NOVARTIS

Nicotinell® oral forms

Medicated chewing-gums and compressed lozenge

30 Nov 2014, Version 2.0

Public Summary of Risk Management Plan

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Smoking represents a major health concern, which affects 22-47% of adults worldwide (EMA, 2009). In the EU, the lowest number of smokers is recorded in Portugal, UK and Italy (19.7%, 22.0% and 22.7% of the general population, respectively) and the highest in Bulgaria (45.7%) (Bogdanovica et al, 2011). Up to 24.7% of teenagers in western countries smoke (EMA, 2009; Turner et al, 2004), indicating that this habit is often acquired during adolescence. Similarly high proportions (10-27%) are found among pregnant women in the EU (EMA, 2009). Interestingly, nicotine dependence is more common in groups with lower social-economic status: UK data from 2006/2007 showed that 33.8% of residents in deprived areas smoked compared to 14.1% of residents in affluent neighborhoods (Simpson et al, 2010).

Smoking is associated with various life-threatening conditions, including cancer and cardiovascular diseases (MHRA, 2005). It has been estimated that if 50% of smokers gave up smoking, 20-30 million premature deaths would be avoided in the first quarter of this century (EMA, 2009).

VI.2.2 Summary of treatment benefits

Nicotine replacement therapy (NRT), including gums and lozenges, remains the first line strategy for smokers who try to quit and need pharmacological help to fight their smoking urges and withdrawal symptoms. Concurrent behavioral support usually improves the success rate (West et al, 2004). NRT acts by providing the principal addictive agent of tobacco smoke, nicotine, without other toxic components, such as tar, carcinogens, and carbon monoxide (CO), and in a less addictive form.

A large number of clinical trials have demonstrated the efficacy and safety of nicotine chewing-gums (Herrera et al, 1995; Silagy et al, 2004; Stead et al, 2012; Cahill et al, 2013). Novartis conducted studies involving 918 subjects in order to investigate the efficacy and safety of Nicotinell lozenges (Studies LZ-04-95-US, LZ-21-97-F). While being generally well tolerated, Nicotinell lozenges reduced craving and significantly increased the smoking cessation rate vs. placebo at weeks 6, 12 (Studies LZ-04-95-US) and, in those smoking >20 cigarettes/day, at week 26 (LZ-21-97-F).

These results are confirmed by analyses of multiple studies comparing NRT to placebo and enrolling over 50,000 patients (Stead et al, 2012; Cahill et al, 2013). Data on long-term abstinence (six months or longer) were collected; compared to placebo, NRT increased the rate of quitting by 50 to 70%, regardless of setting.

VI.2.3 Unknowns relating to treatment benefits

Efficacy and safety studies on NRT were designed to represent the general population expected to use this therapy in the real world. The pharmacological properties of nicotine do not suggest that NRT use for smoking cessation would be accompanied by unknown treatment benefits in special patient populations.

However, limited clinical data exist with regard to two important populations that are known users of NRT:

- Children and adolescents <18 years of age
- Pregnant women

VI.2.4 Summary of safety concerns

Table 13-3 Important identified risk

Risk	What is known	Preventability
Cardiac arrhythmia	Disturbances in heartbeat rhythm rarely occur in patients taking Nicotinell gums or lozenges. Mechanisms that may explain this effect include a marked elevation in serum catecholamine concentration (which blocks inward potassium channels on cardiac cells), and an increase in atrial interstitial fibrosis (D'Alessandro et al, 2012).	Patients with a history of heart disease and/or uncontrolled hypertension should try to stop smoking without pharmacological interventions. If this fails, they should check with a doctor before using Nicotinell gums or lozenges. The CDS clearly provide this information, and also indicates that the use of Nicotinell gums or lozenges at therapeutic doses has rarely been associated with heart rhythm disturbances.

Table 13-4 Missing information

Risk	What is known
Use during pregnancy	Animal experiments have shown that nicotine may increase the rate of post-implantation pregnancy loss and affect foetus growth. There are inadequate data in humans to draw any conclusions, though it has been suggested that nicotine may affect foetal heart rate in the third trimester of pregnancy. Therefore, pregnant women are advised to quit smoking without nicotine replacement therapy. However, should this not be possible because of high dependence, tobacco withdrawal via nicotine replacement therapy may be recommended. Indeed, foetal risk is probably lower than that expected with tobacco smoking, due to: – lower maximal blood nicotine concentration than with inhaled nicotine – no additional exposure to toxic compounds (polycyclic hydrocarbons and carbon monoxide) released via cigarette smoking – improved chances of quitting smoking by the third trimester However, medical supervision is always recommended during the third trimester of pregnancy.
Use in children and adolescents (<18	There are inadequate data to assess the safe use of Nicotinell gums or lozenges in this population. Children and adolescents under 18 years of age

Risk	What is known
years of age)	should use the product only under recommendation from a doctor.

VI.2.5 Summary of additional risk minimization measures by safety concern

Not applicable as no additional risk minimization measures are proposed.

VI.2.6 Planned post authorization development plan

A planned post-authorization development plan is not required for this product.

VI.2.6.1 Studies which are a condition of the marketing authorization

No studies have been established as a condition of the marketing authorization.

VI.2.7 Summary of changes to the Risk Management Plan over time

There are no changes to safety concerns and proposed pharmacovigilance and risk minimization activities compared to version 1.0 of the RMP.