6 SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN

6.1 Overview of disease epidemiology

WHO has calculated that every second smoker will die early because of smoking and in average a smoker will lose 7-8 years of lifetime. Today, tobacco use causes 1 in 10 deaths among adults worldwide. Around 40 different diseases can be directly connected to smoking. The most common diseases are cardiac and vascular diseases, chronic obstructive pulmonary disease, lung cancer and several other types of cancer. If current trends continue, it is estimated that around 500 million people alive today will be killed by tobacco. During this twenty-first century, tobacco could kill up to one billion people. Passive smoking is also associated with increased risk.

In Sweden more than a million people are smoking. In 2011 11% of the Swedish population between 16-84 years smoked on a daily basis while further 11 % smoked occasionally. In Denmark 24 % of the population above 15 years smoked and 18% smoked on a daily basis. In Norway in 2010-2011, 29 % of the population from 16 to 74 years smoked either daily or occasionally. About 18 % smoked daily. In Finland in 2010 about 23 % of men and 16 % of women in the age group 15 – 64 years smoked daily.

Smoking cessation significantly reduces most of the increased health risks that smokers have incurred. The degree of improvement depends on the stage of disease. Nicotine replacement therapy (NRT) has proved to be effective, acceptable, and safe as nicotine replacement in smoking cessation.

6.2 Summary of existing efficacy data

The harmful health effects of tobacco smoking are generally recognised. It is also generally accepted that one of the main difficulties in withdrawing from smoking is due to nicotine dependence. NRT is effective in aiding smoking cessation. It reduces the urges to smoke and other withdrawal symptoms following cessation. There appears to be little difference overall in the effectiveness of different types of nicotine replacement product on cessation rates. All of the commercially available forms like nicotine gum, transdermal patch, the nicotine nasal spray, nicotine inhaler and nicotine sublingual tablets/lozenges are effective as part of a strategy to promote smoking cessation. They increase quit rates approximately 1.5 to 2 fold regardless of setting.

There are many blood vessels in the area between the upper lip and the gum and the fact that Niqopods/Nicovel mint 4 mg oromucosal powder in pouch may be fixed over a long time-period provides the opportunity to both a quick and long-lasting uptake of nicotine over the oral mucosa.

Niqopods/Nicovel mint 4 mg oromucosal powder in pouch releases nicotine similar to Nicorette ® 4 mg chewing gum, and moist tobacco snuff pouches. A study on Niqopods/Nicovel mint 4 mg oromucosal powder in pouch, study MA NS 10 'Pharmacokinetic study of Nicotine 4 mg oromucosal powder in pouch' showed that the rate and the extent of nicotine bioavailability and plasma concentration time curves for Niqopods/Nicovel mint 4 mg oromucosal powder in pouch were very similar to those of the Nicorette 4 mg gum.

One study on efficacy of Niqopods/Nicovel mint 4 mg oromucosal powder in pouch has been performed, study MA NS 11 'The effect of 6 weeks use of the Nicotine 4 mg oromucosal powder in pouch on the oral mucosa. A short-term smoking cessation and tolerability study'. The primary aim of the study was to evaluate the safety and tolerability of Niqopods/Nicovel mint 4 mg oromucosal powder in pouch after 6 weeks' daily use. However, since abstinence from smoking was a prerequisite for assessment of the safety, the efficacy of the drug as a smoking cessation aid was also assessed.

Of the 48 persons in the study, 32 managed to completely stop smoking between weeks 1 to 6 with no slips, i.e. the Short-Term Quit Rate was 66.7 % (32/48). Forty of 48 smokers (83.3 %) managed to abstinence from smoking with no more than 6 occasions of smoking during the 6-wk treatment with the Nicotine 4 mg oromucosal powder in pouch. The slips mainly took place during the initial two weeks.

The time to relapse during treatment with Niqopods/Nicovel mint 4 mg oromucosal powder in pouch in the seven patients who relapsed was between 1 to 5 weeks (mean 4.1 weeks).

Niqopods/Nicovel mint 4 mg oromucosal powder in pouch was well tolerated and typical smoker's oral mucosal lesions were reduced during the treatment.

6.3 Summary of safety concerns

In the tables below several risks are identified. The exact occurrence of these risks (incidence/prevalence) in the target population is generally not known but even a low occurrence may be relevant due to the size of the target population and the number of diseases that potential users of Nicovel Mint oromucosal powder in pouch may have.

6.3.1 Important identified risks

Risk	What is known	Preventability
Cardiovascular disorders (eg occlusive peripheral arterial disease, cerebrovascular disease, stable angina pectoris and uncompensated heart failure)	Incidence/prevalence not known, but even a small incidence/prevalence is relevant due the size of the target population and group of diseases in which nicotine oromucosal powder in pouch can be used. A recent Cochrane meta-analysis of 111 trials with over 40,000 participants compared NRT, any type, and placebo or non-NRT controls (32). The authors concluded that there is no evidence that NRT increases the risk of heart attacks. In another, large systematic review and meta-analysis of 92 RCTs involving 32,185 participants and 28 observational studies involving 145, 205 participants to assess the adverse events associated with NRT, Mills et al. (6) found an increased risk of heart palpitations and chest pain.	Instruction not to use the product in risk population. (Contraindication in the summary of product information (SmPC) and the package information leaflet (PIL))

6.3.2 Important potential risk

Risk	What is known	Preventability
Children and adolescent under age of 18	Nicovel mint oromucosal powder in pouch is not indicated for use in children, but adolescents below 18-years-old may use Nicovel mint oromucosal powder in pouch when recommended by a physician. No experience from clinical studies in children exists. Overdoses with NRT have been reported in the scientific literature. Nicotine poisoning has been observed in children from ingestion of cigarettes, chewing gums, tobacco and from the use of transdermal patches (27).	Dosage restrictions/warnings in the summary of product information (SmPC) and the package information leaflet (PIL). Childproof lid. Storage instructions in PIL and labeling to store out of reach and sight of children. It is stated in the PIL that if a child takes Nicovel Mint contact your doctor or the emergency department at the hospital immediately for evaluation of risk and for advice.

Pregnant and lactating women	Pregnancy: NRT causes dose related increases in maternal blood pressure and heart rate and lesser effects on the fetal heart rate, but these changes are less pronounced than those caused by smoking (13). Nicotine does not exert significant effects on placental blood flow and the hemodynamic effects of nicotine are unlikely to explain foetal growth retardation in smokers. Exposure to both mother and foetus to nicotine from ad libitum nicotine medications, such as nicotine gum, is considerably less than the exposure to nicotine from cigarette smoking. It is unclear how far NRT would carry a risk to the foetus when used in pregnancy but it is almost certainly safer than smoking (14). It is advised that pregnant or breast-feeding smokers should only use NRT after consulting a health care professional. The risk in the use of NRT versus complete smoking cessation or not being able to quit smoking would have to be balanced based on the individual patients' resources, motivation and capacity. Healthcare involvement in this decision is advised. Lactation: Nicotine passes into breast milk in small quantities that may affect the infant, even at therapeutic doses. It is advised that pregnant or breast-feeding smokers should only use NRT after consulting a health care professional. The complex nature of social and psychological factors that modulate maternal smoking may induce some mothers to believe that they should not smoke and breastfeed, and therefore unintentionally lead them to quit breastfeeding, instead of smoking (19). If nicotine replacement therapy is used whilst breast-feeding Niqopods mint should be taken immediately after breast feeding and not within two hours before breast feeding. The risk and benefits in continued breastfeeding with or without complete smoking cessation use of NRT or continued smoking would have to be balanced based on the individual patients' resources, motivation and capacity. Healthcare involvement in this decision is advised.	Warning in the SmPC section 4.6 and in PIL. Sentence stating that pregnant or breast-feeding smokers should only use NRT after consulting a health care professional.

6.4 Summary of risk minimisation by safety concern

No additional risk minimization or pharmacovigilance activities apart from routine pharmacovigilance are deemed necessary at this point.

6.5 Planned post-authorisation development plan

No additional post authorisation studies or development are planned at this point.

6.6 Summary of changes to the risk management plan over time

Not applicable as this is the first RMP for Nicovel Mint.