NICE advice

Severe sialorrhoea (drooling) in children and young people with chronic neurological disorders: oral glycopyrronium bromide

Evidence summary
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Key points

The content of this evidence summary was up-to-date in February 2017. See the summary of product characteristics (SPC) or British national formulary (BNF) for up-to-date information.

Regulatory status: new medicine. Glycopyrronium bromide (Sialanar) is an antimuscarinic (anticholinergic) medicine licensed in September 2016 for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. Sialanar is licensed for short-term intermittent use and is only licensed in children. There is limited clinical trial evidence on the use of glycopyrronium in adults with sialorrhoea. Sialanar 320 micrograms/ml oral solution is the first formulation of glycopyrronium bromide licensed for this indication in the UK.

This evidence summary discusses 2 small randomised controlled trials (RCTs) that compared glycopyrronium bromide with placebo for the treatment of severe sialorrhoea in children and young people with chronic neurological conditions. The majority of participants had cerebral palsy.

In both RCTs, participants treated with glycopyrronium bromide had statistically significantly improved drooling after 8 weeks, (measured using the modified Teacher's Drooling Scale [mTDS]), compared with placebo.

Adverse effects were common with glycopyrronium bromide, mostly due to its anticholinergic action. The most commonly reported adverse effects include dry mouth, constipation, urinary retention, reduced bronchial secretions and flushing. The SPC advises that glycopyrronium bromide can cause thickening of secretions, which may increase the risk of respiratory infection and pneumonia. Glycopyrronium bromide should be used with caution in people with heart problems due to its potential increase in heart rate, blood pressure and rhythm disorders (SPC: glycopyrronium).

There is a lack of long-term safety data for glycopyrronium bromide, and the SPC recommends that the total treatment duration should be kept as short as possible.

It is not possible to determine the relative effectiveness of glycopyrronium bromide compared with other treatments for severe sialorrhoea because glycopyrronium has only been compared to placebo. Because Sialanar is not bioequivalent to other formulations of glycopyrronium bromide, switching to Sialanar should only be conducted under supervision to ensure that efficacy and side effects are balanced. The effectiveness of glycopyrronium bromide should be balanced against the adverse effects associated with treatment.

A summary to inform local decision-making is shown in table 1.

Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

Effectiveness • After 8 weeks treatment, oral glycopyrronium bromide significantly improved drooling, measured using the mTDS, in children and young people with neurological conditions, compared with placebo (2 RCTs, n=77). • One RCT had a high drop-out rate (12/39, 31%), and children who did not complete the study were not included in the efficacy analysis, which may have introduced bias (Mier et al. 2000).

Safety

- The SPC states that adverse effects are common with glycopyrronium bromide due to its anticholinergic action. The most common adverse reactions include dry mouth, constipation, diarrhoea, vomiting, urinary retention, flushing and nasal congestion.
- The SPC advises that anticholinergic adverse effects may be dose dependent and difficult to assess in a child with disabilities. Treatment should be stopped in the event of constipation, urinary retention or pneumonia.
- Due to the lack of long term safety data, glycopyrronium bromide is recommended for short-term intermittent use only.

Patient factors

- Glycopyrronium bromide was associated with more adverse effects and discontinuations because of adverse effects than placebo.
- The SPC recommends that glycopyrronium bromide should be taken at least one hour before or at least two hours after meals or at consistent times with respect to food intake.
- Most children in the clinical trials had cerebral palsy. Glycopyrronium has not been extensively tested in children with other neurological conditions.

Resource implications

- Glycopyrronium bromide 400 microgram/ml oral solution (Sialanar) costs £320 per 250 ml bottle (MIMS, February 2017). At a dose of 1,600 micrograms (4 ml) three times daily the 28-day cost is £430.08 (based on a child weighing 33 kg at a dose of 48 micrograms/kg glycopyrronium bromide).
- Once opened the bottle has a shelf life of 28 days. Any liquid remaining after this time should be discarded.
- The manufacturer estimates that there are approximately 1,500 children in England who may be eligible for treatment with glycopyrronium bromide.

Introduction and current guidance

Sialorrhoea (chronic pathological drooling) may present in children and young people with a neurological disorder, such as cerebral palsy. Chronic drooling is the unintentional loss of saliva from the mouth. Although drooling is normal in infants, it usually stops by 15 to 18 months, and is

considered pathological if it is present after 4 years (Zeller et al. 2012a). Drooling can result in perioral chapping, irritation, maceration and secondary infection of the skin. The prevalence of moderate-to-severe drooling in children, young people and adults with neurological conditions, particularly cerebral palsy, is estimated to be between 10% and 37% (Zeller et al. 2012a; Mier et al. 2000).

The NICE guideline on cerebral palsy in under 25s recommends considering anticholinergic medication to reduce the severity and frequency of drooling in children and young people with cerebral palsy. The guideline recommends glycopyrronium bromide (oral or by enteral tube), transdermal hyoscine hydrobromide or trihexyphenidyl hydrochloride (for children with dyskinetic cerebral palsy, but only with input from specialist services).

Product overview

Mode of action

Glycopyrronium bromide is an antimuscarinic (anticholinergic) medicine that reduces salivary secretions. It has limited ability to penetrate the blood brain barrier, although the extent of penetration is unknown (SPC: glycopyrronium).

Regulatory status

Glycopyrronium bromide (Sialanar) received a European marketing authorisation in September 2016 and was launched in the UK in January 2017. Each millilitre (ml) of Sialanar 320 micrograms/ml oral solution contains 400 micrograms glycopyrronium bromide. Glycopyrronium bromide 400 microgram/ml oral solution is licensed for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders (SPC: glycopyrronium).

Although glycopyrronium bromide is used in clinical practice, Sialanar is the first preparation licensed for this indication in the UK. Previously, people requiring treatment with glycopyrronium bromide have used imported products (including the US product Cuvposa) or formulations made by specials manufacturers. The different formulations of glycopyrronium bromide are not bioequivalent (see dosing information).

Dosing information

The SPC states that each millilitre (ml) of oral solution contains 400 micrograms of glycopyrronium bromide, equivalent to 320 micrograms of glycopyrronium. Care should be taken when calculating the dose of Sialanar, with particular attention to whether the dose is expressed as glycopyrronium or glycopyrronium bromide. The dosing schedule is based on the weight of the child, starting with approximately 12.8 micrograms/kg glycopyrronium per dose (equivalent to 16 micrograms/kg of glycopyrronium bromide per dose) three times daily and increasing the dose every 7 days using the dosing table (see table 1 in the SPC).

Dose titrations should be carried out in discussion with the parent or carer to assess both efficacy and adverse effects until an acceptable maintenance dose is achieved. The maximum single dose is 64 micrograms/kg body weight of glycopyrronium or 6 ml (1,900 micrograms glycopyrronium, equivalent to 2,400 micrograms glycopyrronium bromide) three times daily, whichever dose is less (SPC: glycopyrronium).

Food reduces the absorption of glycopyrronium bromide, and the SPC advises that it should be taken at least 1 hour before food or at least 2 hours after meals, or at consistent times with respect to food intake. Specialists involved in developing this evidence summary advised that this dosing regimen may be challenging in children requiring assisted feeding or in those with a gastrostomy, and particular care should be taken when determining the most effective dosing regimen for these children.

In children and young people with mild to moderate renal impairment (eGFR 30–90 ml/min/1.73m^2) the dose should be reduced by 30% (see dosing table 2 in the SPC).

The EPAR for Sialanar reports on a bioavailability study conducted by the manufacturer in healthy adults. It found that Sialanar is approximately 25% more bioavailable compared with Cuvposa, the glycopyrronium bromide formulation licensed in the US and used in 2 studies by Zeller et al (2012a and 2012b). Because of the difference in bioavailability the dose of Sialanar is approximately 20% lower than the recommended dose of the Cuvposa.

Cost

The company has advised that Sialanar costs £320.00 for a 250 ml bottle (MIMS, February 2017). The manufacturer estimates that the average dosage of glycopyrronium bromide is likely to be 1,600 microgram (4 ml) three times daily. This equates to a 28-day cost of £430.08.

Once opened a bottle of Sialanar has a shelf life of 28 days. Any liquid remaining after this time should be discarded.

Evidence review

A literature search was conducted which identified 62 references (see search strategy for full details). These references were screened using their titles and abstracts and 11 references were obtained and assessed for relevance.

Two randomised controlled trials (RCTs) identified from the search (Mier et al. 2000 and Zeller et al. 2012a) were included in this evidence summary. A summary of the included studies is shown in table 2 (see evidence tables for full details).

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Mier et al. (2000) RCT	Children and young people (aged 4 years and over) with neurological conditions and severe sialorrhoea (n=39)	Glycopyrronium bromide vs. placebo (cross-over study)	Change in mean mTDS score, from baseline to maximum (best) score[a]
Zeller et al. (2012a) RCT	People aged 3 to 23[b] years with cerebral palsy or another neurological condition and severe sialorrhoea (n=38)	Glycopyrronium bromide (n=20) vs. placebo (n=18)	Responder rate (percentage of patients with an improvement of 3 points or more in mTDS score)
[a] The authors do not explicitly state that this is this is the primary outcome of the study, although this is reported first in the paper. [b] After randomisation the study protocol was amended, with a revised upper age limit of 16 years. Two participants were over 16 years and excluded from the efficacy analysis.			
Abbreviations: RCT, Randomised controlled trial; mTDS, modified Teachers Drooling Scale.			

The remaining 8 references were excluded. These are listed in excluded studies with reasons for their exclusion.

Clinical effectiveness

This evidence summary is based on 2 double-blind, placebo-controlled RCTs of children and young people with chronic neurological disorders and severe sialorrhoea (defined in Zeller et al. 2012a as drooling in the absence of treatment such that clothing became damp approximately 5 to 7 days per week). Both studies had an 8 week treatment duration, which included a 4 week dose titration phase.

The formulations of glycopyrronium bromide used in the 2 RCTs were not the new licensed formulation of glycopyrronium bromide (Sialanar). However, in line with Article 10(a) of Directive 2001/83/EC, license applications for a medicine that has a well-established use with a recognised efficacy and safety profile, can be supported by a bibliographic application that does not require the manufacturer to carry out new clinical trials with their formulation of the drug (EPAR: glycopyrronium).

Mier et al. (2000)

Mier et al. (2000) was a dose-ranging, crossover RCT in 39 children and young people aged 4 to 19 years with neurological conditions and severe sialorrhoea. Participants were randomised to 8 weeks of oral glycopyrronium bromide capsules or placebo capsules 3 times daily. This was followed by a 1-week washout period and a second 1-week observation period, then a crossover to 8 weeks of the alternative intervention.

The initial glycopyrronium bromide dose was based on the participant's weight, and increased weekly over 4 weeks. Doses were increased according to a pre-defined schedule unless adverse effects occurred or desired 'dryness' (defined by the parent or carer) occurred. The maximum tolerated dose was then continued for a further 4 weeks.

Over 8 weeks there was a statistically significant improvement in the primary outcome of mean modified Teacher's Drooling Scale (mTDS) score with glycopyrronium bromide (from a mean baseline score of 7.52 to a maximum [best] mean score of 1.85) compared with placebo (from a score of 7.44 to 6.33), with a difference between groups of 4.48 points ($p<0.001$, 95% confidence interval [CI] not reported).

Glycopyrronium bromide appeared to have a dose–response relationship, with participants on the lowest doses of glycopyrronium bromide at the end of the study having the highest mTDS score (indicating more severe drooling), while participants on the higher doses had lower mTDS scores.

Zeller et al. (2012a)

Zeller et al. (2012a) was an RCT in 38 people aged 3 to 23 years with cerebral palsy or another neurological condition, and severe sialorrhoea. Participants were randomised to 8 weeks of 3 times daily glycopyrronium bromide oral solution or placebo oral solution. The initial glycopyrronium bromide dose was based on weight and increased weekly for 4 weeks until the optimal tolerated response was achieved. Participants then continued on the same dose for a further 4 weeks.

After 8 weeks there was a statistically significant improvement in the primary outcome of 'responder rate' (the proportion of participants with an improvement of at least 3 points in mTDS score with glycopyrronium bromide (14/19, 73.7%) compared with placebo (3/17, 17.6%, p=0.001). A statistically significant difference in responder rate was also observed after 2 weeks treatment in the glycopyrronium bromide group (52.6%) compared with the placebo group (0%, p=0.0007).

Mean improvements in mTDS score at 8 weeks were statistically significantly greater with glycopyrronium bromide (3.94 points, 95% CI 2.97 to 4.91) compared with placebo (0.71 points, 95% CI −0.43 to 1.84, p<0.0001), with a difference between groups of 3.23 points.

Statistically significant differences were observed for the global assessments of study medication by investigators and parents or carers. In the glycopyrronium bromide group 84.2% of investigators and 100% of parents or carers felt that the treatment was worthwhile, compared with 41.2% of investigators (p=0.014) and 56.3% of parent or carers in the placebo group (p=0.0017).

An overview of the results for clinical effectiveness can be found in results tables.

Safety and tolerability

The SPC advises that glycopyrronium bromide is contraindicated in children and young people with glaucoma, urinary retention, severe renal impairment, a history of intestinal obstruction, ulcerative colitis, paralytic ileus, pyloric stenosis and myasthenia gravis. Concomitant treatment with oral forms of potassium chloride and other anticholinergics is also contraindicated (SPC: glycopyrronium).

The SPC reports that adverse effects are common with glycopyrronium bromide due to its anticholinergic effects. The SPC states that the most common anticholinergic adverse effects in the RCTs were dry mouth, constipation, diarrhoea and vomiting, all occurring at a rate of 15% or higher. Other common anticholinergic symptoms include urinary retention, flushing and nasal congestion.

The SPC advises that anticholinergic effects may be dose dependent and difficult to assess in a child with disabilities. Monitoring by clinicians and carers is required, and the parent or carer should stop treatment and seek advice from the prescriber in the event of:

- constipation
- urinary retention
- pneumonia
- allergic reaction
- pyrexia
- very hot weather
- changes in behaviour.

After evaluation of the adverse effect, a decision should be made about whether glycopyrronium bromide should be discontinued or restarted at a lower dose.

The EPAR notes that central nervous system effects have been reported with glycopyrronium bromide. The clinical significance of this in children with neurological disorders is uncertain. In addition, the EPAR states that there is no information on neurodevelopment or growth in children, which may be affected, particularly when treatment is taken long-term or in repeated episodes.

The EPAR states that it is uncertain whether the plasma concentration of glycopyrronium bromide in children and young people with neurological conditions would have a clinically relevant effect on blood pressure or heart rate. This means there is uncertainty about the cardiovascular safety of glycopyrronium bromide in this population. The SPC advises caution in children with acute myocardial infarction, hypertension, coronary artery disease, cardiac arrhythmias and conditions characterised by tachycardia. The parent or carer should be advised to measure the pulse rate if the child seems unwell and report a very fast or very slow heart rate.

The EPAR also notes that pneumonia appears to be associated with glycopyrronium bromide use, although there is insufficient information on the severity of this adverse effect. Glycopyrronium bromide can dry bronchial secretions and cause the formation of thick mucus, especially when given at inappropriate doses, which may increase the risk of a person developing pneumonia.

The SPC notes that reduced salivation can increase the risk of oral cavities and periodontal diseases, and it is important that people treated with glycopyrronium bromide receive adequate daily dental hygiene and regular dental health checks.

In Mier et al. 2000 adverse effects were reported for 25 out of 36 participants (69%) while taking glycopyrronium bromide compared with 5 out of 30 participants (17%) while taking placebo (no statistical analysis reported). Four of the 7 participants who dropped out while taking glycopyrronium bromide did so before the end of the first week while on the lowest dose. More participants experienced adverse effects as the dose increased, with only 14% of participants reporting adverse events at the lowest dose, compared with 81% at the highest dose. No hospital admissions or deaths were reported.

In Zeller et al. (2012a), adverse effects occurring during treatment were reported in all (20/20; 100%) participants receiving glycopyrronium bromide compared with 15 out of 18 (83.3%) receiving placebo (no statistical analysis reported). Four people (20%) in the glycopyrronium bromide group had at least 1 severe adverse effect occurring during treatment compared with none in the placebo group.

The SPC notes that published safety data are not available beyond 24 weeks treatment duration. Given the limited long-term safety data and the uncertainties around the potential risk of carcinogenicity, the SPC advises that the total treatment duration should be kept as short as possible.

An overview of the results for safety and tolerability can be found in results tables.

Evidence strengths and limitations

Two double-blind, placebo-controlled RCTs were identified as relevant, evaluating the efficacy of oral glycopyrronium bromide for treating severe sialorrhoea in children and young people with a neurological condition (Mier et al. 2000 and Zeller et al. 2012a). Neither of the RCTs described allocation concealment. In addition, no description of the randomisation method was provided in Mier et al. (2000).

Zeller et al. (2012a) used a modified intention to treat (ITT) analysis, defined as all randomised participants who were within the age range of the final amended protocol and received at least 1 dose of study treatment, with lowest rank observations carried forward for any participants who dropped out of the study.

In Mier et al. (2000), efficacy analyses were not based on the ITT population, but on the population of participants who completed the study. The authors do not describe this population in detail and no account is given for the participants who dropped out. By not including participants who dropped out of the study in the efficacy analysis, the investigators may have introduced bias. For example, if participants had dropped out because of lack of effectiveness, excluding these people from the analysis could result in an overestimate of the effectiveness of the treatment. The EPAR reports that the company presented an analysis of all 39 randomised participants, using a baseline observation carried forward approach for the 12 people who did not complete the study. This analysis reduced the treatment effect from an improvement of 4.56 points in mTDS score to 3.06 points, but it is not clear whether the difference between groups remained statistically significant.

Furthermore, the EPAR states that the statistical tests used in Mier et al. (2000) were sub-optimal for a cross-over study, noting that the standard test would be analysis of variance (ANOVA).

Both trials used the efficacy outcome measure of mTDS, a 9-point drooling rating scale that was reported by the person, parent or carer as a measure of the severity and frequency of drooling. No objective measure was used to quantify the amount of drooling in any of the trials. The subjective nature of this outcome evaluation is a limitation of all the studies.

The 2 RCTs were short-term, with a treatment duration of 8 weeks. They do not provide evidence for the safety and efficacy of long-term use of glycopyrronium bromide for managing severe sialorrhoea in children and young people. In a longer open-label non-randomised study (Zeller et al. 2012b) 52.3% (95% CI 43.7% to 60.9%) of participants responded to treatment (improvement of ≥3 points in mTDS score) at 24 weeks. However, as this study did not include a placebo group, firm conclusions on the long-term effectiveness of glycopyrronium bromide cannot be drawn.

In addition, both RCTs were small, including 40 or fewer participants, and neither study reports whether a power calculation was carried out to support the small sample size.

There was also variation in the severity of the different neurological conditions among participants. Most of the participants in the studies had cerebral palsy so it is difficult to assess the effectiveness or safety of glycopyrronium bromide in children and young people with a neurological condition other than cerebral palsy. However, cerebral palsy is the most common cause of physical disability in children and young people in the developed world.

Glycopyrronium bromide has not been compared to other active treatments for severe sialorrhoea in a published study. However, the EPAR advises that the choice of comparator was supported since no other medicine for severe sialorrhoea has been extensively authorised in the European Union.

In both RCTs previous use of glycopyrronium bromide was permitted, which may have introduced bias. However, the EPAR notes that in Zeller et al. 2012a the number of participants who had previously taken glycopyrronium bromide was similar between treatment groups, and in Mier et al. (2000) only 5 people had been treated previously. In Mier et al. (2000), most parents indicated that they knew when their child was receiving glycopyrronium bromide because of the improvement in drooling. This could have biased both the efficacy results and the reporting of adverse effects.
In Zeller et al. (2012a), because children and young people receiving placebo would be expected to continue drooling chronically, parents and carers were specifically encouraged to keep them in the study until at least the end of the 4-week titration period.

An overview of the quality assessment of each included study can be found in evidence tables.

Estimated impact for the NHS

Other treatments

Other medicines that have been used to manage sialorrhoea include the following (Specialist Pharmacy Service, 2015):

- other antimuscarinic medicines (for example hyoscine hydrobromide, amitriptyline, atropine and trihexyphenidyl hydrochloride)
- beta-blockers (for example, propranolol)
- botulinum toxin.

None of these medicines are licensed in the UK for managing sialorrhoea and their use would be off-label.

Costs of other treatments

See table 3 for the costs of other treatments in comparison to Sialanar.

Table 3 Costs of other treatments

Medicine	Usual dose[a]	28-day cost (excluding VAT)

Glycopyrronium bromide 400 micrograms/ml oral solution (Sialanar)	1,600 micrograms (4 ml) three times daily	£430.08[b]
Hyoscine hydrobromide 150 microgram tablets (Kwells Kids)[c]	150 micrograms three times daily	£11.69[d]
Hyoscine hydrobromide 1.5 mg/72 hours patches (Scopoderm)[c]	Apply every 72 hours	£23.19[d]

[a] Doses shown do not represent the full range that can be used and do not imply therapeutic equivalence.

[b] Costs based on MIMS, February 2017; excluding VAT.

[c] Not licensed for the treatment of sialorrhoea; use would be off-label.

[d] Costs based on Drug Tariff, January 2017; excluding VAT.

Current or estimated usage

Proveca, the manufacturer of glycopyrronium bromide (Sialanar) estimates that there are approximately 18,595 children in England with cerebral palsy, of whom 15% (2,789 children) are estimated to have severe sialorrhoea. The manufacturer estimates that about 55% of these children will be eligible for treatment, giving a potential treated population of 1,534 children.

Likely place in therapy

The NICE guideline on cerebral palsy in under 25s recommends considering anticholinergic medication to reduce the severity and frequency of drooling in children and young people with cerebral palsy. The guideline recommends glycopyrronium bromide (oral or by enteral tube), transdermal hyoscine hydrobromide or trihexyphenidyl hydrochloride (for children with dyskinetic cerebral palsy, but only with input from specialist services).

The results of the 2 RCTs in this evidence summary involving a total of 77 children and young people with neurological conditions and severe sialorrhoea found after 8 weeks treatment glycopyrronium bromide reduced drooling (measured using the modified Teacher's Drooling Scale [mTDS]) compared with placebo. There are no studies supporting the chronic use of glycopyrronium bromide for this indication, and the maximum duration of treatment is 24 weeks (EPAR: glycopyrronium). Adverse effects are more common in people treated with glycopyrronium bromide compared with placebo. Many adverse effects are due to glycopyrronium bromide's anticholinergic action, which include dry mouth, constipation, diarrhoea and urinary retention.

Anticholinergic effects are common with glycopyrronium bromide, may be dose dependent and difficult to assessment in a disabled child (SPC: glycopyrronium).

The majority of participants in the 2 RCTs had cerebral palsy, it is not known if the efficacy and safety results observed in these people will be the same in children with other neurological conditions. Although some participants in the 2 RCTs had previously received medicines to treat sialorrhoea, including glycopyrronium bromide, details of the treatments are not provided. It is not known whether glycopyrronium bromide is an effective treatment for people who have failed to respond to other treatments.

Glycopyrronium bromide oral solution is the first and only medicine licensed in the UK for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. Sialanar is only licensed in children, there is limited clinical trial evidence on the use of glycopyrronium in adults with sialorrhoea. Although glycopyrronium bromide has been used in the UK for many years for this indication, this has been through the use of unlicensed products or preparations made by specials manufacturers. The General Medicine Council's good practice guidelines recommends that prescribers should usually prescribe medicines in accordance with the terms of their license, and that the use of unlicensed medicines should generally be limited to when there is no suitable licensed medicine.

Despite glycopyrronium bromide being used for many years in the UK, the EPAR highlights that it has been primarily used in adults, in both acute and chronic settings and in formulations than Sialanar. The adverse effect profile established in other populations cannot be applied to children with chronic neurological disorders, many of whom have multimorbidity. In addition, each formulation of glycopyrronium bromide has its own bioavailability profile. Sialanar is not bioequivalent to other formulations of glycopyrronium bromide and switching to Sialanar should only be conducted under supervision to ensure that efficacy and side effects are balanced.

The 2 RCTs measured patient-oriented primary outcomes that reported on improvements in drooling, although neither study measured quality of life. The EPAR summarises the results of a mapping exercise that estimated the effect of drooling on quality of life in people with cerebral palsy. The EPAR concluded that quality of life was clearly affected in children with cerebral palsy who had a drooling problem, compared with children who did not drool.

It is not possible to determine the relative effectiveness of glycopyrronium bromide compared with other treatments for severe sialorrhoea because glycopyrronium bromide has only been compared to placebo in all published RCTs. In Zeller et al. (2012a) participants treated with glycopyrronium

bromide had a mean mTDS score of approximately 7 at baseline (severe symptoms- drools to the extent that clothing becomes damp; frequently), which improved after 8 weeks treatment to a score of approximately 3 (mild symptoms- only the lips are wet; frequently). The effectiveness of glycopyrronium bromide should be balanced against the adverse effects associated with the treatment (EPAR: glycopyrronium).

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

Relevance to other NICE programmes

This use of glycopyrronium bromide is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

The NICE guideline on cerebral palsy in under 25s recommends considering anticholinergic medication to reduce the severity and frequency of drooling in children and young people with cerebral palsy. The guideline recommends glycopyrronium bromide (oral or by enteral tube), transdermal hyoscine hydrobromide or trihexyphenidyl hydrochloride (for children with dyskinetic cerebral palsy, but only with input from specialist services).

NICE has issued a guideline on spasticity in under 19s. This guideline does not make recommendations on the management of sialorrhoea.

The NICE evidence summary on hypersalivation: oral glycopyrronium bromide discusses the use of glycopyrronium bromide in adults with Parkinson's disease and in adults with schizophrenia and clozapine-induced hypersalivation (unlicensed indications).

References

Mier RJ, Bachrach SJ, Lakin RC et al. (2000) Treatment of sialorrhea with glycopyrrolate: a double-blind, dose-ranging study. Archives of Pediatrics and Adolescent Medicine 154: 1214–8

Zeller RS, Lee HM, Cavanaugh PF et al. (2012a) Randomized phase III evaluation of the efficacy and safety of a novel glycopyrrolate oral solution for the management of chronic severe drooling in children with cerebral palsy or other neurologic conditions. Therapeutics and Clinical Risk Management 8: 15–23

Zeller RS, Davidson J, Lee HM et al. (2012b) 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 8: 25–32

Evidence tables

Table 4 Mier et al. (2000)

Study reference	Mier RJ, Bachrach SJ, Lakin RC et al. (2000) Treatment of sialorrhea with glycopyrrolate: a double-blind, dose-ranging study. Archives of Pediatrics and Adolescent Medicine 154: 1214–8
Unique identifier	Not known
Study type	RCT
Aim of the study	To evaluate the efficacy and safety of glycopyrronium bromide in the treatment of children with developmental disabilities with sialorrhoea
Study dates	Not stated in the published study. The EPAR reports that the study was conducted from 1998 to 1999
Setting	US (2 centres)
Number of participants	n=39 randomised (27 included in efficacy analysis)
Population	Children and young people aged 4 years and older (mean age 10 years 9 months) with neurodevelopmental conditions and severe sialorrhoea[a]

Inclusion criteria	Children aged 4 years and older, with neurodevelopmental conditions and severe sialorrhoea
Exclusion criteria	Not reported
Intervention(s)	2 dosing regimens of glycopyrronium bromide capsules[b], based on the weight of the child: • <30 kg: 0.6 mg three times daily, increased weekly by 0.6 mg up to 2.4 mg at week 4 • >30 kg: 1.2 mg three times daily, increased weekly by 0.6 mg to 3.0 mg at week 4 The maximum tolerated doses were then continued for a further 4 weeks. Doses were increased according to this schedule unless adverse effects occurred or desired 'dryness' (defined by the parent or carer) occurred[c,d]
Comparator(s)	Placebo[b]
Length of follow-up	8 week treatment phase. A cross-over design was used: the initial 8 week treatment phase was followed by a 1 week washout period, a 1 week observation period and then 8 weeks of the alternative intervention
Outcomes	Primary outcome[e,f]: • Change in mean mTDS score from baseline to mean maximum (best) score, over 8 weeks
	Secondary outcomes[e]: • Mean mTDS score after 4 weeks at highest dose by dose level • Proportion of patients with ≥4-point improvement in mean mTDS score by dose level • Parent or carer assessment of drooling odour • Parent or carer assessment of dryness of clothing

	Safety outcomes: • Any adverse events • Adverse events requiring treatment withdrawal	
Source of funding	Not reported	
Overall risk of bias/quality assessment – CASP RCT checklist	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Unclear[g]
	Were patients, health workers and study personnel blinded?	Yes[h]
	Were the groups similar at the start of the trial?	Unclear[i]
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 6
	How precise was the estimate of the treatment effect?	See table 6
	Can the results be applied in your context? (or to the local population)	Yes[j]
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See key points

Study limitations	• Short-term study (8 weeks) • Only participants who completed the study were included in the analysis. A high proportion of the participants did not complete the study (12/39, 31%) • The study did not include an active comparator • The study did not report on randomisation and blinding methods • It is unclear whether allocation was concealed
Comments	[a] 34/39 participants had cerebral palsy and 2/39 had tracheostomies (1 of whom dropped out of the study because of excessively thick secretions). 5/39 participants had previously received treatment for sialorrhoea, 3 of whom had taken glycopyrronium bromide and had stopped treatment because of adverse effects. [b] Capsules were specially compounded from oral glycopyrronium bromide. Placebo capsules were compounded using identical gelatin capsules. [c] The mean highest dose of glycopyrronium bromide for children who completed the study was 2.49 mg (range 1.2–3.0 mg) per dose. [d] 4 participants were given these doses twice rather than three times a day, at the parent's request. [e] The authors do not specify which outcomes are primary and which are secondary, although mean change in mTDS is reported first in the paper. [f] Drooling was assessed weekly in the afternoon (2 hours after a dose) by parents or carers using mTDS. [g] Randomisation method and allocation concealment not described. [h] Although the study stated that it was double-blind, it was not clear if both investigators and clinicians providing care were blinded. [i] Baseline characteristics not reported. [j] The study population that completed the trial is not described in detail, and no account is given for the subjects who dropped out.
Abbreviations: EPAR, European Public Assessment Report; mTDS, Modified Teacher's Drooling Scale; RCT, randomised controlled trial.	

Table 5 Zeller et al. 2012a

Study reference	Zeller RS, Lee HM, Cavanaugh PF et al. (2012a) Randomized phase III evaluation of the efficacy and safety of a novel glycopyrrolate oral solution for the management of chronic severe drooling in children with cerebral palsy or other neurologic conditions. Therapeutics and Clinical Risk Management 8: 15–23
Unique identifier	NCT00425087
Study type	RCT
Aim of the study	To assess the efficacy and safety of glycopyrronium bromide oral solution in managing problem drooling associated with cerebral palsy and other neurologic conditions in children
Study dates	November 2002 to April 2007
Setting	US (10 centres)
Number of participants	n=38 randomised
Population	People aged 3 to 23 years[a] with cerebral palsy or another neurological condition, and problem drooling[b]. The mean age was approximately 9.5 years; 22/36 (61%) were male
Inclusion criteria	Male and female patients weighing at least 27 lb (12.2 kg) and previously diagnosed with cerebral palsy, mental retardation, or another neurologic condition associated with problem drooling were eligible. People with oral feeding problems or who used a tube for feeding were included
Exclusion criteria	Patients were excluded if their extent of drooling was wetness of the lips and chin but their clothes did not become damp on most days; if they had used glycopyrronium bromide liquid within approximately 24 hours of baseline; if they had used any anticholinergic or cholinergic medications prohibited by the protocol within 3 plasma half-lives of that medication prior to baseline; or if they had medical conditions contraindicating anticholinergic therapy or treatment with the study medication

Intervention(s)	Glycopyrronium bromide (glycopyrrolate) oral solution[c], three times daily,with the dose titrated up weekly to the optimal tolerated dose[b]. There were 5 dose levels: • 0.02 mg/kg three times a day • 0.04 mg/kg three times a day • 0.06 mg/kg three times a da • 0.08 mg/kg three times a day • 0.10 mg/kg three times a day The maximum dose was 1.5–3.0 mg three times a day (based on weight). After the optimal dose level was reached, patients continued to receive the same medication and dose for a total of 8 weeks
Comparator(s)	Placebo
Length of follow-up	8 weeks (including 4-week dose titration phase)
Outcomes	Primary outcome: • Responder rate, defined as percentage of patients with an improvement of 3 points or more in mTDS score
	Secondary outcomes: • Mean improvement in mTDS score at 8 weeks • Daily mean parent/carer mTDS scores at weeks 2, 4, and 6 • AUC analysis of all mTDS evaluations from screening to week 8 • Proportion of patients who discontinued treatment due to lack of efficacy • Proportion of investigators who considered treatment worthwhile[d] • Proportion of parents/carers who considered treatment worthwhile[d]

	Safety outcomes: • Any adverse events All assessed at baseline and at week 8 or study discontinuation	
Source of funding	Shionogi Inc.	
Overall risk of bias/quality assessment – CASP RCT checklist	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Unclear[e]
	Were patients, health workers and study personnel blinded?	Unclear[f]
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 7
	How precise was the estimate of the treatment effect?	See table 7
	Can the results be applied in your context? (or to the local population)	Yes
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See key points
Study limitations	• Short-term study (8 weeks) • The study did not include an active comparator • The study did not report on randomisation and blinding methods • It is unclear whether allocation was concealed	

Comments	[a] After randomisation the study protocol was amended and an upper age limit of 16 years was set. Two participants were excluded from the efficacy analysis, but were included in the safety analysis. [b] Problem drooling was defined as drooling in the absence of treatment such that clothing became damp approximately 5–7 days per week. Of the 36 participants analysed for efficacy, 30 had cerebral palsy, 18 had oral feeding problems and 15 used a tube for feeding. [c] This formulation of glycopyrronium bromide is available in the US as Cuvposa. This is a different product to the licensed product available in the UK (Sialanar), and there are differences in bioavailability. [d] Assessed at week 8 or at the last visit, using a 5-point scale, ranging from 1 (strongly agree) to 5 (strongly disagree) in response to the statement "This is a worthwhile treatment". [e] Unclear if allocation was concealed. [f] Although the study stated that it was double-blind, it was not clear if both investigators and clinicians providing care were blinded.
Abbreviations: AUC, Area under curve; mTDS, Modified Teacher's Drooling Scale; RCT, randomised controlled trial.	

Results tables

Table 6 Mier et al. 2000

	Glycopyrronium	Placebo	Analysis
n[a]	27	27	
Primary outcome			
Mean change in mTDS score from baseline to mean maximum (best) score	From 7.52 at baseline to 1.85	From 7.44 to 6.33	p<0.001
Selected secondary outcomes			

Mean mTDS score at lowest dose level to highest dose level	1st dose level: 6.0 2nd dose level: 4.5 3rd dose level: 3.6 4th dose level: 2.6 After 4 weeks at highest dose level: 2.3	Data not reported	Not reported
% of patients with improvement in mTDS score of ≥4 points	1st dose level: 12% 2nd dose level: 38% 3rd dose level: 54% 4th dose level: 81%	Data not reported	Not reported
Safety and tolerability outcomes			
n[b]	39	39	
Patients reporting any adverse effect	25/36 (69%)	5/30 (17%)	Not reported
Patients discontinued due to adverse effects[c]	7/39 (18%)	1/39 (3%)	
Behavioural changes[d]	9/39 (23%)	1/39 (3%)	
Constipation	7/39 (18%)	0/39 (0%)	
Excessive oral dryness	7/39 (18%)	0/39 (0%)	
Urinary retention	5/39 (13%)	0/39 (0%)	

[a] Efficacy population: only the participants who completed the study were included in the efficacy analysis. No explanation or justification of this is provided by the authors.

[b] Safety population for the individual adverse effects appears to include all randomised participants. For 'any adverse effect' this appears to be reported for only 36/39 patients in glycopyrronium group and 30/39 in the placebo group. The reason for this is not discussed in the paper.

[c] Of the 7 participants who stopped treatment in the glycopyrronium bromide group due to adverse events, 4 stopped before the end of the first week.

[d] Includes drowsiness, restlessness, hyperactivity, short attention span, frustration, irritability, mood changes, temper outbursts, explosive behaviour, excessive sensitivity, seriousness, sadness, frequent crying episodes, fearfulness.

Abbreviations: mTDS, modified Teacher's Drooling Score.

Table 7 Zeller et al 2012a

	Glycopyrronium	Placebo	Analysis
n[a]	19	17	
Primary outcome			
Responder rate (% of patients with improvement in mTDS score of ≥3 points)	Week 2: 52.6% (10/19)	Week 2: 0% (0/17)	Week 2: p=0.0007
	Week 4: 57.9% (11/19)	Week 4: 17.6% (3/17)	Week 4: p value not reported
	Week 6: 68.4% (13/19)	Week 6: 11.8% (2/17)	Week 6: p value not reported
	Week 8: 73.7% (14/19)	Week 8: 17.6% (3/17)	Week 8: p=0.0011
Selected secondary outcomes			
Mean improvement in mTDS score at 8 weeks (95% CI)	3.94 (2.97 to 4.91)	0.71 (−0.43 to 1.84)	p<0.0001
Proportion of investigators who considered treatment worthwhile[b]	84.2%	41.2%	p=0.0140
Proportion of parents/carers who considered treatment worthwhile[b]	100%	56.3%	p=0.0017
Safety and tolerability outcomes			
n[c]	20	18	
Patients discontinued due to adverse events	1/20 (5%)	1/18 (6%)	Not reported
Patients reporting a severe adverse event	4/20 (69%)	0/18 (0%)	
Patients reporting any adverse event	20/20 (23%)	15/18 (83%)	

Patients reporting an adverse event considered to be treatment-related	15/20 (75%)	7/18 (39%)	
Dry mouth	8/20 (40%)	2/18 (11%)	
Constipation	6/20 (30%)	4/18 (22%)	
Vomiting	6/20 (30%)	2/18 (11%)	
Nasal congestion	6/20 (30%)	1/18 (5%)	
Flushing	5/20 (25%)	3/18 (17%)	
AE: urinary retention	3/20 (15%)	0/18 (0%)	
[a] Efficacy population: modified ITT set, defined as all randomised participants who were within the age range of the amended protocol and received at least one dose of study medication. [b] Assessment performed at week 8 or at the last visit. [c] Safety population: all randomised participants who received at least one dose of study medication.			
Abbreviations: 95% CI, 95% confidence interval; AE, adverse effect; ITT, intention to treat; mTDS, modified Teacher's Drooling Score.			

Excluded studies

Study reference	Reason for exclusion
Blasco P A, and Stansbury J C (1996) Glycopyrrolate treatment of chronic drooling. Archives of Pediatrics & Adolescent Medicine 150: 932–5.	Study not prioritised (not the best available evidence – open-label study without a comparator)
Davidson J, Wang C, Neiman R, and Cavanaugh P (2011) A Phase-3 multicenter, open-label study assessing the safety of glycopyrrolate oral solution for the management of pathologic drooling in pediatric patients with cerebral palsy or other neurologic conditions. Annals of Neurology 70: S171.	Abstract only – results of this study discussed in Zeller et al. 2012b
Evatt M L (2011) Oral glycopyrrolate for the treatment of chronic severe drooling caused by neurological disorders in children. Neuropsychiatric Disease & Treatment 7: 543–7.	Not a relevant study

Montgomery J, McCusker S, Lang K, Grosse S, Mace A, Lumley R, and Kubba H (2016) Managing children with sialorrhoea (drooling): Experience from the first 301 children in our saliva control clinic. International Journal of Pediatric Otorhinolaryngology 85: 33–9.	Study not prioritised (not the best available evidence – clinician survey)
Parr J R, Buswell C A, Banerjee K, Fairhurst C, Williams J, O'Hare A, Pennington L, British Academy of Childhood Disability Drooling Study Development, and Group (2012) Management of drooling in children: a survey of UK paediatricians' clinical practice. Child: Care, and Health & Development, 38: 287-91.	Study not prioritised (not the best available evidence – clinician survey)
Parr J R, Todhunter E, Pennington L, Cole M, Morrison J, Stocken D, and Colver A. (2016) The drooling reduction intervention (DRI) trial: Is hyoscine or glycopyrronium more effective and acceptable for the treatment of drooling in children with neurodisability?. Archives of Disease in Childhood 101: A55-A56.	Abstract only
Stern L M. (1997) Preliminary study of glycopyrrolate in the management of drooling. Journal of Paediatrics & Child Health 33: 52–4.	Study not prioritised (not the best available evidence – preliminary study using parent/ carer questionnaires)
Walshe M, Smith M, Pennington L (2012) Interventions for drooling in children with cerebral palsy. Cochrane Database of Systematic Reviews issue 11. Art. No.: CD008624. DOI: 10.1002/ 14651858.CD008624.pub3	Study not prioritised (not the best available evidence – meta-analysis that did not include key studies)

Terms used in this evidence summary

Modified Teacher's Drooling Scale (mTDS)

The modified Teacher's Drooling Scale (mTDS) is a 9-point scoring system measured by parents/ carers. Scores range from 1 to 9, with a higher score indicates more severe drooling:

1 = Dry: never drools

2 = Mild: only the lips are wet; occasionally

3 = Mild: only the lips are wet; frequently

4 = Moderate: wet on the lips and chin; occasionally

5 = Moderate: wet on the lips and chin; frequently

6 = Severe: drools to the extent that clothing becomes damp; occasionally

7 = Severe: drools to the extent that clothing becomes damp; frequently

8 = Profuse: clothing, hands, tray, and objects become wet; occasionally

9 = Profuse: clothing, hands, tray, and objects become wet; frequently

Search strategy

Medline (1946-present)

Search date: 21st October 2016

1 Glycopyrrolate/ (835)

2 (glycopyrronium or glycopyrrolate or sialanar).tw. (960)

3 1 or 2 (1137)

4 Sialorrhea/ (1184)

5 (drool* or hypersalivat* or sialorrhea).tw. (1708)

6 4 or 5 (2156)

7 3 and 6 (43)

Medline in-process

Search date: 21st October 2016

1 Glycopyrrolate/ (0)

2 (glycopyrronium or glycopyrrolate or sialanar).tw. (99)

3 1 or 2 (99)

4 Sialorrhea/ (0)

5 (drool* or hypersalivat* or sialorrhea).tw. (170)

6 4 or 5 (170)

7 3 and 6 (3)

Embase (1974 to 21th October 2016)

Search date: 21st October 2016

1 Glycopyrrolate/ (5454)

2 (glycopyrronium or glycopyrrolate or sialanar).tw. (1554)

3 1 or 2 (5585)

4 Sialorrhea/ (3973)

5 (drool* or hypersalivat* or sialorrhea).tw. (2723)

6 4 or 5 (5413)

7 3 and 6 (191)

8 limit 7 to English language (177)

9 *randomized controlled trial/ (37703)

10 *Randomization/ (2020)

11 *Placebo/ (55996)

12 *Crossover Procedure/ (3810)

13 (random or randomi$ or randoml$).tw. (1137254)

14 rct$.tw. (43365)

15 (phase 4 or phase iv or phase 3 or phase iii).tw. (67806)

16 placebo$.tw. (246741)

17 (crossover$ or (cross adj over$)).tw. (85155)

18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (1319359)

19 Nonhuman/ (4934829)

20 Human/ (17907880)

21 19 not (19 and 20) (3675982)

22 18 not 21 (1216959)

23 Clinical study/ (243890)

24 Case control study/ (121345)

25 Family study/ (24891)

26 Longitudinal study/ (104067)

27 Retrospective study/ (504524)

28 comparative study/ (736482)

29 Prospective study/ (380576)

30 Randomized controlled trials/ (121519)

31 29 not 30 (375968)

32 Cohort analysis/ (294471)

33 cohort analy$.tw. (7596)

34 (Cohort adj (study or studies)).tw. (175045)

35 (Case control$ adj (study or studies)).tw. (101756)

36 (follow up adj (study or studies)).tw. (53183)

37 (observational adj (study or studies)).tw. (98943)

38 (epidemiologic$ adj (study or studies)).tw. (88348)

39 (cross sectional adj (study or studies)).tw. (128781)

40 case series.tw. (65992)

41 prospective.tw. (618773)

42 retrospective.tw. (562957)

43 or/23-28,31-42 (2923018)

44 22 or 43 (3831639)

45 8 and 44 (39)

Cochrane library databases

Search date: 21st October 2016

#1 MeSH descriptor: [Glycopyrrolate] this term only 245

#2 glycopyrronium or glycopyrrolate or sialanar:ti,ab,kw (Word variations have been searched) 969

#3 #1 or #2 969

#4 MeSH descriptor: [Sialorrhea] this term only 71

#5 drool* or hypersalivat* or sialorrhea:ti,ab,kw (Word variations have been searched) 301

#6 #4 or #5 301

#7 #3 and #6 11

Development of this evidence summary

The evidence summary: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Dr Anand Iyer, Consultant Paediatric Neurologist, Alder Hey Children's NHS Foundation Trust

Dr Karen Pysden, Consultant Paediatric Neurologist, Leeds Teaching Hospitals NHS Trust

Venkat Thiyagesh, Consultant in Paediatrics, Calderdale & Huddersfield NHS Foundation Trust

Declarations of interest

Anand Iyer: No interests declared

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About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

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