Summary of risk management plan for SUBLIVAC® Birch

This is a summary of the risk management plan (RMP) for SUBLIVAC® Birch 40,000 AUN/mL. The RMP details important risks of SUBLIVAC® Birch 40,000 AUN/mL, how these risks can be minimised, and how more information will be obtained about SUBLIVAC® Birch 40,000 AUN/mL risks and uncertainties (missing information).

SUBLIVAC® Birch 40,000 AUN/mL summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how SUBLIVAC® Birch 40,000 AUN/mL should be used.

I. The medicine and what it is used for

SUBLIVAC® Birch 40,000 AUN/mL is authorised for sublingual immunotherapy in adult patients for treatment of by birch pollen induced allergic rhinitis or rhino-conjunctivitis, with controlled allergic bronchial asthma or without allergic bronchial asthma (see SmPC for the full indication). It contains *betula verrucosa* pollen as the active substance and it is given sublingually.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SUBLIVAC® Birch 40,000 AUN/mL, together with measures to minimise such risks and the proposed studies for learning more about SUBLIVAC® Birch 40,000 AUN/mL risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of SUBLIVAC® Birch 40,000 AUN/mL, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of SUBLIVAC® Birch 40,000 AUN/mL is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of SUBLIVAC® Birch 40,000 AUN/mL are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely

administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SUBLIVAC® Birch 40,000 AUN/mL. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 15 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Severe local reactions Systemic reactions including Anaphylaxis Eosinophilic oesophagitis
Missing information	Safety and efficacy in elderly population

II.B Summary of important risks

Table 16 Summary of important identified and potential risks

Important identified risk – Severe local reactions	
Evidence for linking the risk to the medicine	Severe local reactions can lead to dose reduction or even discontinuation of the treatment. Please refer to eCTD module 2 for the complete clinical study data. Severe local reactions can be bothersome enough to lead to study discontinuation. Therefore severe local reactions considered to be an important identified risk.
Risk factors and risk groups	There are no risks groups identified. All patients receiving immunotherapy could experience a severe local reaction. However, patients having asthma symptoms or having performed intense physical activity shortly before administration are at greater risk of developing a severe local reaction.

Risk minimisation measures	Routine risk minimisation measures - The first drop is administered in the physicians' office (see patient information section 3) - After administration of the first drop the patient should wait for 30 minutes in the practice (see patient information section 2) - The patient starts with one drop and only increases the dose if this is well tolerated (see patient information section 3) - The patient should contact the treating physician for advice in case of side effects (see patient information section 4) - The option to reduce the dose by one or more drops in the case of severe local or moderate to severe systemic reactions (see patient information section 3)

	Additional risk minimisation measures - Specific DHCP letter - Sticker on the package for six months to increase awareness to the patient that this is a new product - Specific Pharmacy Delivery Note
Important identified risk – Systemic reactions including anaphylaxis	
Evidence for linking the risk to the medicine	Systemic reactions are known to occur after administration of SLIT. Systemic reactions which often occur are cough, dyspnoea, sneezing, allergic rhinitis. They can range in severity from mild to very severe life-threatening anaphylaxis. Systemic reactions have been observed in the clinical development program with the 10,000 AUN/mL product and with the 40,000 AUN/mL product (see Module 2 of the eCTD). In addition, post-marketing data with the 40,000 AUN/mL product also shows that systemic reactions might occur after intake of SUBLIVAC® Birch. From literature anaphylaxis has been observed after administration of sublingual immunotherapy(24). As anaphylaxis is always considered severe and can lead to life-threatening situations, it should be included as an identified risk. But up to now no grade IV reactions have been reported with SUBLIVAC® Birch 40,000 AUN/mL.

Risk factors and risk groups	There are no risks groups identified for systemic reaction I-II-III. All patients receiving immunotherapy could experience a systemic reaction. However, patients having asthma symptoms or having performed intense physical activity shortly before administration are at greater risk of developing a systemic reaction. Diseases which induce prompt recognition of symptoms like vision or hearing impairment, neurologic disorders, psychiatric disorders, autism spectrum disorders and development delay place patients at an increased risk for anaphylaxis. Also severe allergic rhinitis and eczema, and especially asthma and other respiratory diseases are risk factors associated with an increased risk of severe, lifethreatening or fatal anaphylaxis(25).
Risk minimisation measures	Routine risk minimisation measures - The first drop is administered in the physicians' office (see patient information section 3) - After administration of the first drop the patient should wait for 30 minutes in the practice (see patient information section 2) - The patient starts with one drop and only increases the dose if this is well tolerated (see patient information section 3) - The patient should contact the treating physician for advice in case of side effects (see patient information section 4) - The option to reduce the dose by one or more drops in the case of severe local or moderate to severe systemic reactions (see patient information section 3)

	Additional risk minimisation measures - Specific DHCP letter - Sticker on the package for six months to increase awareness to the patient that this is a new product - Specific Pharmacy Delivery Note

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Important identified risk – Eosinophilic oesophagitis	
Evidence for linking the risk to the medicine	Eosinophilic oesophagitis is considered a class effect of sublingual immunotherapy. During the clinical development patients reported events which could be symptoms of eosinophilic oesophagitis. After treatment with SUBLIVAC® FIX Birch 10,000 AUN/mL symptoms like oesophageal irritation, dysphagia and dyspepsia were reported. Similar events were reported after intake of SUBLIVAC® Birch 40,000 AUN/mL (see Module 2 of the eCTD). No cases of eosinophilic oesophagitis were reported post-marketing. Thus far one case of eosinophilic oesophagitis has been reported for SUBLIVAC® Trees (40,000 AUN/mL). Because of the class effect, eosinophilic oesophagitis has now been upgraded to identified risk also for SUBLIVAC® Birch 40,000 AUN/mL.
Risk factors and risk groups	There are no risk factors or risk groups for this event.
Risk minimisation measures	Routine risk minimisation measures - The first drop is administered in the physicians' office (see patient information section 3) - After administration of the first drop the patient should wait for 30 minutes in the practice (see patient information section 2) - The patient starts with one drop and only increases the dose if this is well tolerated (see patient information section 3) - The patient should contact the treating physician for advice in case of side effects (see patient information section 4)
	- The option to reduce the dose by one or more drops in the case of severe local or moderate to severe systemic reactions (see patient information section 3) Additional risk minimisation measures - Specific DHCP letter - Sticker on the package for six months to increase awareness to the patient that this is a new product - Specific Pharmacy Delivery Note

Table 17 Summary of important missing information

Missing information – Safety and efficacy data in elderly population

Evidence for linking the risk to the medicine	The clinical development program with SUBLIVAC® Birch 40,000 AUN/mL was performed in the adult population between the age of 18 and 65 years. Therefore, the safety and efficacy of SUBLIVAC® Birch 40,000 AUN/mL is only established in the adult population and not in the elderly population. Based on the post-marketing data, it is not expected that the safety profile in elderly is different than in adults. The elderly population is an important part of the target population and therefore the safety and efficacy will also be assessed in this population.
Risk minimisation measures	Routine risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of SUBLIVAC® Birch 40,000 AUN/mL.

II.C.2 Other studies in post-authorisation development plan

PASS in paediatric population

Study short name and title:

Randomized, double-blind, placebo-controlled, parallel-group, multicentre, clinical efficacy study.

Rationale and study objectives:

Clinical efficacy, dose dependency and safety of sublingual immunotherapy have been demonstrated. Although the exact mechanism of action by which sublingual immunotherapy desensitizes is still not clear, it is assumed to be identical in adults and paediatric populations. However, the magnitude of the effect and the safety profile could differ between adults and paediatric patients. Furthermore, it is expected that paediatric populations will have a greater benefit from immunotherapy to inhalant allergens. Therefore, dedicated studies in the paediatric populations are considered necessary. The aim of specific immunotherapy (particularly in paediatric patients) is persistent efficacy, which can only be demonstrated in long-term studies. The present study is designed to show long-term efficacy and disease modifying capacities and also to gather safety data of SUBLIVAC® Birch in paediatric populations.

The objectives are to assess the long term clinical efficacy after 3 years of treatment and 2 years posttreatment of SUBLIVAC® Birch in paediatric populations. This will be done based on a combined

symptom medication score reflecting rhinitis/rhinoconjunctvitis symptoms and the use of rescue medication during the birch pollen seasons compared to placebo during the treatment and post-treatment years. The study will also provide data on safety and the development of new sensitizations and asthma.

Non-interventional study with SUBLIVAC® Birch 40,000 AUN/mL

Short name and study title:

Safety of treatment with SUBLIVAC® Birch or SUBLIVAC® Trees 40,000 AUN/mL in daily routine.

Rational and study objectives:

Allergen immunotherapy is an effective form of treatment for both allergic rhinitis and allergic bronchial asthma. The aim of this study is to collect clinical data on the safety of the treatment with SUBLIVAC® Birch and SUBLIVAC® Trees 40,000 AUN/mL. This is done by collection of safety data with emphasis on the occurrence and intensity of local and systemic reactions.

Safety results:

Data from 432 subjects (43.8% male, 56.3% female) with a mean age of 44 years were collected. The subjects were treated with either SUB-B or SUB-T for 8 months and the safety and tolerability was assessed by documentation of adverse events. In total 23.6% of all subjects experienced at least one AE. Most of the AEs considered local reactions (22.2% of all subjects) while systemic reactions were less frequent (6.3% of all subjects). The vast majority of the AEs were of mild intensity. Moderate and severe events occurred less frequently. 96% of the subjects reached the maintenance dose and all subjects took the first drop in the physician’s office. The patient compliance accounted to 71% and more than 98% of the subjects who completed all visits were very satisfied or satisfied with the sublingual treatment. In addition, the subgroup analysis of SUB-B and SUB-T treated subjects revealed a comparable safety profile of the two medicinal products (SUB-B: 23.1% of the subjects experienced at least one AE vs.
SUB-T: 24.1% of the subjects experienced at least one AE).