Clinical efficacy

A 52-week, randomized, multicenter, double blind, placebo-controlled, parallel group study to measure the efficacy and safety of ONS showed statistically significantly higher continuous abstinence rates at weeks 6 (26.1% vs 16.1%, p=0.014), 24 (15.7% vs 6.8%, p=0.006), and 52 (13.8% vs 5.6%, p=0.007) compared to placebo.

IV.5 Clinical safety

The systemic effects of nicotine reported in trials of ONS 1 mg/spray are similar in nature to those seen for all other forms of NRT and include amongst others: nausea, vomiting, headache and gastrointestinal discomfort/pain. Withdrawal rates due to AE’s were proportionally similar between treatment arms.

IV.6 Risk Management Plans

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 Nicorette Fruktmint.

Safety specification

Summary table of safety concerns as approved in RMP

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 RMP is approved.

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 Nicorette Pepparmint 1mg/spray SE/H/904/01/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Nicorette Fruktmint, 1 mg/spray, Oromucosal spray, solution. is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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 Mutual recognition/Decentralised procedure for Nicorette Fruktmint, 1 mg/spray, Oromucosal spray, solution was positively finalised on 2017-01-19.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se