European Union Risk Management Plan (EU-RMP)
Xylometazoline hydrochloride

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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Summary of Risk Management Plan for Xylometazoline nasal spray

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

The Summary of Product Characteristics (SmPC) and Package Leaflet of xylometazoline nasal spray give essential information to healthcare professionals and patients on how the product should be used.

Important new concerns or changes to the current ones will be included in the RMP updates for xylometazoline nasal spray.

I. The Medicine and What it is Used For

Xylometazoline nasal spray is authorised for the symptomatic relief of nasal congestion and swelling, to facilitate the discharge of secretion, and preparation of patients for procedures involving the nasal passage (see SmPC for the full indications). It contains xylometazoline as the active substance and is given via nasal route.

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

Important risks of xylometazoline nasal spray, together with measures to minimise such risks and the proposed studies for learning more about such 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 to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (eg, 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 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 xylometazoline nasal spray is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of xylometazoline nasal spray are those 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 product use. Potential risks are concerns for which an association with product use is possible based on available data but has not been established 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 (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Drug interactions with monoamine oxidase inhibitors and tricyclic antidepressants
Important potential risks	Off-label use in children including overdose in children Medication errors Rhinitis medicamentosa associated with off-label use Myocardial infarction when used off-label Stroke when used off-label Nasal mucosal damage associated with preservative benzalkonium chloride especially following long-term use
Missing information	Use during pregnancy or breastfeeding

II.B. Summary of Important Risks

Important Identified Risk: Drug interactions with monoamine oxidase inhibitors and tricyclic antidepressants	
Evidence for linking the risk to the medicine	Interactions between monoamine oxidase inhibitors (MAOIs) and sympathomimetic amines may lead to release of increased amounts of noradrenaline from sympathetic nerve endings after monoamine oxidase (MAO) inhibition. The effects of any amine, whether a substrate of MAO or not, may be enhanced by MAOIs producing postganglionic block due to denervation supersensitivity of adrenergic receptors (Sjöqvist, 1965).
Risk factors and risk groups	Patients on the extremes of age, organ transplant patients, and patients with the human immunodeficiency virus appear to have an increased risk of adverse drug effects from interactions between OTC and prescription drugs (Indermitte et al, 2007).

Risk minimisation measures	Please refer to Section 4.4 (Special warnings and precautions for use) and Section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC.
Important Potential Risk: Off-label use in children including overdose in children	
Evidence for linking the risk to the medicine	Imidazoline derivatives can stimulate postsynaptic α2-adrenergic receptors at cardiovascular and central nervous system control centres, leading to an inhibition of cerebral sympathetic outflow. This may manifest as bradycardia, arterial hypotension, and neurological or respiratory depression. Use in the paediatric population may often result in the product being taken at much higher doses and for longer than recommended, leading to a wide range of symptoms. Adverse effects reported in literature include hypotonia, dyspnoea, obtundedness and prolonged somnolence; no consequential damage has been reported in the cases presented (Musshoff et al, 2014).
Risk factors and risk groups	The risk of off label use in children was reported to be significantly higher among boys compared to girls. In addition, there also appear to be significant differences in the risk of off label medication use with respect to age, with younger children having increased risk over adolescents. Other influencing factors include place of residence and health status; the risk of off label use appears to be lower among children who live in rural areas and those with excellent general health as reported by parents (Knopf et al, 2013).
Risk minimisation measures	Please refer to Section 4.2 (Posology and Method of Administration), Section 4.3 (Contraindications), Section 4.4 (Special Warnings and Special Precautions for Use), and Section 4.9 (Overdose) of the CCDS.
Important Potential Risk: Medication errors	
Evidence for linking the risk to the medicine	Leading causes of medication errors may arise from the health care provider (inadequate knowledge of the drug or the individual patients case, poor communication with patients), the patient (literacy, language barriers, multiple existing medical conditions, polypharmacy), or the product (naming, labelling, packaging).
Risk factors and risk groups	Risk factors for medication errors include multiple morbidities, high number of medications, being hospitalised, and belonging to either extreme of age (WHO, 2016).
Risk minimisation measures	Please refer to Section 4.2 (Posology and Method of Administration) of the CCDS.
Important Potential Risk: Rhinitis medicamentosa associated with off-label use	
Evidence for linking the risk to the medicine	Although the exact mechanism of rhinitis medicamentosa (RM) is unknown, it is believed to be secondary to the decreased production of endogenous sympathetic norepinephrine through a negative feedback mechanism. With prolonged use or following discontinuation, the sympathetic nerves may be unable to maintain vasoconstriction because norepinephrine release is suppressed (Ramey et al, 2006). In a clinical study of long-term use of vasoconstrictors in 13 healthy volunteers with no history of allergy or other diseases involving the nose, 7 subjects received xylometazoline nasal spray (1.0 mg/mL; 2 puffs=0.28 mL in each nostril during each administration), after which they were given increasing concentrations of histamine solutions. Histamine sensitivity was enhanced after 10 days and 20 days on the drug, reflecting evidence of nasal hyperreactivity and rhinitis medicamentosa (Graf and Juto, 1994).
Risk factors and risk groups	Individuals with increased risk for having RM include those with underlying chronic nasal obstruction, young to middle-aged adults, and those exposed to benzalkonium chloride (Graf, 1999; Ramey et al, 2006).

Risk minimisation measures	Please refer to Section 4.2 (Posology and Method of Administration) and Section 4.4 (Special Warnings and Special Precautions for Use) of the CCDS.
Important Potential Risk: Myocardial infarction when used off-label	
Evidence for linking the risk to the medicine	Coronary arterial constriction—considered an important component in the pathogenesis of acute myocardial ischemia—may be induced by potent vasoactive mediators such as cysteinyl leukotrienes and thromboxane A2, which are produced during acute inflammatory episodes. Drugs with vasoconstrictive properties, such as xylometazoline, may prolong the duration of this effect (Biyik and Ergene, 2006).
Risk factors and risk groups	The following risk factors account for increased odds of suffering myocardial infarction in both genders and across all ages: abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, and psychosocial factors (Yusuf et al, 2004).
Risk minimisation measures	Please refer to Section 4.9 (Overdose) of the CCDS.
Important Potential Risk: Stroke when used off-label	
Evidence for linking the risk to the medicine	Although short term use of topical alpha-2 agonists is not associated with systemic toxicity, long term abuse has been reported to cause systemic vasoconstriction and severe cardiovascular complications (Buysschaert et al, 2011). Ischaemic stroke is a disease entity that in many cases shares a similar pathophysiologic mechanism as ischaemic heart disease, namely arteriosclerosis, which usually affects the patient systemically, thus increasing the risk for both acute stroke and acute coronary syndrome. In both cases, a sudden change of circulation occurs, with resultant decrease in blood supply to the affected part(s) of the brain or heart (Soler and Ruiz, 2010).
Risk factors and risk groups	Reported risk factors for stroke include smoking, obesity, elevated blood pressure, elevated cholesterol, and diabetes mellitus (Kotseva et al, 2009).
Risk minimisation measures	Please refer to Section 4.9 (Overdose) of the CCDS.
Important Potential Risk: Nasal mucosal damage associated with preservative benzalkonium chloride especially following long-term use	
Evidence for linking the risk to the medicine	Benzalkonium chloride is a known dermal irritant and is also known to produce a toxic effect on the mucosal cilia of the rat (Cho et al, 2000), and as such is thought to cause irritation and/or damage to the nasal mucosa. In addition, benzalkonium chloride may increase the risk of developing RM by inducing mucosal swelling (Ramey et al, 2006). A review of 18 studies (14 in vivo, 4 in vitro) evaluating short- and long-term exposure of BKC (at concentrations ranging from 0.00045% to 0.1%) on human nasal epithelia found that 8 studies (including treatment studies lasting for 6 months and 1 year) did not demonstrate any toxic effects associated with BKC, indicating that BKC was neither harmful nor prone to exacerbating RM. In addition, of the 10 studies concluding that BKC resulted in degenerative changes in human nasal epithelia or that BKC exacerbates RM, only 2 of them were supported by statistically significant differences between BKC and the placebo or control group. It is important to note that in both studies, the protocol incorporated the use of oxymetazoline, which is associated with RM, in some or all subjects. The review concluded that intranasal products containing BKC appear to be safe and well tolerated for both long and short term clinical use (Marple et al, 2004).
Risk factors and risk groups	A comprehensive search of published literature did not reveal any studies describing the risk factors for nasal mucosal damage associated with benzalkonium chloride. Individuals with increased risk for having nasal mucosal damage including rhinitis medicamentosa include those

	with underlying chronic nasal obstruction, young to middle aged adults, and those exposed to benzalkonium chloride (Graf, 1999; Ramey et al, 2006).
Risk minimisation measures	Please refer to Section 4.4 (Special Warnings and Precautions for Use) of the SmPC. In relation to other xylometazoline products containing this preservative, the European Commission Volume 3B provides information about potential side effects. The CCDS also contains a statement on maximum recommended duration of use of 7 days and effects of long-term use.
Missing Information: Use during pregnancy or breastfeeding	
Risk minimisation measures	Please refer to Section 4.6 (Pregnancy and Lactation) of the CCDS.

Key: BKC=Benzalkonium chloride; CCDS=Company Core Data Sheet; MAO=Monoamine oxidase; MAOI=Monoamine oxidase inhibitor; OTC=Over-the-counter; RM=Rhinitis medicamentosa; SmPC=Summary of Product Characteristics

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 xylometazoline nasal spray.

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

There are no studies required for xylometazoline nasal spray.