North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

Sialanar 320 micrograms/ml Glycopyrronium (400 micrograms/ml Glycopyrronium Bromide) Oral Solution

Verdict:	
Formulary inclusion:	Sialanar® is to be included in the North Staffordshire Joint Formulary
Formulary category:	Amber
Restrictions:	1.For Initiation and stabilisation by a specialist prior to transferring into primary care 2. Prescribe by brand.
Reason for inclusion:	The Committee was satisfied with the evidence for efficacy and safety, dosing convenience, cost implications and intended place in therapy.
Link to formulary:	Primary care: http://www.northstaffordshirejointformulary.nhs.uk/ Secondary care: http://uhns/clinicians/clinical-guidance/clinical-guidelines/prescribing-formularies/
Link to medicine review summary:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians→ Support services → Pharmacy → Joint Formulary Related Documentation → North Staffordshire & Stoke-on-Trent Area Prescribing Committee Medicine Review Summary Verdict Sheets
Link to full review:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians → Support Services → Pharmacy → Joint Formulary Related Documentation → New Medicine Committee (NMC) Medicines Reviews

Author: Xin Wei Tan, Secondary/Primary Care Interface Pharmacist, UHNM Date approved by APC: 27/02/2019

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Review summary:

Formulary application:
Sialanar® is licensed for symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

Effective management of sialorrhoea improves quality of life for patients and carers, reduces risk of dehydration, facial skin maceration, choking, aspiration, pneumonia and respiratory crises. Effective management of sialorrhea also decreases the need for suctioning.

Glycopyrronium bromide is a well-established treatment for sialorrhoea, however until the launch of Sialanar®, a licensed formulation has not been available in the UK. Patients are currently prescribed a range of unlicensed preparations (tablets, injections to be administered orally or via PEG, or oral formulations of various strengths)

It is proposed that Sialanar® will be prescribed following an initial unsuccessful trial of hyoscine patches then hyosicne tablets.

Sialanar® can be prescribed on FP10 prescriptions.

It is predicted up to 30 patients per annum will be prescribed Sialanar® instead of unlicensed glycopyrronium bromide formulations.

If Sialanar® is added to the NSJF, it could save at least £24316.55 across North and South Staffordshire.

Dr Martin Samuels (consultant paediatrician) presented the formulary submission to the New Medicines Committee on 6th February 2019. The formulary application is supported by Dr Caroline Groves (UHNM clinical director for paediatric medicine)

Licensed indications:

Sialanar® is licensed for symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

Dosing:

Dosing table for children and adolescents with normal renal function (dosed tds).

Weight	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4	Dose Level 5
Kg	**(~12.8µg/kg glycopyrronium)** [1]	**(~25.6µg/kg glycopyrronium)** [1]	**(~38.4µg/kg glycopyronnium)** [1]	**(~51.2µg/kg glycopyronnium)** [1]	**(~64µg/kg = glycopyronnium)** [1]
	= 16mcg/kg glycopyrronium bromide	= 32mcg/kg glycopyrronium bromide	= 48mcg/kg glycopyrronium bromide	= 64mcg/kg glycopyrronium bromide	= 80mcg/kg glycopyrronium bromide
	ml	**ml**	**ml**	**ml**	**ml**
13-17	0.6	1.2	1.8	2.4	3
18-22	0.8	1.6	2.4	3.2	4
23-27	1	2	3	4	5
28-32	1.2	2.4	3.6	4.8	6
33-37	1.4	2.8	4.2	5.6	6
38-42	1.6	3.2	4.8	6	6

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43-47	1.8	3.6	5.4	6	6
≥48	2	4	6	6	6

Patients with mild to moderate renal impairment (eGFR <90 - ≥30 ml/min/1.73m^2) should have doses reduced by 30% (see table below)

Dosing table for children and adolescents with mild to moderate renal impairment. (eGFR <90 - ≥30 ml/min/1.73m^2) – dosed tds

Weight	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4	Dose Level 5
Kg	**(~8.8µg/kg glycopyronnium)** [1]	**(~17.6µg/kg glycopyronnium)** [1]	**(~27.2µg/kg glycopyronnium)** [1]	**(~36µg/kg glycopyronnium)** [1]	**(~44.8µg/kg glycopyronnium)** [1]
	= 11 mcg/kg glycopyrronium bromide	= 22mcg/kg glycopyronnium bromide	= 33mcg/kg glycopyronnium bromide	= 45mcg/kg glycopyrronium bromide	=56mcg/kg glycopyrronium bromide
	ml	**ml**	**ml**	**ml**	**ml**
13-17	0.4	0.8	1.2	1.7	2.1
18-22	0.6	1.1	1.7	2.2	2.8
23-27	0.7	1.4	2.1	2.8	3.5
28-32	0.8	1.7	2.5	3.4	4.2
33-37	1	2	2.9	3.9	4.2
38-42	1.1	2.2	3.4	4.2	4.2
43-47	1.2	2.5	3.8	4.2	4.2
≥48	2	2.8	4.2	4.2	4.2

Related guidance:

NICE: Hypersalivation: oral glycopyrronium bromide (Evidence summary [ESUOM15] .Published date: July 2013

SMC: http://www.scottishmedicines.org.uk Sialanar® was approved by the SMC on 10th July 2017.

RDTC: The request for glycopyrronium bromide 2mg/5ml (Sialanar®) was approved for the treatment of severe sialorrhoea in children and adolescents with chronic neurological disorders in October 2017

MTRAC: http://www.keele.ac.uk. Not reviewed by MTRAC

Background information:

Glycopyrronium bromide is well-established in the United Kingdom for the treatment of sialorrhoea in children with neurological disorders. Apart from Sialanar®, the only available formulations In the UK are not licensed to treat hypersalivation.

The overall prevalence of significant sialorrhoea in children is estimated at up to 0.6%. Sialorrhoea is much more common in neurologically impaired children including those with cerebral palsy (CP). It is estimated prevalence of sialorrhoea in neurologically impaired children ranges from 10% to 40% but may be even higher in some subgroups, especially those with quadriplegic CP.

Uncontrolled sialorrhoea can have negative consequences for health and quality of life. Sialorrhoea increases risk of aspiration, pneumonia, choking and acute respiratory crises. Sialorrhoea also leads to dehydration, facial skin maceration and can cause social isolation and damage electronic communication devices.

Currently patients are prescribed glycopyrronium bromide formulations which are not licensed for use in

hypersalivation
-tablets (1mg or 2mg) which may require crushing
- 200mcg/1ml ampoules. The dose is drawn up using a syringe and filter for administration sublingually or via PEG. Some patients require up to 30 ampoules per day.
-unlicensed oral solutions of varying strength (1mg/5ml, 500mcg/5ml, 5mg/5ml and 400mcg/ml)

Efficacy:
Glycopyrronium is a quaternary ammonium antimuscarinic .Antimuscarinics are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves. They also inhibit the action of acetylcholine where smooth muscle lacks cholinergic innervation.

Glycopyrronium competitively inhibits cholinergic muscarinic receptors in salivary glands and other peripheral tissues, thus indirectly reducing the rate of salivation. Glycopyrronium has little effect on cholinergic stimuli at nicotinic acetylcholine receptors, on structures innervated by postganglionic cholinergic neurons, and on smooth muscles that respond to acetylcholine but have no cholinergic innervation.

Glycopyrronium has a long duration of action compared to other antimuscarinics, and is less likely to cause CNS side effects or cardiovascular side effects compared to hyoscine.

As an antisecretory agent, by injection, it is 2 to 5 times more potent than hyoscine hydrobromide . Therefore it may be considered when hyoscine has failed, although efficacy would appear to be similar in clinical practice.

Dr Samuels and his colleagues currently prescribe glycopyrronium bromide following initial unsuccessful trial of hyoscine patches and then hyoscine tablets. In practice he has observed that glycopyrronium bromide can successfully treat patients who previously could not effectively control sialorrhoea with hyoscine.

NICE state there is moderate evidence that oral glycopyrronium bromide (tablets and solution or suspension) reduces hypersalivation (sialorrhoea) or drooling in children and young people with a neurological condition.
There is no evidence of its long-term efficacy or safety in treating hypersalivation. No efficacy data exist to compare different formulations of glycopyrronium or to compare its efficacy to other antimuscarinics used for treatment of hypersalivation.

Although oral absorption is poor, most of the published evidence of efficacy is for administration by the oral route, particularly in children and young adults with neurodevelopmental disabilities, where it has been used with some success in relatively small studies. Parenteral use, mainly by subcutaneous injections or infusion, has also been described for reducing excessive secretions, including saliva, in palliative care.

Mier et. al studied 39 children with neurodevelopmental conditions and severe sialorrhea. Ages at enrollment ranged from 4 years 4 months to 19 years, with a mean age of 10 years 9 months. After an initial physical evaluation and a 1-week baseline medication-free observation period, each child was assigned randomly to either the drug or placebo treatment arm, each of which was 8 weeks long. At the end of the first arm, there was a 1-week washout period and a second week-long observation period, followed by the reciprocal arm, also 8 weeks in length. Drooling was scored on a scale that ranged from 1 (never drools) to 9 (clothing, hands, and objects frequently become wet). Drooling was assessed by the carer 2 hours post dose. Carers were also questioned each week by telephone regarding the presence of any adverse reactions.
There were 2 dosing schedules depending on weight. Children weighing less than 30 kg began at 0.6 mg, increasing weekly to 1.2 mg, 1.8 mg, and 2.4 mg. Children weighing more than 30 kg began by taking 1.2 mg, increasing weekly to 1.8 mg, 2.4 mg, and 3.0 mg. Medication was given in the morning, early afternoon, and evening. Four

children were given these same doses twice (rather than 3 times) daily in the morning and early afternoon, at parental request. No specific recommendations were given with regard to timing of medication and food.
27 children (69%) completed the study. Of the 12 children who did not complete the study, 8 dropped out because of adverse effects to medication, 1 of these while receiving placebo. Four children were dropped because of failure to comply with the protocol or because it was inconvenient for their families to continue.
All 27 children who completed the study demonstrated improvement in drooling. The mean baseline drooling score improved with glycopyrrolate from 7.52 to a maximum mean score of 1.85. A mean score of 1.85 corresponds to a description between "dry, never drools" and "mild drooling; only the lips are wet occasionally." With placebo, the baseline score improved slightly from 7.44 to 6.33. Mean drooling score on glycopyrrolate (1.85) compared with placebo (6.33) is statistically different, with P<.001. Only 2 of the children failed to improve their drooling score by at least 4 points, and only 3 were left with a score of 4 (wet on lips and chin occasionally) or worse.
Drooling scores improved with increasing dose in a linear manner. The mean score for children finishing the study was 6.0 on their first dose level, 4.5 on the second dose level, 3.6 on the third dose level, 2.6 on the fourth dose level, and 2.3 after 4 weeks at their highest dose. Using an improvement-in-drooling score of 4 points or greater as a standard for significant clinical improvement, 12%, 38%, 54%, and 81% of study participants met this standard on the first, second, third, and fourth dosing levels, respectively
The children were maintained at their highest tolerated dose for 4 weeks to determine if drug effects changed during that period; the drooling score improved in 9 children, decreased in 9, and remained the same in 9.
Six (22%) of the 27 children who completed the study achieved their best drooling score while receiving doses lower than their fourth dosing level. Four of these 6 reached their best score 1 dosing level below their highest tolerated level. One child reached the best drooling score 2 dosing levels below the highest tolerated level, and another child reached the best score on the first dosing level.
Of the caretakers who responded, 15 (65%) of 23 reported that their child exhibited less drooling odor while receiving glycopyrrolate compared with the placebo, and 21 (87%) of 24 caretakers reported improved dryness of clothing compared with placebo
Adverse effects were common, affecting 25 (69%) of 36 children taking glycopyrrolate. The most frequently noted adverse reactions included behavioral changes (9 children), constipation (7), excessive dryness of the mouth or secretions (7), and urinary retention (5). One child with a history of seizures exhibited worsening symptoms while receiving glycopyrrolate, although the child did finish the study. Adverse effects were most frequently reported as the dose was increased. Five (26%) of 19 children reported at least 1 adverse effect at the third dosing level, and 21 (81%) of 26 reported at least 1 adverse effect at the fourth (highest) dosing level. This dramatic increase in the number of children with at least 1 adverse effect occurred between dosing levels corresponding to 0.08 mg/kg per dose (third level) and 0.11 mg/kg per dose (fourth level).
The study concluded all children tolerating glycopyrrolate will demonstrate marked improvement in drooling at individual doses of about 0.1 mg/kg per dose. Individual doses of glycopyrrolate greater than 2.4 mg for children weighing less than 30 kg, and 3.0 mg for children weighing more than 30 kg, were not studied for safety but are not usually necessary.

Zeller, Cavanaugh et. al investigated the efficacy of glycopyrronium oral solution (1mg/5ml) in 36 patients aged 3-16 years old with neurologic conditions associated with problem drooling.The trial was randomised and placebo controlled. Data from this trial were used to demonstrate efficacy for Sialanar®. Patients were randomised to receive matching placebo or glycopyrronium 20 microgram/kg three times a day titrated over 4 weeks to a maximum dose of 100 microgram/kg or 1.5 - 3mg per dose (based on weight) three times a day, whichever was less, and remained on that dose for a further 4 weeks. Doses were administered at least one hour before or two hours after meals, since high-fat foods reduce the oral bioavailability of glycopyrrolate oral solution administered shortly after a meal. The mean daily dose of glycopyrronium was 150 microgram/kg. At week 8, 14 of 19 patients (73.7%) in the glycopyrronium group and 3 of 17 (17.6%) in the placebo group showed at least a 3-point improvement in the modified Teacher's Drooling Scale (mTDS) score (p=0.0011). The most common adverse reactions were dry mouth, vomiting, nasal congestion and constipation. One patient in each treatment group

withdrew from the study due to adverse effects

Zeller, Davidson et al. conducted a 24-week open-label study investigated the safety and efficacy of glycopyrronium 1mg/5ml oral solution in 137 patients aged 3-18 years with cerebral palsy, mental retardation, or any other neurologic impairment or condition with chronic drooling After a washout, screening period and 2-day baseline period, patients received 20 microgram/kg glycopyrronium three times daily, titrated by 20 microgram/kg every 5-7 days for 4 weeks to an optimal dose or a maximum dose of 100 microgram/kg (maximum dose 3mg three times a day). The mean daily glycopyrronium dose was 150 microgram/kg. The most commonly reported adverse effects included constipation, vomiting, diarrhoea and pyrexia and four serious treatment-related adverse events were observed (nystagmus, oesophageal candidiasis, dehydration and gastrointestinal motility disorder). Of the 34 patients who did not complete the study, 14 withdrew due to adverse effects. At 24 weeks, 52.3% (95% confidence interval 43.7 to 60.9) of patients had an at least three-point decrease in mTDS from baseline and were classified as responders. 15% of patients no longer drooled

There are also 4 case reports involving use of oral glycopyrronium (tablets, oral solution) or injection vial nebuliser to manage sialorrhoea in adults. All case studies report that the patients had improvement in symptoms whilst using glycopyrronium. The 3 case reports involving oral glycopyrronium record that the patients had no apparent ill effects whilst on treatment. Reported treatment duration ranged from 9 weeks to 6 months. 1 case report states that profuse drooling occurred when treatment with glycopyrronium tablets was withdrawn, but was unable to rule out if this was coincidental. The 1 case report involving nebulised glycopyrronium states that there was an improvement in drooling and treatment was tolerated for 2 months (treatment was discontinued due to rash around mouth).

Safety:
Undesirable effects may be minimised by using the lowest effective dose necessary to control symptoms.
These side effects are dry mouth, urinary retention, constipation and confusion, which are reported for other antimuscarinic agents.

Contraindications are similar to that for glycopyrronium preparations currently used.

- Hypersensitivity to the active substance or to any of the excipients
- Pregnancy and breast-feeding.
- Glaucoma.
- Urinary retention.
- Severe renal impairment (eGFR <30 ml/min/1.73m2), including those with end-stage renal disease requiring dialysis.
- History of intestinal obstruction, ulcerative colitis, paralytic ileus, pyloric stenosis and myasthenia gravis.
- Concomitant treatment with
    - potassium chloride solid oral dose

  (Glycopyrronium may potentiate the risk of upper gastrointestinal injury associated with oral solid formulations of potassium chloride due to increased gastrointestinal transit time creating a high localized concentration of potassium ions. An association with upper GI bleeding and small bowel ulceration, stenosis, perforation, and obstruction has been observed)
    - anticholinergics

Place in therapy:
It is proposed that Sialanar® will be prescribed following an initial unsuccessful trial of hyoscine patches then hyoscine tablets.

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Cost:
It is estimated 30 patients per annum would be prescribed Sialanar®

Average purchase price of Sialanar® in primary care (400mcg/ml – 250ml bottle – expires 2 months after opening) = [redacted]
This equates to [redacted] per 400mcg/ml
If patients are using Sialanar® regularly on a daily basis, one bottle will last 14-28 days.

Weight	**Maximum dose (nb can be administered up to tds)**	Maximum daily dose	Daily cost per patient in primary care	Cost per patient pa in primary care
Kg	**(~64µg/kg = glycopyronnium)** [1]			
	= 80mcg/kg glycopyrronium bromide			
	ml	**ml**		
13-17	3	9	[redacted]	[redacted]
18-22	4	12	[redacted]	[redacted]
23-27	5	15	[redacted]	[redacted]
28-32	6*	18	[redacted]	[redacted]
33-37	6	18	[redacted]	[redacted]
38-42	6	18	[redacted]	[redacted]
43-47	6	18	[redacted]	[redacted]
≥48	6	18	[redacted]	[redacted]

It is difficult to determine how many patients are within each dose band, and thus the cost per patient.

Assuming each patient incurs a maximum cost of £7818.30 per annum if prescribed Sialanar®, it is presumed that annual expenditure for 30 patients would be £234,549.

Expenditure for glycopyrronium bromide formulations for this cohort from October 2017 to September 2018 was £258,865.55

It is therefore predicted that introducing Sialanar® to the NSJF will result in a minimum cost saving of £24316.55 for North and South Staffordshire, but this is may be greater.

References:

1. Summary of Product Characteristics - Sialanar 320 micrograms/ml Glycopyrronium (400 micrograms/ml Glycopyrronium Bromide) Oral Solution. Last updated 20th April 2017. Accessed via www.medicines.org.uk on 8th October 2018
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3. UKMI – "Hypersalivation – can glycopyrronium be used to treat it?" 8th May 2017
4. https://bnfc.nice.org.uk/drug/glycopyrronium-bromide.html Accessed 23/10/2018
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8. Zeller RS, Davidson J, Lee H-M et al. Safety and efficacy of glycopyrrolate oral solution for management of pathologic drooling in pediatric patients with cerebral palsy and other neurologic conditions. Therapeutics and Clinical Risk Management 2012;8:25-32.