

Appendix to study protocol

STUDY PRODUCTS

TRADITIONAL SNUS

1. Active substance: Nicotine

1.1 Product name: Snus

1.2 Appearance: Paper sachets

1.3.Content : Snus is made from ground tobacco leaves, water, and food-allowed additives (salt, humidifier, acidity regulator, and flavour substances). The finished product adheres to the industrial standard GothiaTek[®] which includes limits for undesired substances, see below. No nicotine is added or removed from the product which implies that the nicotine in the product solely comes from the tobacco.

1.3.1 Content (large sachets):	Tobacco	0.5 g
	Water	0.5 g
	Salt (NaCl)	6%
	Nicotine	8 mg
	Propylene glycol (E 1520)	
	Sodium carbonate (E 500)	
	Flavour substances	

1.3.2 Content (small sachets):	Tobacco	0.25 g
	Water	0.25 g
	Salt (NaCl)	6%
	Nicotine	4mg
	Propylene glycol (E 1520)	
	Sodium carbonate (E 500)	
	Flavour substances	

1.3.3 pH	8.1-8.9 (accepted range)
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1.4 Administration: The sachets are placed in the mouth between the gingiva and cheek. Usage is *ad libitum*. Typically, the sachets are retained for 20-30 minutes up to 60 minutes. There is large individual variation in total number of sachets used per day, and the time the sachets are retained in the mouth, which reflects the wide variation in nicotine dose required by habitual users of nicotine products.

1.5 Nicotine absorption: 10-20% of the nicotine in the sachets is absorbed to the blood through the mucous membranes. The potential nicotine uptake is thus 1-2 mg from the large sachets and 0.5 – 1 mg from the small sachets.

1.6 Side effects: The side effects of the nicotine in snus are the same as those from other sources of nicotine such as cigarettes, and are dose dependent. As is known by every habitual smoker, the side effects are reversible when the dose is reduced or when usage is interrupted.

Common side effects of nicotine include:

Cardiology: Increased heart rate, slight elevation of blood pressure

Neurology: Vertigo, head ache.

GI: Nausea, stomach ache, heart burn

The content of sodium carbonate in the product makes it slightly alkaline. This may cause a slight burning sensation in the mouth at the location of the sachet, particularly among those unaccustomed to the product. However, short term use of snus (months) is not associated with any known mucosal side effects. Long term use (several years) may be associated with a mucosal “snus lesion”, that is, a slight whitish thickening of the mucosa. Such lesions are reversible if the placement of the snus sachet is changed, or usage stopped. Snus lesions are not associated with cellular atypia and do not have malignant potential. They are thus quite distinct from oral leukoplakias.

1.7 Weight variation of study product: Sachet weight may vary between -10% and +20% of the labelled weight, the mean weight is: 1g (large sachets) and 0.5g (small sachets)

1.8 Undesired substances: Snus contains traces of undesired substances occurring naturally in tobacco and other agricultural products. The levels are well below the limits of the industrial standard GothiaTek[®], and are listed in the table.

Component ¹	Limit ²	Content ³	Component ¹	Limit ²	Content ³
<u>Nitrite</u> (mg/kg)	3.5	1.1 (<0.5 - 1.9)	<u>Cadmium</u> (mg/kg)	0.5	0.2 (0.1 - 0.3)
<u>TSNA</u> (mg/kg)	5	0.8 (0.4 - 1.1)	<u>Lead</u> (mg/kg)	1.0	0.2 (0.1 - 0.2)
<u>NDMA</u> (µg/kg)	5	0.6 (<0.5 - 1.1)	<u>Arsenic</u> (mg/kg)	0.25	0.08 (<0.03 - 0.13)
<u>BaP</u> (µg/kg)	10	0.9 (<0.5 - 1.8)	<u>Nickel</u> (mg/kg)	2.25	0.8 (0.3 - 1.2)
<u>Pesticides</u>	According to the Swedish Match pesticide policy		<u>Chromium</u> (mg/kg)	1.5	0.5 (0.3 - 0.7)

1: Main undesired components defined by GothiaTek[®], 2: According to GothiaTek[®], 3: Results for batches produced by Swedish Match AB 2005, based on a water content of 50%

1.9 Packaging & storage: The snus sachets are distributed in round plastic containers. The packaging material is food allowed according to the Swedish Food Act. As the unique production method entails a heat treatment similar to pasteurization, the product is virtually

sterile. However, snus should preferably be stored in a refrigerator (6-8 °C) to preserve the water content and freshness of the product.

The product is marked with a best-before date which is c. 20 weeks after production date. It should be noted that the levels of undesired, potentially toxic substances, such as, nitrosoamines, do not increase during storage, even in room temperature. It is mainly the water content that decreases which affects the subjective freshness of the product. There is also a slight decline in the pH level during storage which decreases the amount of bio-available nicotine.

If the product is stored in a freezer (< -18 °C) the best before date is postponed almost indefinitely.

PLACEBO SNUS

2. Placebo: No active substance

2.1 Appearance: Paper sachets. The physical appearance and flavouring is the same as that of the traditional snus.

2.2.1 Content: Large sachets

Fibres from maize	0.6g (lignine and cellulose 70%, starch 15%, protein 6%, sugar 2%, fat 2%, water 3%, other 2%)
Water	0.4 g
Salt	6%
Glycerol (E 422)	
Acidity regulator (E 500)	
Flavour substances (same as in the traditional snus)	

2.2.2 Content: Small sachets

Fibres from maize	0.3g
Water	0.2 g
Salt	6%
Glycerol (E 422)	
Acidity regulator (E 500)	
Flavour substances (same as in the traditional snus)	

2.2.3 pH 8.1-8.9 (accepted range)

2.3 Weight variation of study products: Sachet weight may vary between -20% and +20% of the labelled weight, the mean weight is: 0.9g (large sachets) and 0.45g (small sachets)

2.4 Administration and usage. Same as with traditional snus

2.5 Side effects: None reported. However, because the product is slightly alkaline just as traditional snus, users may initially experience a slight burning sensation in the oral mucosa at the location of the sachet, particularly among those unaccustomed to the product. As a result of the pH, long term use (several years) may theoretically be associated with mucosal “snus lesions”, just as traditional snus. Such lesions, should they occur, are of minor clinical significance and are expected to be infrequent.

2.6 Packaging & storage: The sachets come in round plastic containers identical to those used for traditional snus. The packaging material is food allowed according to the Swedish Food Act. The product is marked with a best-before date which is c. 20 weeks after production date. The product should preferably be stored in a refrigerator (6-8 °C) to preserve the water content and freshness.

If the product is stored in a freezer (< -18 °C) the best before date is postponed almost indefinitely.