PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

This is a summary of the risk management plan (RMP) for Asmanex Twisthaler. The RMP details important risks of Asmanex, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) of Asmanex.

The summary of product characteristics (SmPC) and package leaflet for Asmanex give essential information to healthcare professionals and patients on how Asmanex should be used.

Important new concerns or changes to the current ones will be included in updates of the RMP for Asmanex.

I. The Medicine and What it is Used For

Asmanex is authorised for adults and adolescents 12 years of age and older for regular treatment to control persistent asthma (see SmPC for the full indication). It contains 200mcgs and 400mcgs of mometasone furoate as the active substance and it is for inhalation use only.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Asmanex, together with measures to minimise such risks and the proposed studies for learning more about the 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 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 Asmanex is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Asmanex are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Asmanex. 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 II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Adrenal suppression Cataract Glaucoma Growth retardation Bone density decreased Oral candidiasis Pharyngitis
Important potential risks	Psychological or behavioral effects • Psychomotor hyperactivity • Sleep disorder • Anxiety • Depression • Aggression (particularly in children)
Missing information	Use in pregnancy Use in lactation

II.B Summary of Important Risks

The safety information in the proposed Prescribing Information is aligned to the reference medicinal product.

Table II.B.1: Important Identified Risk: Adrenal Suppression

Evidence for linking the risk to the medicine	MF SmPC and clinical trial /post-marketing data, literature
Risk factors and risk groups	Primary adrenal insufficiency occurring in childhood and adolescence is due to abnormalities of gland development, gland responsiveness, and steroid biosynthesis or target organ response. Causes include autoimmune Addison's disease, tuberculosis, HIV, adrenoleukodystrophy, and adrenal hypoplasia congenita. [Ref. 5.4: 00VKFP] The most common cause of secondary adrenal insufficiency is abrupt discontinuation of glucocorticoid therapy or stress while on suppressive doses. [Ref. 5.4: 00VHW2]
Risk minimisation measures	Routine risk minimisation measures : Described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC and Package leaflet Section 2 What you need to know before you use Asmanex and Section 4 Possible side effects

Table II.B.2: Important Identified Risk: Cataract

Evidence for linking the risk to the medicine	MF SmPC and clinical trial /post-marketing data, literature
Risk factors and risk groups	In the developed world, most cases of bilateral congenital cataracts are idiopathic, while one-third are hereditary (excluding cases of systemic disease). Other causes include metabolic disorders, mental retardation, and intrauterine infections. Most cases of unilateral congenital cataracts are also idiopathic, and they are rarely inherited and usually not associated with systemic disease. [Ref. 5.4: 00VKFT] Among adults, cortical and posterior subcapsular cataracts appear to be most closely related to environmental stresses such as ultraviolet exposure, diabetes, and drug ingestion, including corticosteroids and . Nuclear cataracts appear to be associated with smoking. Alcohol use seems to be associated with all cataract types. Consistent evidence also suggests that the prevalence of all cataract types is lower among those with higher education. [Ref. 5.4: 00VHW3]
Risk minimisation measures	Routine risk minimisation measures: Described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC and Package leaflet Section 2 What you need to know before you use Asmanex and Section 4 Possible side effects

Table II.B.3: Important Identified Risk: Glaucoma

Evidence for linking the risk to the medicine	MF SmPC and clinical trial /post-marketing data, literature
Risk factors and risk groups	Primary congenital glaucoma (PCG) is a hereditary childhood glaucoma secondary to abnormal development of the filtration angle, which occurs unassociated with systemic abnormalities. The majority of PCG cases are sporadic but 10% to 40% are familial with frequent association with consanquinity. In most familial cases, transmission is autosomal recessive with variable expression and penetrance of 40% to 100%.
Risk minimisation measures	Routine risk minimisation measures: Described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC and Package leaflet Section 2 What you need to know before you use Asmanex and Section 4 Possible side effects

Table II.B.4: Important Identified Risk: Growth Retardation

Evidence for linking the risk to the medicine	MF SmPC and clinical trial /post-marketing data, literature
Risk factors and risk groups	Severe chronic diseases and some medications that are used in large doses or for long periods of time may affect growth. Diseases which involve the kidneys, digestive tract, heart, or lungs are examples of such conditions that may influence growth. [Ref. 5.4: 00VKFV, 00VKFW] Failure of the kidneys in paediatrics with chronic renal insufficiency leads to the accumulation of toxins in the child's bloodstream that prevent normal growth. [Ref. 5.4: 00VKFY]
Risk minimisation measures	Routine risk minimisation measures: Described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC and Package leaflet Section 2 What you need to know before you use Asmanex and Section 4 Possible side effects

Table II.B.5: Important Identified Risk: Bone Density Decreased

Evidence for linking the risk to the medicine	MF SmPC and clinical trial /post-marketing data, literature
Risk factors and risk groups	**Pediatrics** Primary forms of osteoporosis in children and adolescents are relatively rare, and some of them are familial or genetically determined. Secondary forms of osteoporosis are increasingly observed in many chronic conditions. In these cases, low bone mass and an increased risk of fractures may be the consequence of the primary disease itself (because of reduced physical activity, intestinal malabsorption, malnutrition, hormonal or metabolic derangements, hypovitaminosis D, inflammation, cytokine increase, etc) and/or of its treatment (eg, corticosteroids, immunosuppressors). [Ref. 5.4: 00VKC7] Adults Risk factors for osteoporosis in adults include gender (female), age, White or Asian race, family hsitory of osteoporosis or fractures, small body frame, menopause and reduction of estrogen levels, dietary factors inlcuding low calcium intake and weight-loss surgery. Risk is increased with limited weightbearing exercise. Alcohol consumption and tobacco use are also associated with incrased risk of osteoporosis. High doses of glucocorticosteroids for long duration are associated with increased risk of osteroporosis. [Ref. 5.4: 00VHVM, 00VHW8]
Risk minimisation measures	Routine risk minimisation measures: Described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC and Package leaflet Section 2 What you need to know before you use Asmanex and Section 4 Possible side effects

Table II.B.6: Important Identified Risk: Oral Candidiasis

Evidence for linking the risk to the medicine	MF SmPC and clinical trial /post-marketing data, literature
Risk factors and risk groups	*Candida* causes pathologic change when the host's defense mechanism is compromised. In infants, this may result from the immaturity of the immune response. In older children, decreased resistance to infection may result from and be a sign of a compromised immune system (eg, HIV and other disease processes such as diabetes). External systemic and local insults to the immune response also may lead to oral candidiasis (eg, antineoplastic or immunosuppressive therapies, inhaled corticosteroids), as can local insults to the natural ecology of the oral flora (eg, frequent courses of antibiotics). Impaired salivary flow caused by disease or medication and poor oral hygiene also may lead to candidal pathology. [Ref. 5.4: 00VKC8]
Risk minimisation measures	Routine risk minimisation measures: Described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC and Package leaflet Section 2 What you need to know before you use Asmanex and Section 4 Possible side effects

Table II.B.7: Important Identified Risk: Pharyngitis

Evidence for linking the risk to the medicine	MF SmPC and clinical trial /post-marketing data, literature
Risk factors and risk groups	Approximately 40% to 60% of cases of acute pharyngitis are caused by a virus. Group A *Streptococcus* (GAS) is the most common bacterial cause of acute pharyngitis, accounting for 15% to 30% of acute pharyngitis in children. [Ref. 5.4: 00VKCC]
Risk minimisation measures	Routine risk minimisation measures: Described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC and Package leaflet Section 2 What you need to know before you use Asmanex and Section 4 Possible side effects

Table II.B.8: Important Potential Risk: Psychological or Behavioral Effects (Psychomotor Hyperactivity, Sleep Disorder, Anxiety, Depression and Aggression (Particularly in Children)

Evidence for linking the risk to the medicine	MF SmPC and clinical trial /post-marketing data, literature
Risk factors and risk groups	Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Poor asthma control was associated with anxiety plus depression. [Ref. 5.4: 00VK96] The rates of developmental and behavioral problems are consistently higher among children with asthma compared with those without asthma.[Ref. 5.4: 00VK8D]
Risk minimisation measures	Routine risk minimisation measures: Described in Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC and Package leaflet Section 2 What you need to know before you use Asmanex and Section 4 Possible side effects

Table II.B.9: Missing Information: Use in Pregnancy

Risk minimisation measures	Routine risk minimisation measures Described in the SmPC, Section 4.6 Fertility, pregnancy and lactation. This is labeled and monitored on an ongoing basis.

Table II.B.10: Missing Information: Use in Lactation

Risk minimisation measures	Routine risk minimisation measures Described in the SmPC, Section 4.6 Fertility, pregnancy and lactation. This is labeled and monitored on an ongoing basis.

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 MF DPI

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no Post-Authorisation studies required for MF DPI