Hypersalivation: oral glycopyrronium bromide

Evidence summary
Published: 2 July 2013
nice.org.uk/guidance/esuom15

Key points from the evidence

The content of this evidence summary was up-to-date in July 2013. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Summary

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, and adults with Parkinson's disease, compared with placebo. There is also limited evidence of its efficacy in adults with schizophrenia and clozapine-induced hypersalivation. The most commonly reported adverse effects of oral glycopyrronium bromide are antimuscarinic, for example dry mouth. There is no evidence of its long-term efficacy or safety in treating hypersalivation.

Regulatory status: unlicensed.
### Effectiveness
- Oral glycopyrronium bromide significantly improved drooling in children and young people with neurological conditions compared with placebo (2 randomised controlled trials [RCTs], 8 weeks, n=77).
- Oral glycopyrronium bromide significantly improved drooling in adults with Parkinson's disease compared with placebo (1 RCT, 1 week, n=23).
- Oral glycopyrronium bromide significantly improved drooling in adults with schizophrenia and clozapine-induced hypersalivation compared with oral biperiden (1 RCT, 4 weeks, n=13).

### Safety
- The US product, Cuvposa (glycopyrronium bromide oral solution), is contraindicated in medical conditions that preclude antimuscarinic (anticholinergic) therapy and with concomitant oral potassium chloride.
- The most commonly reported adverse effects listed are dry mouth, vomiting, constipation, flushing and nasal congestion.

### Patient factors
- Glycopyrronium bromide tablets and oral solution or suspension are imported or prepared by 'specials' manufacturers.
- Dosage varies: generally given 3 times daily, titrated and dependent on weight in children (Cuvposa labelling advises to give either 1 hour before, or 2 hours after, meals).
- Oral glycopyrronium bromide has been associated with more adverse effects and discontinuations because of adverse effects than placebo.

### Resource implications
- Around £160 for 4 weeks' treatment, based on use of glycopyrronium bromide 1 mg/5 ml oral solution/suspension (approx. £2100 per year).

### Key points
Glycopyrronium bromide is an antimuscarinic drug that can potentially reduce salivary secretions. This evidence summary describes the efficacy and safety of oral preparations of glycopyrronium.
bromide (tablets and solution or suspension) when used to treat hypersalivation in adults, children and young people. Hypersalivation is the excessive production of saliva that can cause 'chronic drooling' or 'problem drooling'.

Oral preparations of glycopyrronium bromide (tablets and solution or suspension) are not licensed in the UK. Therefore, using these preparations, which are either imported or prepared by 'specials' manufacturers, for treating hypersalivation would be unlicensed. In 2010, glycopyrrolate (glycopyrronium bromide) 1 mg/5 ml oral solution was licensed in the USA to treat chronic severe drooling in children and young people aged 3–16 years with a neurological condition.

Two double-blind, placebo-controlled, randomised controlled trials (RCTs) were identified that examined the efficacy and safety of oral glycopyrronium bromide for treating hypersalivation in children and young people with a neurological condition (Mier et al. 2000 and Zeller et al. 2012a), and 1 double-blind, placebo-controlled RCT in adults with Parkinson's disease (Arbouw et al. 2010). An additional RCT (Liang et al. 2010) was identified comparing oral glycopyrronium bromide with the centrally acting antimuscarinic biperiden (unlicensed use) for treating clozapine-induced hypersalivation in adults with schizophrenia. All of the identified trials were small, with fewer than 40 participants in each trial, and were short term (8 weeks or less).

The 2 RCTs in children and young people with a neurological condition (predominantly cerebral palsy) showed that oral glycopyrronium bromide significantly improved drooling after 8 weeks of treatment. The dosage of glycopyrronium bromide was titrated and dependent on weight in these trials, up to a maximum of 3 mg per dose given 3 times daily. In 1 of the trials (Mier et al. 2000), the mean parent- or carer-reported drooling score was significantly improved from severe drooling to no drooling or mild drooling with glycopyrronium bromide; drooling remained severe with placebo. In the other trial (Zeller et al. 2012a), there was a significant clinical improvement in drooling from baseline to 8 weeks in 73.7% of children and young people receiving glycopyrronium bromide compared with 17.6% receiving placebo.

The RCT in adults with Parkinson's disease (Arbouw et al. 2010) showed a significant improvement in drooling score with 1 week of glycopyrronium bromide 1 mg 3 times daily compared with placebo.

The RCT in adults with schizophrenia and clozapine-induced hypersalivation (Liang et al. 2010) showed that drooling improved with either oral glycopyrronium bromide 1 mg twice daily or oral biperiden 2 mg twice daily (a centrally acting antimuscarinic agent) for 4 weeks. Drooling significantly improved from baseline with both medicines but glycopyrronium bromide was superior. Participants taking biperiden had a significant reduction in Mini Mental State Examination
(MMSE) scores; there were no significant differences from baseline in MMSE scores with glycopyrronium bromide.

Glycopyrronium bromide was associated with more reported adverse effects than placebo in the 2 trials in children and young people with a neurological condition (Mier et al. 2000 and Zeller et al. 2012a), but statistical significance was not reported. In the Mier et al. (2000) trial, 7 of 36 people stopped treatment while taking glycopyrronium bromide, compared with 1 of 36 people while receiving placebo. In the Zeller et al. (2012a) trial, 1 participant in each group stopped treatment because of adverse effects occurring during treatment.

Additional safety and adverse event warnings are included in the labelling of the US product, Cuvposa (glycopyrrolate [glycopyrronium bromide] 1 mg/5 ml oral solution), which is licensed to treat chronic severe drooling in children and young people aged 3–16 years with a neurological condition. Cuvposa is contraindicated in children and young people with medical conditions that preclude antimuscarinic (anticholinergic) therapy and in people taking concomitant oral forms of potassium chloride.

Constipation is listed as a dose-limiting adverse reaction in the Cuvposa label. Other adverse effect warnings include intestinal pseudo-obstruction (that may present as abdominal distension, pain, nausea or vomiting) and incomplete mechanical intestinal obstruction (that may present as diarrhoea). The most commonly reported adverse effects listed, with an incidence of 30% or more, are: dry mouth, vomiting, constipation, flushing and nasal congestion.

The 4 RCTs included in this evidence summary do not provide evidence for the efficacy or safety of long-term oral glycopyrronium bromide use. Larger RCTs are needed to further evaluate oral preparations of glycopyrronium bromide for treating hypersalivation in adults, children and young people.
About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

Overview for healthcare professionals

Regulatory status of glycopyrronium bromide

Glycopyrronium bromide does not have marketing authorisation in the UK for treating hypersalivation in children, young people or adults. However, it is available in the UK as:

- a 200 microgram/ml solution for injection licensed for preoperative and intraoperative use in adults and children (Amdipham Mercury Company; Accord Healthcare)
- a powder for solution licensed for iontophoretic treatment (electromotive drug administration) of idiopathic hyperhidrosis (excessive sweating) of the feet and hands in children and adults (Robinul powder, Amdipham Mercury Company)
- a single-dose dry-powder inhaler licensed for maintenance therapy to relieve symptoms of chronic obstructive pulmonary disease in adults (Seebri Breezhaler inhalation powder, Novartis Pharmaceuticals).

Oral preparations of glycopyrronium bromide (tablets and solution or suspension) are not licensed in the UK, so use of these preparations, which are either imported or prepared by specialist manufacturers, is unlicensed.

Glycopyrrolate (glycopyrronium bromide) 1 mg/5 ml oral solution (Cuvposa) was licensed in the USA in 2010 for treating chronic severe drooling in children and young people aged 3–16 years with neurological conditions associated with problem drooling, for example, cerebral palsy.
In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using glycopyrronium bromide outside its authorised indications.

**Evidence statements**

- Two small, double-blind, placebo-controlled, randomised controlled trials (RCTs; Mier et al. 2000 [a crossover, dose-ranging study] and Zeller et al. 2012a) were identified that evaluated the efficacy and safety of oral glycopyrronium bromide for treating drooling in children and young people with a neurological condition. Parent- or carer-reported drooling was found to be significantly improved with 8 weeks of 3-times daily oral glycopyrronium bromide compared with placebo.

- One small, double-blind, placebo-controlled, crossover RCT (Arbouw et al. 2010) was identified that evaluated oral glycopyrronium bromide for treating drooling in adults with Parkinson's disease. One week of glycopyrronium bromide treatment significantly improved drooling compared with placebo.

- One small, double-blind, crossover RCT (Liang et al. 2010) was identified that compared oral glycopyrronium bromide with oral biperiden (a centrally acting antimuscarinic agent) for treating clozapine-induced hypersalivation in adults with schizophrenia. Drooling significantly improved from baseline with both agents after 4 weeks treatment but glycopyrronium bromide was superior. Participants taking biperiden had a significant reduction in Mini Mental State Examination (MMSE) scores; there were no significant differences from baseline in MMSE scores with glycopyrronium bromide.

- Oral glycopyrronium bromide was frequently associated with adverse effects in the 2 trials in children and young people with a neurological condition. More people stopped glycopyrronium bromide treatment because of adverse effects compared with those taking placebo in Mier et al. (2000), and more people reported serious adverse effects with glycopyrronium bromide compared with placebo in Zeller et al. (2012a); statistical significance was not reported.

- No serious adverse effects were reported in the 1-week trial in adults with Parkinson's disease (Arbouw et al. 2010), and there was no statistically significant difference in non-serious adverse effects between the glycopyrronium bromide and placebo groups.

- The most common adverse effects listed in the labelling of the US product, Cuvposa (glycopyrronium bromide oral solution), with an incidence of 30% or more, are dry mouth, vomiting, constipation, flushing and nasal congestion.
The identified placebo-controlled RCTs provide moderate evidence that oral glycopyrronium bromide reduces drooling, but increases antimuscarinic adverse effects, compared with placebo. However, all the RCTs were small, with fewer than 40 participants in each trial, and were also short term. They do not provide evidence of the long-term use of oral glycopyrronium bromide for treating hypersalivation in adults, children and young people.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the Evidence review section.

Efficacy

This evidence summary includes 2 double-blind, placebo-controlled RCTs that examined the efficacy and safety of oral glycopyrronium bromide for treating hypersalivation in children and young people with a neurological condition that was predominantly cerebral palsy (Mier et al. 2000 and Zeller et al. 2012a), and 1 double-blind, placebo-controlled RCT in adults with Parkinson’s disease (Arbouw et al. 2010). An additional double-blind, crossover RCT (Liang et al. 2010) compared oral glycopyrronium bromide to a centrally acting antimuscarinic drug (biperiden; unlicensed) for treating clozapine-induced hypersalivation in adults with schizophrenia.

All the RCTs had fewer than 40 participants, and none assessed the long-term efficacy and safety of oral glycopyrronium bromide for treating hypersalivation. The dosage of glycopyrronium bromide varied in the trials, was titrated, and was dependent on weight in the 2 trials of children and young people. All the trials used a 9-point drooling rating scale, with rating reported by the participant, parent or carer, to measure the severity and frequency of drooling.

The 2 RCTs in children and young people showed that oral glycopyrronium bromide significantly improved drooling after 8 weeks of treatment. In the Mier et al. (2000) trial, the mean drooling score changed from a rating of severe at baseline to a mean score equating to no drooling or mild drooling at 8 weeks when people received glycopyrronium bromide. Drooling remained severe at 8 weeks when people received placebo. In the Zeller et al. (2012a) trial, there was at least a 3-point improvement in a 9-point drooling score from baseline to week 8 in 73.7% of participants receiving glycopyrronium bromide compared with 17.6% receiving placebo.

In both trials, more adverse effects were reported among children and young people receiving glycopyrronium bromide, and more people stopped treatment because of adverse effects with glycopyrronium bromide in the Mier et al. (2000) trial, but statistical significance was not reported.
The crossover RCT in adults with Parkinson's disease (Arbouw et al. 2010) found that drooling improved by a clinically-relevant 30% in 9 participants (39.1%) with glycopyrronium bromide compared with 1 (4.3%) on placebo (p=0.021).

One small, double-blind, crossover RCT (Liang et al. 2010) was identified that compared oral glycopyrronium bromide with oral biperiden (a centrally acting antimuscarinic agent) for treating clozapine-induced hypersalivation in adults with schizophrenia. Drooling statistically significantly improved from baseline with both agents after 4 weeks but glycopyrronium bromide was statistically superior. Participants taking biperiden had a statistically significant reduction in Mini Mental State Examination (MMSE) scores; there were no significant differences from baseline in MMSE scores with glycopyrronium bromide.

The RCTs do not provide evidence for the efficacy or safety of long-term use of oral glycopyrronium bromide for treating adults, children and young people with hypersalivation. This evidence summary has not compared different oral formulations of glycopyrronium bromide and does not describe oral use of solution for injection.

### Table 1 Summary of the 2 trials of oral glycopyrronium bromide in children and young people with a neurological condition and hypersalivation

<table>
<thead>
<tr>
<th></th>
<th>Glycopyrronium bromide</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mier et al. (2010)</strong> double-blind, dose-ranging, crossover RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>&lt;30 kg: 0.6 mg capsules 3 times daily, increased weekly by 0.6 mg up to 2.4 mg &gt;30 kg: 1.2 mg capsules 3 times daily, increased weekly by 0.6 mg to 3.0 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Randomised</strong></td>
<td>n=39</td>
<td>n=39</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>n=27</td>
<td>n=27</td>
<td></td>
</tr>
<tr>
<td>Mean post-treatment drooling score(^a) improvement from baseline to week 8</td>
<td>From 7.52 to 1.85</td>
<td>From 7.44 to 6.33</td>
<td>(p&lt;0.001) Scores improved in a linear manner with increasing dose.</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Mean drooling score at lowest dose level to highest dose level</td>
<td>1(^{st}) dose level: 6.0</td>
<td>2(^{nd}) dose level: 4.5</td>
<td>3(^{rd}) dose level: 3.6</td>
</tr>
<tr>
<td></td>
<td>4(^{th}) dose level: 2.6</td>
<td>After 4 weeks at highest dose level: 2.3</td>
<td></td>
</tr>
<tr>
<td>Improvement in drooling score of (\geq 4) points</td>
<td>1(^{st}) dose level: 12%</td>
<td>2(^{nd}) dose level: 38%</td>
<td>3(^{rd}) dose level: 54%</td>
</tr>
<tr>
<td></td>
<td>4(^{th}) dose level: 81%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>n=39</td>
<td>n=39</td>
<td></td>
</tr>
<tr>
<td>Discontinuation because of AE</td>
<td>7/39</td>
<td>1/39</td>
<td>(p) value not reported. Of the 7 people that stopped treatment in the glycopyrronium bromide group, 4 stopped before the end of the first week.</td>
</tr>
<tr>
<td>Patients reporting any AE</td>
<td>69% (25/36)</td>
<td>17% (5/30)</td>
<td>(p) value not reported</td>
</tr>
<tr>
<td>AE: behavioural changes(^b)</td>
<td>23% (9/39)</td>
<td>3% (1/39)</td>
<td>(p) value not reported</td>
</tr>
<tr>
<td>AE: constipation</td>
<td>18% (7/39)</td>
<td>0%</td>
<td>(p) value not reported</td>
</tr>
<tr>
<td>AE: excessive oral dryness</td>
<td>18% (7/39)</td>
<td>0%</td>
<td>(p) value not reported</td>
</tr>
<tr>
<td>AE: urinary retention</td>
<td>13% (5/39)</td>
<td>0%</td>
<td>(p) value not reported</td>
</tr>
<tr>
<td>Zeller et al. (2012a) double-blind RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.02 mg/kg oral solution 3 times daily, increased weekly for 4 weeks by 0.02 mg/kg up to 0.1 mg/kg or 3 mg 3 times daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Randomised</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=20</td>
<td>n=18</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=19</td>
<td>n=17</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome: responder rate (improvement ≥3 units on mTDS³)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2: 52.6% (10/19)</td>
<td>Week 2: 0% (0/17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4: 57.9% (11/19)</td>
<td>Week 4: 17.6% (3/17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 6: 68.4% (13/19)</td>
<td>Week 6: 11.8% (2/17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8: 73.7% (14/19)</td>
<td>Week 8: 17.6% (3/17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Selected secondary outcome: mean improvement on mTDS at 8 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.94 (SD 1.95)</td>
<td>0.71 (SD 2.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=20</td>
<td>n=18</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Discontinuation because of AE occurring during treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/20</td>
<td>1/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients reporting severe AE occurring during treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% (4/20)</td>
<td>0% (0/18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© NICE 2017. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Page 10 of 35
Patients reporting at least 1 AE occurring during treatment & Patients reporting at least 1 AE occurring during treatment

| AE: dry mouth | 40% (8/20) | 11% (2/18) |
| AE: constipation | 30% (6/20) | 22% (4/18) |
| AE: vomiting | 30% (6/20) | 11% (2/18) |
| AE: nasal congestion | 30% (6/20) | 5% (1/18) |
| AE: flushing | 25% (5/20) | 17% (3/18) |
| AE: urinary retention | 15% (3/20) | 0% (0/18) |

Abbreviations: AE, adverse effect; mTDS, modified Teacher's Drooling Scale; n, number of participants; RCT, randomised controlled trial; SD, standard deviation.

a Drooling was assessed using a 9-point scale ranging from 1 'dry: never drools' to 9 'profuse: clothing, hands, objects become wet frequently'.

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

c Drooling was assessed using a modified 9-point Teachers Drooling Scale (mTDS) ranging from 1 'dry: never drools' to 9 'profuse: clothing, hands, tray and objects become wet frequently'.

Table 2 Summary of the trial of oral glycopyrronium bromide in adults with Parkinson's disease and hypersalivation
<table>
<thead>
<tr>
<th></th>
<th>Glycopyrronium bromide</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arbouw et al. (2010)</strong> double-blind, crossover RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>1 mg (5 ml) oral solution or suspension, 3 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Randomised</strong></td>
<td>n=23</td>
<td>n=23</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>n=23</td>
<td>n=23</td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome: responder rate on drooling scale (≥30% improvement)(^a)</strong></td>
<td>39.1% (9/23)</td>
<td>4.3% (1/23)</td>
<td>Difference in responder rate 34.8%, 95% CI 13.0% to 56.5%, (p=0.021)</td>
</tr>
<tr>
<td><strong>Secondary outcome: mean drooling scores after 1 week of study medication</strong></td>
<td>3.8 (SD 1.6)</td>
<td>4.6 (SD 1.7)</td>
<td>Mean difference 0.8 points, 95% CI 0.02 to 1.4, (p=0.01)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>n=23</td>
<td>n=23</td>
<td></td>
</tr>
<tr>
<td><strong>Patients reporting serious AE</strong></td>
<td>0/23</td>
<td>0/23</td>
<td></td>
</tr>
<tr>
<td><strong>AE: dry mouth</strong></td>
<td>52.2% (12/23)</td>
<td>30.4% (7/23)</td>
<td>(p=0.18)</td>
</tr>
<tr>
<td><strong>AE: nervousness</strong></td>
<td>21.7% (5/23)</td>
<td>21.7% (5/23)</td>
<td>(p=1.0)</td>
</tr>
<tr>
<td><strong>AE: change in motor symptoms</strong></td>
<td>13.0% (3/23)</td>
<td>17.4% (4/23)</td>
<td>(p=1.0)</td>
</tr>
<tr>
<td><strong>AE: constipation</strong></td>
<td>13.0% (3/23)</td>
<td>13.0% (3/23)</td>
<td>(p=1.0)</td>
</tr>
<tr>
<td><strong>AE: vision problems</strong></td>
<td>13.0% (3/23)</td>
<td>13.0% (2/23)</td>
<td>(p=1.0)</td>
</tr>
<tr>
<td><strong>AE: urine retention</strong></td>
<td>13.0% (3/23)</td>
<td>8.6% (2/23)</td>
<td>(p=1.0)</td>
</tr>
<tr>
<td><strong>AE: nausea</strong></td>
<td>4.3% (1/23)</td>
<td>8.6% (2/23)</td>
<td>(p=1.0)</td>
</tr>
</tbody>
</table>
AE: Palpitations | 4.3% (1/23) | 4.3% (1/23) | p=1.0

Abbreviations: AE, adverse effect; CI, confidence interval; n, number of participants; RCT, randomised controlled trial; SD, standard deviation.

Drooling was assessed using a 9-point scale, ranging from 1 'dry: never drools' to 9 'profuse: clothing, hands, tray and objects become wet frequently. Response to treatment was pre-defined as a mean score improvement of at least 30% from baseline.

### Table 3 Summary of the trial of oral glycopyrronium bromide in adults with schizophrenia and drug-induced hypersalivation

<table>
<thead>
<tr>
<th>Glycopyrronium bromide</th>
<th>Biperiden</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liang et al. (2010) double-blind crossover RCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>1 mg oral capsules, twice daily</td>
<td>2 mg capsules, twice daily</td>
</tr>
<tr>
<td><strong>Randomised</strong></td>
<td>n=13</td>
<td>n=13</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>n=12</td>
<td>n=12</td>
</tr>
<tr>
<td><strong>Primary outcome: change in mean DRS score from baseline to week 4</strong></td>
<td>From 6.08 (SD 1.62) to 3.10 (SD 1.31), p=0.002</td>
<td>From 5.92 (SD 1.73) to 4.33 (SD 2.05), p=0.003</td>
</tr>
</tbody>
</table>
Secondary outcome: difference in DRS score between treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Individual weekly score not provided</th>
<th>Individual weekly score not provided</th>
<th>Week 1: glycopyrronium bromide scores lower than biperiden, p=0.026</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline: 20.75 (SD 7.39)</td>
<td>Baseline: 19.50 (SD 6.17)</td>
<td>Baseline: p=0.94</td>
</tr>
<tr>
<td>Week 1</td>
<td>Week 1: 20.50 (SD 6.93)</td>
<td>Week 1: 17.42 (SD 7.03)</td>
<td>Week 1: p=0.025</td>
</tr>
<tr>
<td>Week 2</td>
<td>Week 2: 20.67 (SD 7.55)</td>
<td>Week 2: 17.75 (SD 7.14)</td>
<td>Week 2: p=0.012</td>
</tr>
<tr>
<td>Week 3</td>
<td>Week 3: 20.25 (SD 7.37)</td>
<td>Week 3: 17.08 (SD 7.05)</td>
<td>Week 3: p=0.007</td>
</tr>
<tr>
<td>Week 4</td>
<td>Week 4: 21.50 (SD 7.21)</td>
<td>Week 4: 17.33 (SD 6.71)</td>
<td>Week 4: p=0.008</td>
</tr>
</tbody>
</table>

Secondary outcome: difference in MMSE between treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline: 20.75 (SD 7.39)</th>
<th>Baseline: 19.50 (SD 6.17)</th>
<th>Baseline: p=0.94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>20.50 (SD 6.93)</td>
<td>17.42 (SD 7.03)</td>
<td>p=0.025</td>
</tr>
<tr>
<td>Week 2</td>
<td>20.67 (SD 7.55)</td>
<td>17.75 (SD 7.14)</td>
<td>p=0.012</td>
</tr>
<tr>
<td>Week 3</td>
<td>20.25 (SD 7.37)</td>
<td>17.08 (SD 7.05)</td>
<td>p=0.007</td>
</tr>
<tr>
<td>Week 4</td>
<td>21.50 (SD 7.21)</td>
<td>17.33 (SD 6.71)</td>
<td>p=0.008</td>
</tr>
</tbody>
</table>

Safety

<table>
<thead>
<tr>
<th></th>
<th>MMSE 4-week average values 20.85 (SD 7.21), p=0.767 for change from baseline</th>
<th>MMSE 4-week average values 17.52 (SD 6.95), p=0.034 for change from baseline</th>
<th>The authors stated that other adverse effects did not differ appreciably by study group, data not reported. 1 person dropped out while receiving biperiden because of an unstable psychiatric condition.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=12; MMSE</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DRS, Drooling Rating Scale; MMSE, Mini Mental State Examination; n, number of participants; RCT, randomised controlled trial; SD, standard deviation.

a Drooling was assessed using the Drooling Rating Scale (range 2 to 9, with higher score indicating worse drooling).

Safety

The labelling of the US product, Cuvposa (glycopyrronium bromide oral solution), which is licensed to treat chronic severe drooling in children and young people aged 3–16 years, states that the drug is contraindicated in children and young people with medical conditions that preclude antimuscarinic (anticholinergic) therapy including glaucoma, paralytic ileus, unstable...
cardiovascular status in acute haemorrhage, severe ulcerative colitis, toxic megacolon ulcerative colitis and myasthenia gravis. Cuvposa is also contraindicated in people taking concomitant oral forms of potassium chloride.

The Cuvposa label warns that constipation is a common dose-limiting adverse reaction, and that intestinal pseudo-obstruction has been reported, which may present as abdominal distension, pain, nausea or vomiting. It also warns of incomplete mechanical intestinal obstruction, which may present as diarrhoea, and that high environmental temperatures should be avoided because glycopyrronium bromide inhibits sweating. Caution is advised in children and young people with conditions that are exacerbated by the effects of antimuscarinic drugs.

The most commonly reported adverse effects listed, with an incidence of 30% or more, are: dry mouth, vomiting, constipation, flushing and nasal congestion.

**Safety in trials of oral glycopyrronium bromide**

In the 2 trials in children and young people (Mier et al. 2000 and Zeller et al. 2012a), more adverse effects were reported in the groups receiving glycopyrronium bromide than those receiving placebo. However, the statistical significance of differences between the groups was not reported in either study. In the Mier et al. (2000) trial, 8 participants stopped treatment; 7 while taking glycopyrronium bromide and 1 while taking placebo. In the Zeller et al. (2012a) trial, 4 participants receiving glycopyrronium bromide had at least 1 severe adverse effect while taking the drug compared with none in the placebo group, and 1 participant in each group stopped treatment because of an adverse effect occurring during treatment. The most commonly reported adverse effects in these trials were:

- behavioural changes (for example, drowsiness, restlessness, hyperactivity and irritability)
- excessively dry mouth
- constipation
- urinary retention
- vomiting
- nasal congestion
- flushing.
In the trial in adults with Parkinson’s disease (Arbouw et al. 2010), no serious adverse effects were reported in either group and there were no statistically significant differences between groups in reported non-serious adverse effects.

In the trial in adults with schizophrenia and clozapine-induced hypersalivation (Liang et al. 2010) patients taking biperiden had a significant reduction in Mini Mental State Examination (MMSE) scores; there were no significant differences from baseline in MMSE scores with glycopyrronium bromide. Other adverse effects did not differ appreciably between adults receiving glycopyrronium bromide and those receiving biperiden.

**Cost effectiveness and cost**

No cost-effectiveness studies of glycopyrronium bromide for use in hypersalivation were identified.

The [NHS Electronic Drug Tariff (May 2013)](https://www.nice.org.uk/conditions/hypersalivation) lists the following prices for glycopyrronium bromide oral solution and suspension in Part VIIIIB, Arrangements for payment for specials and imported unlicensed medicines:

- Glycopyrronium bromide 1 mg/5 ml oral solution/suspension: £150.92 for minimal volume of 100 ml plus £0.01 for each extra ml.
- Glycopyrronium bromide 2 mg/5 ml oral solution: £262.61 for minimal volume of 100 ml plus £0.14 for each extra ml.
- Glycopyrronium bromide 2 mg/5 ml oral suspension: £197.59 for minimal volume of 100 ml plus £0.15 for each extra ml.

Based on the use of glycopyrronium bromide 1 mg/5 ml oral solution/suspension, the cost of 7 days’ treatment is estimated at £152.02 (2 mg dose, 3-times daily) or £153.07 (3 mg dose, 3-times daily).

No price is listed for glycopyrronium bromide oral tablets and the cost of these will differ depending on the source. [NHS prescription cost analysis for England 2012](https://www.nice.org.uk/conditions/hypersalivation) reported that various glycopyrronium bromide tablets cost between £268.57 and £712.34 per item (the number of tablets per item is not known).
Relevance to NICE guidance programmes

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

NICE has issued a clinical guideline Parkinson's disease: diagnosis and management in primary and secondary care, which states that people with Parkinson's disease should be treated appropriately for drooling (also known as sialorrhoea). The full clinical guideline states that management may include drug treatment, such as sublingual 1% atropine ophthalmic solution twice daily or injection of salivary glands with botulinum toxin A (neither of which are licensed in the UK for treating hypersalivation); there is no reference to the use of glycopyrronium bromide in the clinical guideline (see Alternative treatment options).

Intervention and alternatives

Glycopyrronium bromide is an antimuscarinic agent that reduces salivary secretions and does not cross the blood–brain barrier. No oral preparations (tablets and solution or suspension) of glycopyrronium bromide are licensed in the UK. Therefore, the use of imported oral preparations or those prepared by 'specials' manufacturers for treating hypersalivation in adults, children and young people is unlicensed.

Glycopyrrolate (glycopyrronium bromide) tablets 1 mg and 2 mg are available in the USA, licensed for adjunctive therapy in treating peptic ulcer. Glycopyrrolate (glycopyrronium bromide) 1 mg/5 ml oral solution (Cuvposa) was licensed in the USA in 2010 to reduce chronic severe drooling in children and young people aged 3–16 years with a neurological condition associated with problem drooling, such as cerebral palsy.

The recommended dosage is 0.02 mg/kg 3 times daily initially, with doses titrated in increments of 0.02 mg/kg every 5–7 days based on therapeutic response and adverse effects. The maximum recommended dose is 0.1 mg/kg 3 times daily (not to exceed 1.5 to 3 mg per dose based on weight). Doses should be given at least 1 hour before, or 2 hours after, meals.

Glycopyrronium bromide is licensed in the UK as an injection for preoperative and intraoperative use, as a powder for solution for iontophoretic treatment (electromotive drug administration) of hyperhidrosis (excessive sweating), and for use in a single-dose dry-powder inhaler for chronic obstructive pulmonary disease.
Condition

Hypersalivation (sialorrhoea) is the excessive production of saliva. This presents as drooling in children, young people and adults with a neurological condition, such as cerebral palsy or Parkinson's disease. Hypersalivation can also be an adverse effect of drug treatment (for example, clozapine).

Chronic drooling can be defined as the unintentional loss of saliva from the mouth. Zeller et al. (2012a) reported that although drooling is normal in infants, it usually stops by 15–18 months of age, and is considered pathological if present after 4 years. 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 and Mier et al. 2000).

The full NICE clinical guideline on Parkinson's disease states that excessive saliva or drooling occurs in 70–80% of people with Parkinson's disease and may be more common in men. Drooling is thought to result from oropharyngeal dysfunction, including reduced swallowing frequency.

Bird et al. (2011) reported that, second to sedation, hypersalivation is one of the most common adverse effects attributed to clozapine, occurring in 30–80% of people taking the drug.

Alternative treatment options

A review of the management of drooling in adults with neurological conditions (Squires et al. 2012) stated that management is best accomplished using a multidisciplinary team approach. Initial management is conservative (mostly behavioural) if symptoms are mild and infrequent. When conservative management is no longer adequate, drug treatment (usually with an antimuscarinic agent) is considered. Similar approaches have been tried in children and young people with neurological conditions (Mier et al. 2000, Walshe et al. 2012 and Zeller et al. 2012a).

Drug treatments other than glycopyrronium bromide that have been used to manage hypersalivation include the following (UKMI, Medicines Q&A, 2012):

- antimuscarinic drugs (amitriptyline, atropine, benzatropine, trihexyphenidyl hydrochloride, hyoscine hydrobromide)
- beta-blockers.
- botulinum toxin.
None of these are licensed in the UK for treating hypersalivation.

The full NICE clinical guideline on Parkinson’s disease states that management of sialorrhoea or drooling may include:

- referral to a speech and language therapist for assessment of swallowing ability
- behavioural management techniques to encourage regular saliva swallows
- use of a portable metronomic brooch as a reminder for saliva swallows
- lip seal and swallow exercises
- sublingual 1% atropine ophthalmic solution twice daily
- injection of salivary glands with botulinum toxin A.

Current strategies for clozapine-induced hypersalivation include topical and oral antimuscarinic drugs, alpha-adrenergic drugs (for example, clonidine), botulinum toxin and substitute benzamide derivatives (such as amisulpride) (Bird et al. 2011).

**Evidence review: efficacy**

Two randomised controlled trials (RCTs) of oral glycopyrronium bromide for treating drooling in children and young people with a neurological condition (predominantly cerebral palsy) were identified. One RCT used capsules compounded from oral tablets, and the other used glycopyrronium bromide oral solution. Another RCT was identified in adults with Parkinson’s disease, which used an oral solution; a further RCT was identified in people with schizophrenia and clozapine-induced hypersalivation, which again used tablets put into capsules. No RCTs were identified of oral use of glycopyrronium bromide solution for injection.

**Children and young people with a neurological condition**

Two RCTs were identified: Mier et al. (2000) and Zeller et al. (2012a). Both trials were carried out in the USA where oral preparations of glycopyrronium bromide (tablets and oral solution) are available.
Mier et al. (2000) was a double-blind, placebo-controlled, dose-ranging, crossover RCT in 39 children and young people aged 4–19 years (mean age 10 years 9 months) with neurological conditions and severe drooling. The study aimed to investigate the dose at which glycopyrronium bromide could control drooling with a minimum of adverse effects. Of the 39 participants, 34 had cerebral palsy. Two participants had tracheostomies, 1 of whom dropped out of the study because of excessively thick secretions. Five participants had previously received treatment for drooling, 3 of whom had taken glycopyrronium bromide and had stopped because of adverse effects.

Participants completed a 1-week drug-free observation period and were then randomised to 8 weeks of 3 times-daily oral glycopyrronium bromide capsules or placebo. 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. It is unclear if allocation was concealed.

Capsules were specially compounded from oral tablets because identical placebo tablets were not available. Children and young people that were unable to take capsules were given the powder contents of the capsule in their food. Two glycopyrronium bromide dose ranges were used:

- Participants weighing less than 30 kg received 0.6 mg per dose, increased weekly by 0.6 mg up to 2.4 mg over 4 weeks.
- Participants weighing more than 30 kg received 1.2 mg per dose increased by 0.6 mg weekly up to 3.0 mg over 4 weeks.

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. Four participants were given these doses twice rather than 3 times a day, at parental request. The mean highest dose of glycopyrronium bromide in the trial was 2.49 mg (range 1.2–3.0 mg) per dose.

The main outcomes were change in drooling and adverse effects. Drooling was assessed weekly in the afternoon 2 hours after a dose by parent report using a 9-point rating scale ranging from 1 'dry: never drools' to 9 'profuse: clothing, hands and objects become wet frequently'.

After 8 weeks of treatment, mean drooling scores statistically significantly improved with glycopyrronium bromide (from a mean baseline score of 7.52 to a maximum mean score of 1.85) compared with placebo (from a score of 7.44 to 6.33) in the 27 children and young people who completed the study (mean difference 4.48, p<0.001). The authors defined an improvement of
4 points or more as a standard for significant 'clinical improvement'. A score of 1.85 corresponds to a drooling rating between 'dry: never drools' and 'mild: only the lips are wet occasionally' and a score of 6.33 corresponds to 'severe: drools to the extent that clothing becomes damp occasionally'.

Drooling scores improved with increasing dose of glycopyrronium bromide, with mean scores of:

- 6.0 for participants on the first dose level
- 4.5 on the second dose level
- 3.6 on the third dose level
- 2.6 on the fourth dose level
- 2.3 after 4 weeks at the highest dose.

In the final 4 weeks of treatment when the maximum tolerated dose was maintained, drooling scores improved in 9 children and young people, decreased in 9 and remained the same in another 9. Eight children and young people withdrew from the study because of adverse effects, 7 when they were taking glycopyrronium bromide, and 1 when they were taking placebo. Adverse effects reported by Mier et al. (2000) are described in the safety section.

Zeller et al. (2012a)

Zeller et al. (2012a) was a double-blind, placebo-controlled RCT in 38 people aged 3 to 23 years with cerebral palsy or another neurological condition, and problem drooling. Problem drooling was defined as drooling in the absence of treatment such that clothing became damp approximately 5–7 days per week.

Two participants were excluded from the efficacy analysis because they did not meet the amended upper-age limit of 16 years. Of the 36 participants analysed for efficacy, 30 had cerebral palsy, 18 had oral feeding problems and 15 used a tube for feeding; the mean age was 9–10 years. Participants were excluded if they had medical conditions that would contraindicate antimuscarinic agents.

Participants were randomised to 8 weeks of 3 times-daily glycopyrronium bromide oral solution or placebo oral solution. It is unclear if allocation was concealed. The initial glycopyrronium bromide dosage was 0.02 mg/kg per dose increased weekly by 0.02 mg/kg for 4 weeks until the optimal tolerated response was achieved for each participant up to a maximum of 0.1 mg/kg or 3 mg per
dose, whichever was less. Participants then continued on the same dose for a further 4 weeks. Doses were administered via oral syringe at least 1 hour before, or 2 hours after, meals, and 5 dose levels were assessed. The mean daily dose of glycopyrronium bromide oral solution was 0.15 mg/kg.

The primary outcome was 'responder rate' based on the change in severity and frequency of drooling, assessed by parents or carers using a modified 9-point Teachers Drooling Scale (mTDS) at baseline and at weeks 2, 4, 6 and 8. Scores ranged from 1 'dry: never drools' to 9 'profuse: clothing, hands, tray and objects become wet frequently'. The authors reported that this primary outcome was changed at the request of the Food and Drug Administration (FDA) to 'dichotomised mTDS', which defined 'responders' to treatment as those with an improvement of at least 3 points on the mTDS. This was defined in the study as a clinical response.

Secondary outcomes included: mean mTDS scores; proportion of children and young people who stopped treatment because of lack of efficacy; and adverse effects.

After 8 weeks of treatment, statistically significantly more participants had a clinical response rate with glycopyrronium bromide (14 of 19; 73.7%) compared with placebo (3 of 17; 17.6%, p=0.001). The percentage of 'responders' during treatment with glycopyrronium bromide compared with placebo was:

- 52.6% compared with 0% at week 2
- 57.9% compared with 17.6% at week 4
- 68.4% compared with 11.8% at week 6.

Mean improvements in mTDS scores at 8 weeks were statistically significantly greater with glycopyrronium bromide (3.94±1.95) compared with placebo (0.71±2.14; p<0.0001); a difference of more than 3 points on the mTDS, which was defined in the study as a clinical response. Adverse effects reported by Zeller et al. (2012a) are described in the safety section.

**Adults with Parkinson's disease**

Arbouw et al. (2010) was a double-blind, placebo-controlled, crossover, fixed-dose RCT in 23 adults (mean age 70 years) in The Netherlands. Participants had Parkinson's disease and moderate-to-severe drooling (assessed as a score of 5 or above on a 9-point scale, with higher scores indicating more severe drooling). Mean baseline drooling score was 6.5±1.3, indicating severe drooling.
Adults were excluded from the trial if they had drooling caused by factors other than Parkinson's disease; previous treatment or hypersensitivity to glycopyrronium bromide; medical conditions that would contraindicate antimuscarinic agents; or concomitant use of potassium chloride tablets, digoxin or oral corticosteroids.

Participants were randomised to a baseline week without study treatment, then 1 week of oral glycopyrronium bromide 1 mg/5 ml oral solution 3 times daily or placebo, followed by a 1-week washout, and a crossover to 1 week of the alternative. Allocation appeared to be concealed.

The primary outcome was the difference in responder rates based on the change in severity and frequency of drooling between treatments. This was assessed by the participant or carer 3 times daily before administration of the study treatment using a 9-point scale, which ranged from 1 ‘dry: never drools’ to 9 ‘profuse: clothing, hands, tray and objects become wet frequently’. Response to treatment was pre-defined as a mean score improvement of at least 30% from baseline, which the investigators suggested could be clinically relevant. Secondary outcomes were difference in mean scores between treatments and adverse effects.

After 1 week of treatment, drooling responded to treatment in statistically significantly more people when they were taking glycopyrronium bromide (9 of 23; 39.1%) compared with when they were taking placebo (1 of 23; 4.3%) (mean difference in responder rate 34.8%, 95% confidence interval [CI] 13.0 to 56.5%, p=0.021). Mean drooling score after 1 week of glycopyrronium bromide was 3.8±1.6 compared with 4.6±1.7 with placebo (mean difference 0.8 points, 95% CI 0.02 to 1.4, p=0.011). A score of 4 on the drooling scale corresponds to 'moderate, wet on the lips and chin, occasionally', and a score of 5 to 'moderate, wet on the lips and chin, frequently'.

The investigators reported that 1 person inadvertently used 5 times the prescribed dose in the first 3 days of treatment with glycopyrronium bromide. When this person was excluded in a per-protocol analysis, the primary and secondary efficacy outcomes remained statistically significantly in favour of glycopyrronium bromide. Adverse effects reported by Arbouw et al. (2010) are described in the safety section.

People with schizophrenia and clozapine-induced hypersalivation

Liang et al. (2010) was a double-blind, crossover, fixed-dose RCT comparing glycopyrronium bromide with the centrally acting antimuscarinic biperiden in 13 adults aged 20–65 years with schizophrenia and clozapine-induced drooling. To be included, participants needed to have received clozapine for at least 1 year and have a score of 4 or greater on the Drooling Rating Scale (DRS; range 2–9, with higher score indicating worse drooling). Mean baseline DRS score was
approximately 6, indicating severe drooling. Adults were excluded from the trial if they had a serious or unstable medical condition, including conditions that would contraindicate antimuscarinic agents, or were receiving other drugs responsible for drooling.

Participants were randomised to 4 weeks oral glycopyrronium bromide 1 mg twice daily or oral biperiden 2 mg twice daily (both in identical capsules), followed by a 4-week washout period and then a crossover to the alternative for 4 weeks. It is unclear whether allocation was concealed. Throughout the trial, clozapine was maintained at pre-trial doses and no other antimuscarinic agents were used.

The primary outcomes were change in DRS to assess drooling, and change in Mini Mental State Examination (MMSE) to assess cognitive function, between baseline and the 4-week mean score. Assessments were carried out weekly, apart from during the washout period. The secondary outcome was the difference in the DRS and MMSE scores between treatments throughout the trial.

After 4 weeks of treatment, drooling was statistically significantly improved with glycopyrronium bromide (from a DRS score of 6.08±1.62 at baseline to 3.10±1.31 at 4 weeks, p=0.002) and biperiden (from a DRS score of 5.92±1.73 at baseline to 4.33±2.05 at 4 weeks, p=0.003) compared with baseline. Drooling changed from a mean rating of severe at baseline to a rating of mild to moderate at 4 weeks with glycopyrronium bromide compared with a change from severe to moderate with biperiden. Glycopyrronium bromide was found to statistically significantly improve DRS scores compared with biperiden at all 4-weekly assessments.

Compared with baseline, the mean MMSE score over 4 weeks was statistically significantly lower in the biperiden group (p=0.034), indicating worsening cognitive impairment. The mean 4-week MMSE score did not change in the glycopyrronium bromide group (p=0.767).

Other adverse effects of Liang et al. (2010) are reported in the safety section.

Evidence review: safety

The labelling of the US product, Cuvposa (glycopyrronium bromide oral solution), licensed to treat chronic severe drooling in children and young people aged 3–16 years, provides useful safety information. Cuvposa is contraindicated in children and young people with medical conditions that preclude antimuscarinic (anticholinergic) therapy (including glaucoma, paralytic ileus, unstable cardiovascular status in acute haemorrhage, severe ulcerative colitis, toxic megacolon ulcerative colitis and myasthenia gravis), and in people taking concomitant oral forms of potassium chloride.
The US label warns that constipation is a common dose-limiting adverse reaction, and that intestinal pseudo-obstruction has been reported, which may present as abdominal distension, pain, nausea or vomiting. It also warns of incomplete mechanical intestinal obstruction, which may present as diarrhoea, and that exposure to high environmental temperatures should be avoided because glycopyrronium bromide inhibits sweating. Caution is advised in children and young people with conditions that are exacerbated by the effects of antimuscarinic drugs (including autonomic neuropathy, renal disease, ulcerative colitis, hyperthyroidism, coronary heart disease, congestive heart failure, cardiac tachyarrhythmias, tachycardia and hypertension).

The US label reports data on adverse effects from 151 children and young people exposed to Cuvposa. This includes 20 participants from the placebo-controlled RCT by Zeller et al. 2012a, and a further 137 who participated in a 24-week open-label study (Zeller et al. 2012b). The most commonly reported adverse effects listed, with an incidence of 30% or more are: dry mouth, vomiting, constipation, flushing and nasal congestion.

**Children and young people with neurological conditions**

In the placebo-controlled, crossover RCT by Mier et al. (2000), the presence of adverse effects was assessed weekly by parent report using a 4-point scale ranging from 1 'not at all' to 4 'very much' and were considered significant if they were present 'quite a bit' or 'very much' when not present at baseline. Adverse effects were reported for 25 of 36 children and young people (69%) while taking glycopyrronium bromide compared with 5 of 30 children and young people (17%) while taking placebo. Statistical significance was not reported.

The most commonly reported adverse effects associated with glycopyrronium bromide were: behavioural changes such as drowsiness, restlessness, hyperactivity and irritability (9 people), constipation (7 people), excessively dry mouth (7 people) and urinary retention (5 people). Eight people withdrew from the study because of adverse events, 7 while taking glycopyrronium bromide (for reasons listed above or diarrhoea, blurred vision, facial flushing, nasal congestion, vomiting and thickened secretions in 1 child with a tracheostomy) and 1 while taking placebo. Four of the 7 children or young people who dropped out while taking glycopyrronium bromide did so before the end of the first week while on the lowest dose level. More participants experienced adverse effects as dosage levels increased. No hospitalisation admissions or deaths were reported, and the statistical significance of differences between study treatments was not reported.

In the placebo-controlled RCT by Zeller et al. (2012a), adverse effects occurring during treatment were reported among all (20 of 20; 100%) of the children and young people receiving glycopyrronium bromide compared with 15 of 18 (83.3%) receiving placebo. Of these, 15 (75%)
people in the glycopyrronium bromide group and 7 (39%) in the placebo group had adverse events that were considered by the investigator to be treatment related. Four people in the glycopyrronium bromide group had at least 1 severe adverse effect occurring during treatment compared with none in the placebo group. One person in each group stopped treatment because of an adverse effect occurring during treatment, and 1 person in the glycopyrronium bromide group experienced a generalised seizure with convulsions 8 days after study completion, which was not considered treatment related.

The most common adverse effects occurring in the glycopyrronium bromide group were: dry mouth (8 of 20; 40%), constipation (6 of 20; 30%), vomiting (6 of 20; 30%), nasal congestion (6 of 20; 30%), flushing (5 of 20; 25%) and urinary retention (3 of 20; 15%). The most common adverse effects occurring in the placebo group were constipation (4 of 18; 22%) and flushing (3 of 18; 17%). The statistical significance of differences between groups was not reported.

**Adults with Parkinson's disease**

In the placebo-controlled, crossover RCT by Arbouw et al. (2010), adverse effects were assessed using a questionnaire at the end of each treatment week. No serious adverse effects were reported in people taking glycopyrronium bromide or placebo, and there were no statistically significant differences between study treatments in non-serious adverse effects. Dry mouth was the most common adverse effect, experienced by 12 of 23 (52.2%) people while taking glycopyrronium bromide compared with 7 of 23 (30.4%) while taking placebo (p=0.18). A change in motor symptoms was reported among 13% of people in the glycopyrronium bromide group and 17.4% in the placebo group (p=1.0). The following adverse effects were reported equally among the groups: nervousness (21.7%), constipation (13%), vision problems (13%) and palpitations (4.3%). The participant that had 5 times the dosage of glycopyrronium bromide in the first 3 days of treatment experienced marked dryness of the mouth, which resolved within a day of stopping the trial.

**People with schizophrenia and clozapine-induced hypersalivation**

In the crossover RCT Liang et al. (2010) reported that adverse effects did not differ appreciably by study treatment (data not provided). One person stopped treatment while receiving biperiden because of an unstable psychiatric condition. It is not reported whether this was thought to be treatment related. Two adverse effects were reported in the treatment phases: 1 person complained of constipation and 1 complained of 'inner unrest'; the treatment group to which these people were assigned when they reported these effects is not provided.
Evidence review: economic issues

Cost effectiveness

No cost-effectiveness studies of oral glycopyrronium bromide for treating hypersalivation were identified.

Cost

The NHS Electronic Drug Tariff (May 2013) lists the following prices for glycopyrronium bromide oral solution or suspension in Part VIIIIB, Arrangements for payment for specials and imported unlicensed medicines:

- Glycopyrronium bromide 1 mg/5 ml oral solution/suspension: £150.92 for minimal volume of 100 ml plus £0.01 for each extra ml.
- Glycopyrronium bromide 2 mg/5 ml oral solution: £262.61 for minimal volume of 100 ml plus £0.14 for each extra ml.
- Glycopyrronium bromide 2 mg/5 ml oral suspension: £197.59 for minimal volume of 100 ml plus £0.15 for each extra ml.

Based on the use of glycopyrronium bromide 1 mg/5 ml oral solution/suspension, the cost of 7 days' treatment is estimated at £152 (2 mg dose, 3-times daily [210 ml]) or £153 (3 mg dose, 3-times daily [315 ml]). The cost of 4 weeks treatment is estimated at £158 (840 ml) or £162 (1260 ml). This gives annual costs of about £2100 based on 13 4-weekly prescriptions.

No price is listed for glycopyrronium bromide oral tablets, and the cost of these will differ depending on the source. NHS prescription cost analysis for England 2012 reported that various glycopyrronium bromide tablets cost between £268.57 and £712.34 per item (the number of tablets per item is not known).

Current drug usage

NHS prescription cost analysis for England 2012 reported that the following oral glycopyrronium bromide items were dispensed in 2012:

- Glycopyrronium bromide 200 microgram/5 ml liquid special: 400 items at a net cost of £138,200.
• Glycopyrronium bromide 500 microgram/5 ml liquid special: 300 items at a net cost of £112,000.

• Glycopyrronium bromide 2 mg/5 ml liquid special: 800 items at a net cost of £212,100.

• Glycopyrronium bromide 5 mg/5 ml liquid special: 700 items at a net cost of £196,900.

• Glycopyrronium bromide 1 mg/5 ml oral solution: 5800 items at a net cost of £966,000.

• Glycopyrronium bromide 1 mg/5 ml oral suspension: 1000 items at a net cost of £164,400.

• Glycopyrronium bromide 1 mg tablets: 8300 items at a net cost of £2,239,400.

• Glycopyrronium bromide 2 mg tablets: 3500 items at a net cost of £1,199,900.

• Robinul 1 mg tablets (import): 500 items at a net cost of £314,400.

• Robinul forte 2 mg tablets (import): 200 items at a net cost of £136,100.

The total number of items dispensed for oral glycopyrronium bromide was 21,600 at a net cost of £5,732,400. It is not known for which indications these items were prescribed.

No data were identified on the extent of oral use of solution for injection in UK clinical practice.

Evidence strengths and limitations

Four double-blind, randomised controlled trials (RCTs) were identified as relevant, evaluating the efficacy of oral glycopyrronium bromide for treating hypersalivation in children, young people and adults:

• A placebo-controlled, dose-ranging, crossover trial in children and young people with a neurological condition (Mier et al. 2000)

• A placebo-controlled trial in children and young people with a neurological condition (Zeller et al. 2012a)

• A placebo-controlled crossover trial in adults with Parkinson's disease (Arbouw et al. 2010)

• A comparative crossover trial in adults with schizophrenia and clozapine-induced hypersalivation (Liang et al. 2010).

Only 1 of the 4 identified RCTs described allocation concealment (Arbouw et al. 2010).
Arbouw et al. (2010) used an intention to treat (ITT) analysis with last observation carried forward for missing data. Zeller et al. (2012a) used a modified 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. In the Mier et al. (2000) and Liang et al. (2010) studies, efficacy analyses were not based on ITT populations, but on the population of participants who completed the trial.

All of the RCTs were small, including 40 or fewer participants in each trial, and there was variation in the severity of the different neurological conditions among participants. Most of the children and young people in the trials had cerebral palsy, and little inferences can be made for the effectiveness or safety of glycopyrronium bromide in children and young people with a neurological condition other than cerebral palsy.

The RCTs were all short term, with treatment lengths of 1 week in Arbouw et al. (2010), 4 weeks in Liang et al. (2010), and 8 weeks in Mier et al. (2000) and Zeller et al. (2012a). They do not provide evidence for the safety and efficacy of long-term use of oral glycopyrronium bromide for treating adults, children and young people with hypersalivation.

The dosage of glycopyrronium bromide varied in the trials. It was titrated and dependent on weight in the 2 trials of children and young people, up to a maximum of 3 mg per dose given 3-times daily. The other 2 trials had lower fixed doses: 1 mg 3-times daily in adults with Parkinson's disease and 1 mg twice daily in adults with schizophrenia and clozapine-induced hypersalivation.

All of the trials used 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 evaluation is a limitation of all the trials.

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.

No relevant RCTs were identified which compared oral glycopyrronium bromide with placebo for treating hypersalivation in people with drug-induced hypersalivation. Liang et al. (2010) compared glycopyrronium bromide with another drug (biperiden), but there was no placebo group. This
evidence summary has not compared different oral formulations of glycopyrronium bromide and does not describe oral use of solution for injection.

Summary for patients

A summary written for patients is available on the NICE website.

References


Amdipharm Mercury Company Ltd (2012) Robinul powder. [online; accessed 23 April 2013]

Amdipharm Mercury Company Ltd (2012) Glycopyrrolate injection USP 200 microgram/ml, 1 ml and 3 ml. [online; accessed 23 April 2013]


Center for Drug Evaluation and Research. Application number: 022571Orig1s000. Labelling: Cuvposa [online; accessed 16 May 2013]

General Medical Council (2013) Prescribing guidance: prescribing unlicensed medicines. [online; accessed 23 April 2013]


Novartis Pharmaceuticals UK Ltd (2012) Seebri Breezhaler inhalation powder, hard capsules 44 microgram. [online; accessed 23 April 2013]


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

Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

Project team

Bazian Ltd
Peer reviewers and contributors

Lizzie Amis, Senior Public Involvement Adviser, Public Involvement Programme, NICE

Rashmi Papneja, Amdipharm Mercury Company Ltd

Expert advisers

Dr Paul Cooper, Consultant Neurologist, Greater Manchester Neuroscience Centre, Honorary Senior Lecture in Medicine, University of Manchester

Dr Jan Dudley, Chair of the Clinical Standards Committee at Royal College of Paediatrics and Child Health (RCPCH)

Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

1. NICE Evidence Services
2. NICE
3. Euroscan
4. Broad internet search: Google e.g.: (Glycopyrronium OR Glycopyrrolate OR Cuvposa OR Robinul) AND (~guideline OR ~algorithm) filetype:pdf
5. Scirus

MEDLINE (via Ovid)

1. (Glycopyrronium or Glycopyrrolate or Cuvposa or Robinul).mp.
2. Glycopyrrolate/

3. (Hypersalivation or hyper-salivation or salivation or saliva or drooling or secretion* or sialorrhoea or sialorrhea).mp.

4. Sialorrhea/

5. (1 or 2) and (3 or 4)

**Embase (via Ovid)**

1. (Glycopyrronium or Glycopyrrolate or Cuvposa or Robinul).mp.

2. Glycopyrrolate/

3. (Hypersalivation or hyper-salivation or salivation or saliva or drooling or secretion* or sialorrhoea or sialorrhea).mp.

4. hypersalivation/

5. (1 or 2) and (3 or 4)

6. limit 5 to exclude medline journals

**Cochrane Central Register of Controlled Trials (CENTRAL)**

1. MeSH descriptor: [Sialorrhea] this term only

2. Hypersalivation or hyper-salivation or salivation or saliva or drooling or secretion* or sialorrhoea

3. Glycopyrronium or Glycopyrrolate or Cuvposa or Robinul

4. MeSH descriptor: [Glycopyrrolate] explode all trees

5. (#1 or #2) and (#3 or #4)

**CRD HTA, DARE and EED database**

(Hypersalivation or hyper-salivation or salivation or saliva or drooling or secretion* or sialorrhoea or sialorrhea) AND (Glycopyrronium or Glycopyrrolate or Cuvposa or Robinul)
Grey literature and ongoing trials

1. FDA
2. EMA
3. MHRA
4. Scottish Medicines Consortium
5. All Wales Medicine Strategy Group
6. metaRegister of Controlled Trials (mRCT)
7. ClinicalTrials.gov

Manufacturers' websites

MerzPharma http://www.merz.com/

Mercury Pharma Group http://www.mercurypharma.com/[^1]

Evidence selection

This evidence summary has included randomised controlled trials (RCTs) that have investigated the efficacy and safety of oral glycopyrronium bromide (tablets or solution or suspension) for treating adults, children and young people with hypersalivation. We excluded studies that were cohort studies, case series or case reports from the initial search.

Two relevant placebo-controlled RCTs were identified for children and young people with a neurological condition and hypersalivation and 1 relevant placebo-controlled RCT was identified among adults with Parkinson's disease and hypersalivation. A further comparative RCT was identified for adults with schizophrenia and drug-induced hypersalivation. These 4 trials have formed the evidence base for this evidence summary.

No RCTs were identified comparing different oral formulations (tablets versus solution or suspension) of glycopyrronium bromide and no RCTs were identified that studied oral use of solution for injection.

No RCTs were identified that compared oral glycopyrronium bromide with placebo for drug-induced hypersalivation.
This website changed its name to Amdipharm Mercury Company Limited after it was searched on 10 April 2013.

**About 'Evidence summaries: unlicensed or off-label medicines'**

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

> This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

**Copyright**

© Bazian Ltd 2013. All rights reserved. This material may be freely reproduced for educational and not-for-profit purposes. If you wish to reproduce this information for use by commercial organisations or for commercial purposes, please email NICE.

**Contact NICE**

National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT

www.nice.org.uk; nice@nice.org.uk; 0845 003 7780