Summary of the risk management plan

Summary of risk management plan for Sialanar (glycopyrronium bromide)

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

Sialanar's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Sialanar should be used.

This summary of the RMP for Sialanar should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Sialanar's RMP.

I. The medicine and what it is used for

Sialanar is authorised for the symptomatic treatment of severe sialorrhoea (chronic pathologic drooling) (see SmPC for the full indication). It contains glycopyrronium as the active substance and it is given orally.

Further information about the evaluation of Sialanar’s benefits can be found in Sialanar’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage https://www.ema.europa.eu/en/medicines/human/EPAR/sialanar.

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

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

II.A List of important risks and missing information

Important risks of Sialanar 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 Sialanar. 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);

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Anticholinergic side effects due to dosing errors o constipation o urinary retention o pneumonia o risk of overheating o cardiac disorders o dental caries o CNS effects
Missing information	• None

II.B Summary of important risks

Important potential risk – Anticholinergic side effects due to dosing errors **Constipation**	
Evidence for linking the risk to the medicine	Constipation is a known adverse event associated with cerebral palsy. A cross-sectional observational study was performed in specialized day-care centres and schools in the Netherlands which included 152 children (81 males, 71 females; mean age 9y 6mo, SD 4y 6mo), Veugelers, 2010. Of the studied population, 57% were constipated and 55% used laxatives, 27% of whom showed symptoms of constipation. In addition, constipation is a known adverse event associated with anticholinergic drugs and was seen in the placebo-controlled efficacy study by Zeller, 2012.
Risk factors and risk groups	• Patients with a history of intestinal obstruction, ulcerative colitis, paralytic ileus, and pre-existing constipation • Long term Sialanar use • Off label use in patients with severe renal failure • Patients receiving concomitant therapy with opioids, other anticholinergic agents, and other medicinal products with anticholinergic properties such as antidepressants and antihistamines. • Patients receiving concomitant therapy with solid oral formulations of potassium chloride.
Risk minimisation measures	Routine risk communication • SmPC section 4.2, 4.4, 4.8, 4.9 • PL section 2, 3, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 Additional risk minimisation measures: • Physician educational material that contains Prescriber checklist • Patient information pack that contains the Reminder card for patient's carer

Important potential risk – Anticholinergic side effects due to dosing errors **Urinary retention**	
Evidence for linking the risk to the medicine	Urinary retention is a recognised side effect of anticholinergic drugs. It is believed to be secondary to their inhibitory effect on bladder contraction in the presence of outlet obstruction, an effect achieved primarily by antagonizing postjunctional excitatory muscarinic receptors [M(2)/M(3)] in the detrusor (Cladellas, 2008). Urinary retention was also seen at in 15% of participants taking glycopyrronium bromide in the placebo-controlled efficacy study by Zeller, 2012.
Risk factors and risk groups	• Long term Sialanar use • Off label use in patients with severe renal failure • Patients receiving concomitant therapy with other anticholinergic agents, and other medicinal products with anticholinergic properties such as antidepressants and antihistamines.
Risk minimisation measures	Routine risk communication • SmPC section 4.2, 4.3, 4.4, 4.8, 4.9 • PL section 2, 3, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Additional risk minimisation measures: • Physician educational material that contains Prescriber checklist • Patient information pack that contains the Reminder card for patient's carer

Important potential risk – Anticholinergic side effects due to dosing errors **Pneumonia**	
Evidence for linking the risk to the medicine	Pneumonia is a known adverse event associated with the use of anticholinergic drugs. Children with the most severe pharyngeal dysphagia are at medical risk due to saliva aspiration to the lungs, which can lead to recurrent episodes of pneumonia (Erasmus, 2012). Pneumonia was reported as one of the treatment-emergent adverse events in the 24 week safety study conducted by Zeller, 2012b. It was one of the TEAEs occurring more frequently in the high-dose (<0.2 mg/kg) and middle-dose (≥0.1 to ≤0.2 mg/kg) than in the low-dose (>0.1 mg/kg) group, 7.9% versus 5.7% versus 0%.
Risk factors and risk groups	• Long term Sialanar use • Off label use in patients with severe renal failure • Patients receiving concomitant therapy with other anticholinergic agents, and other medicinal products with anticholinergic properties such as antidepressants and antihistamines.
Risk minimisation measures	Routine risk communication • SmPC section 4.2, 4.4, 4.8, 4.9 • PL section 2, 3, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Additional risk minimisation measures: • Physician educational material that contains Prescriber checklist • Patient information pack that contains the Reminder card for patient's carer

Important potential risk – Anticholinergic side effects due to dosing errors **Risk of overheating**	
Evidence for linking the risk to the medicine	Hyperthermia and increased body temperature are known adverse effects of anticholinergic drugs due to inhibition of correct sweat gland functions which can produce difficulties in temperature regulation, Bavikatte 2019.

Important potential risk – Anticholinergic side effects due to dosing errors **Risk of overheating**	
Risk factors and risk groups	• Existing pyrexia or exposure to high ambient temperatures • Patients receiving concomitant therapy with other anticholinergic agents, and other medicinal products with anticholinergic properties such as antidepressants and antihistamines.
Risk minimisation measures	Routine risk communication • SmPC section 4.2, 4.4, 4.5, 4.8, 4.9 • PL section 2, 3, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Additional risk minimisation measures: • Physician educational material that contains Prescriber checklist • Patient information pack that contains the Reminder card for patient's carer

Important potential risk – Anticholinergic side effects due to dosing errors **Cardiac disorders**	
Evidence for linking the risk to the medicine	Children with CP frequently have concurrent cardiac abnormalities, higher HR and more ECG abnormalities than normal controls, irrespective of treatment with glycopyrronium (Rankin, 2010; Garne, 2008; Pastore, 2011). Glycopyrronium as an anticholinergic, is expected to increase the HR (Preiss, 1983). In a pooled population of children with problem drooling associated with neurologic conditions, glycopyrrolate oral solution was associated with a moderate increase from baseline in mean systolic blood pressure (+3.4mmHg), a small decrease in mean diastolic blood pressure (-0.3mmHg), and a small (but clinically relevant) increase in mean heart rate (+1.9 beats/min; +10.5 beats/min in the placebo-controlled study alone. No changes in mean respiratory rate or body temperature were observed, and the small increase in mean body weight (+1.15 kg) may be attributed to normal growth over a 6-month study period (Garnock-Jones, 2012).

Important potential risk – Anticholinergic side effects due to dosing errors **Cardiac disorders**	
Risk factors and risk groups	• Long term Sialanar use • Off label use in patients with severe renal failure • Patients with underlying cardiac disorders
Risk minimisation measures	Routine risk communication • SmPC section 4.2, 4.4, 4.8, 4.9 • PL section 2, 3, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 Additional risk minimisation measures: • Physician educational material that contains Prescriber checklist • Patient information pack that contains the Reminder card for patient's carer

Important potential risk – Anticholinergic side effects due to dosing errors **Dental caries**	
Evidence for linking the risk to the medicine	A consequence of hyposalivation is an increased risk of developing dental caries. Lähteenmäki et al studied the effect of i.v. glycopyrronium bromide on oral mucous host defences in 12 healthy male subjects (Lähteenmäki, 2000). After administration of a single dose of i.v. glycopyrronium bromide (4 µg/kg), salivary concentrations of both immunological and non-immunological defence factors were increased. However, their secretion per time (output) decreased as a result of reduced salivary flow rate in comparison with i.v. saline (placebo). Decreased immunoglobulin (Ig) G secretion lasted for at least six hours after glycopyrronium bromide administration, but there were no differences in the output of IgA or IgM three hours after injection compared with placebo. The authors concluded that hyposalivation induced by glycopyrronium bromide causes marked and prolonged impairment of the secretion of oral host defence factors, which may be harmful to patients who have systemic disease or conditions related to hyposalivation. Decreased salivation may also increase the risk of developing oral diseases and make patients susceptible to mucositis, especially candidiasis (Närhi, 1999). A common consequence of reduced salivary flow is an increased risk of dental caries. Therefore, where treatment is to be continued for a considerable period of time, attention to dental care should be encouraged (Arnrup, 1990).
Risk factors and risk groups	• Severe dry mouth
Risk minimisation measures	Routine risk communication • SmPC section 4.2, 4.4, 4.9 • PL section 2, 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 Additional risk minimisation measures: • Physician educational material that contains Prescriber checklist • Patient information pack that contains the Reminder card for patient's carer

Important potential risk – Anticholinergic side effects due to dosing errors **CNS effects**	
Evidence for linking the risk to the medicine	Anticholinergic drugs work by decreasing the volume of saliva secreted from the salivary glands and thus the severity of drooling. Hyoscine (scopolamine) (Lewis, 1994), benztropine mesylate (Camp-Bruno, 1989) and benzhexol (Reddihough, 1990) have all been shown to be useful for controlling drooling in children with neurological disorders. However, their lack of selectivity leads to widespread, undesirable, and often poorly tolerated central and peripheral effects, including restlessness, irritability, drowsiness, constipation, urinary retention, and flushing (Mier, 2000). Glycopyrronium is a quaternary ammonium member of the anticholinergic class of drugs which has also been demonstrated to be effective in reducing sialorrhoea. As a consequence of its quaternary charge, glycopyrronium has limited ability to penetrate the blood brain barrier (Ali-Melkkilä, 1990b; Rautakorpi, 1996) and so in theory centrally mediated adverse effects should be relatively low.
Risk factors and risk groups	• Children with compromised blood brain barrier. • Long term Sialanar use • Off label use in patients with severe renal failure • Patients receiving concomitant medication with other drugs with CNS effects.
Risk minimisation measures	Routine risk communication • SmPC section 4.2, 4.4, 4.8, 4.9 • PL section 2, 3, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Additional risk minimisation measures: • Physician educational material that contains Prescriber checklist • Patient information pack that contains the Reminder card for patient's carer

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 Sialanar.

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

There are no studies required for Sialanar.