NICE advice

# Postural hypotension in adults: fludrocortisone

Evidence summary
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## Key points from the evidence

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

## Summary

There is limited evidence from 2 small short-term studies that fludrocortisone improves postural blood pressure and orthostatic symptoms. In another slightly larger study fludrocortisone had no effect on supine blood pressure or wellbeing in a population with chronic fatigue syndrome.

**Regulatory status:** off-label

| Effectiveness | Safety |
| --- | --- |
| • Statistically significant increase in mean tilted and supine systolic blood pressure (~30–40 mmHg) and tilted diastolic blood pressure (~10 mmHg) compared with placebo (1 randomised controlled trial [RCT], 3 weeks, n=6).<br>• Statistically significant improvement in orthostatic domain of Composite Autonomic Symptom Scale (1 RCT, 3 weeks, n=17).<br>• No effect on wellbeing or mean supine systolic blood pressure or diastolic blood pressure in those with chronic fatigue syndrome (1 RCT, 9 weeks, n=100). | • Fludrocortisone is a potent mineralocorticoid.<br>• Dosage and salt intake should be monitored to avoid development of hypertension, oedema or weight gain. Monitoring of serum electrolyte levels advisable during prolonged therapy.<br>• Adverse effects reported include oedema, weight gain, headache and electrolyte disturbances. Limited data on long-term safety. Common adverse effects may be associated with more serious consequences in old age. |
| **Patient factors** | **Resource implications** |
| • Patients should carry a steroid treatment card.<br>• Tolerance to long-term treatment may be an issue. In an observational study of 64 older adults, 17 stopped treatment because of adverse effects after a mean of 5 months.<br>• Needs to be stored in the fridge with bottle tightly closed to protect from moisture. | • Cost of £5.05 for 100 tablets. |

# Key points

Use of fludrocortisone acetate (Florinef) for treating postural (orthostatic) hypotension is off label because it does not have a UK marketing authorisation for this indication, but it

does have marketing authorisation for other indications. No other drugs currently have a UK marketing authorisation for postural hypotension.

Three small randomised controlled trials (RCTs) were identified for inclusion in this evidence summary. In all of the trials, postural blood pressure was investigated using a head-up tilt-test, in which the body is tilted head-up to at least a 60° angle on a tilt-table.

Campbell et al. (1975) was a double-blind, crossover RCT that included 6 adult males (mean age 52 years) with symptomatic postural hypotension as a result of diabetic autonomic neuropathy. Participants were randomised to 3 weeks of 100 micrograms fludrocortisone twice daily or placebo, followed by a 3-week washout period, then crossover to 3 weeks of the alternative treatment.

This study found a statistically significant increase in mean tilted position systolic blood pressure (SBP) with fludrocortisone compared with placebo (154 [±29] mmHg versus 110 [±16] mmHg; p<0.005). There was also a statistically significant increase in mean supine SBP with fludrocortisone compared with placebo (180 [±26] mmHg versus 149 [±21] mmHg; p<0.05) and tilted position diastolic blood pressure (DBP) (88 [±11] mmHg versus 76 [±4] mmHg; p<0.05).

A second, small, double-blind, crossover RCT (n=17) in adults (mean age 69 years) with symptomatic postural hypotension and Parkinson's disease (Schoffer et al. 2007) is included in this evidence summary. The active comparator in this crossover trial was domperidone (off-label use); however, no direct comparisons with fludrocortisone were made. Instead, non-pharmacological treatment alone was compared with non-pharmacological treatment plus drug treatment.

This study found a statistically significant improvement in the orthostatic domain score of the Composite Autonomic Symptom Scale (COMPASS\u2011\OD) after taking 100 micrograms fludrocortisone daily for 3 weeks compared with non-pharmacological treatment alone. The clinical significance of this improvement (a decrease in the mean score of 3 points; on a 16-point scale) is unclear. The authors concluded that there was a trend towards reduced blood pressure drop on tilt-table testing with fludrocortisone and domperidone. However, no statistical analysis for the results of tilt-table testing was provided.

The third RCT included in this evidence summary (Rowe et al. 2001) was a double-blind, placebo-controlled trial (n=100) carried out in a population with chronic fatigue syndrome

(see Evidence review: efficacy for details). This RCT found that 9 weeks' treatment with fludrocortisone titrated to 100 micrograms daily had no significant effect on global wellness score, mean supine SBP or DBP compared with placebo.

Safety of fludrocortisone has not been adequately assessed in these 3 RCTs. However, fludrocortisone is a potent mineralocorticoid and its adverse effect profile in its summary of product characteristics (Florinef) reflects this. The incidence of predictable adverse effects is dependent on the dosage, frequency and duration of treatment. Patients should be advised to carry a steroid treatment card.

Because the studies included in this evidence summary are all short term, they provide no information on the long-term safety and efficacy of fludrocortisone for treating postural hypotension.

**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 fludrocortisone

Fludrocortisone acetate (Florinef) 100 micrograms tablets are licensed in the UK for partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease and for treating salt-losing adrenogenital syndrome. Fludrocortisone does not have marketing authorisation in the UK for treating postural hypotension, so use for this indication is **off label**.

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 fludrocortisone outside its authorised indications.

# Evidence statements

- One small double-blind, placebo-controlled, crossover randomised controlled trial (RCT) (Campbell et al. 1975) in 6 adult males with postural hypotension as a result of diabetic autonomic neuropathy found that 100 micrograms fludrocortisone taken twice daily for 3 weeks increased both tilted position and supine systolic blood pressure (SBP) [~30–40 mmHg] and tilted position diastolic blood pressure (DBP) [~10 mmHg] compared with placebo.

- One small double-blind crossover RCT (Schoffer et al. 2007) in 17 adults with postural hypotension and Parkinson's disease found a statistically significant improvement in the orthostatic domain of the Composite Autonomic Symptom Scale (COMPASS\u2011\OD) with 3 weeks of 100 micrograms fludrocortisone daily plus non-pharmacological treatment compared with non-pharmacological treatment alone. The clinical significance of this improvement (a decrease in the mean score of 3 points; on a 16-point scale) is unclear.

- One placebo-controlled RCT (Rowe et al. 2001) in 100 adults with chronic fatigue syndrome found no significant effect of 9 weeks of fludrocortisone titrated to 100 micrograms daily compared with placebo on global wellness score, supine SBP and DBP.

- Safety of fludrocortisone use has not been adequately assessed in these 3 RCTs. Side effects reported in the studies included ankle oedema, weight increase, electrolyte disturbances, hypertension, depression, abdominal discomfort, nausea, headache, light-headedness and dizziness.

- Withdrawals were higher with fludrocortisone than placebo in the longest trial (Rowe et al. 2001) (26% of people taking fludrocortisone withdrew compared with 16% receiving placebo).

- The longer-term (more than 9 weeks) efficacy and safety of fludrocortisone has not been studied in these RCTs.

- A prospective observational study (Hussain et al. 1996) over a mean follow-up of 12 months (range 2–21 months) in 64 older adults with 1 or more hypotensive disorders (including 17 people given fludrocortisone for postural hypotension) reported that 38 people (59.4%) experienced side effects and 17 stopped treatment after a mean of 5 months. However, the observational nature of this study in a mixed population with 1 or more hypotensive disorders and the lack of a control arm limit the conclusions that can be drawn.

# Summary of the evidence

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

## Efficacy

All of the trials identified were small, with 100 participants or fewer. Two double-blind, crossover RCTs examined the efficacy and safety of fludrocortisone for treating postural hypotension (postural drop of at least 20–30 mmHg in systolic blood pressure [SBP] or 10 mmHg in diastolic blood pressure [DBP]) in adult males with autonomic diabetic neuropathy (n=6; Campbell et al. 1975; when compared with placebo) and adults with Parkinson's disease (n=17; Schoffer et al. 2007; when compared with domperidone; off-label use) for 3 weeks.

There was no direct comparison between fludrocortisone and domperidone in Schoffer et al. (2007). Doses of fludrocortisone in these trials were 100 micrograms taken 1 or 2 times daily. Both Schoffer et al. (2007) and Campbell et al. (1975) investigated postural drop using a head-up tilt-test, in which the person is tilted head-up to at least a 60° angle on a tilt table.

One additional double-blind randomised placebo-controlled trial (Rowe et al. 2001; n=100) was identified comparing 9 weeks' treatment with fludrocortisone (titrated to 100 micrograms daily) with placebo in adults with chronic fatigue syndrome (see Evidence review: efficacy for details).

Results of the RCT in men with autonomic diabetic neuropathy (Campbell et al. 1975) found that 3 weeks' treatment with 100 micrograms fludrocortisone daily increased both tilted position and supine SBP (~30–40 mmHg) and tilted position DBP (~10 mmHg) compared with placebo.

A total of 5 participants were analysed with 1 excluded because of 'default' while taking fludrocortisone (Campbell et al. 1975). No further information is provided about why this participant dropped out. Out of 5 participants, 4 were reported to notice a marked improvement in their symptoms of postural hypotension while taking fludrocortisone. However, it is not reported how this was assessed.

The RCT in people with Parkinson's disease (Schoffer et al. 2007) had 2 phases. Phase 1 evaluated non-pharmacological treatment for postural hypotension, and phase 2 evaluated drug treatment (fludrocortisone and domperidone). Non-pharmacological treatment was continued throughout the course of the study and then an analysis was performed of non-pharmacological treatment plus drug treatment compared with non-pharmacological treatment alone. It found that there was a statistically significant improvement (a decrease in the mean score of 3 points; on a 16-point scale) in the orthostatic domain of the Composite Autonomic Symptom Scale (COMPASS-OD) after 3 weeks' treatment with 100 micrograms fludrocortisone daily compared with non-pharmacological treatment alone. There was a very slight improvement (an increase in the mean score of 0.2; on a scale of +3 to −3) in the global impression of change score after treatment with fludrocortisone compared with non-pharmacological treatment alone; no statistical analysis reported. The authors concluded that there was a trend towards reduced blood pressure drop on tilt-table testing with both fludrocortisone and domperidone. However, no statistical analysis of the tilt-table test results was provided (see table 2 for results).

The RCT in adults with chronic fatigue syndrome (Rowe et al. 2001) found no statistically significant difference between fludrocortisone and placebo for improvement in global wellness score and mean supine SBP and DBP.

### Table 1 Summary of Campbell et al. (1975) (adult males with diabetic autonomic neuropathy and postural hypotension)

| | Fludrocortisone | Placebo | Analysis |
|---|---|---|---|
| Campbell et al. (1975): double-blind randomised crossover trial | | | |
| Dose | 100 micrograms oral tablets 2 times daily | | |
| Randomised | n=6 | | |
| **Efficacy** | | | |

| | | | |
|---|---|---|---|
| Analysed | n=5 | | |
| Supine SBP, mmHg, mean (SD) | 180 (26) | 149 (21) | p<0.05 |
| Tilted position SBP, mmHg, mean (SD) | 154 (29) | 110 (16) | p<0.005 |
| Mean supine SBP versus mean tilted position SBP | No statistically significant difference between mean supine and tilted position SBP with fludrocortisone (p<0.10) | Statistically significant difference between mean supine and tilted position SBP with placebo (p<0.001) | |
| Supine DBP, mmHg, mean (SD) | 95 (17) | 87 (10) | NS, p value not reported |
| Tilted position DBP, mmHg, mean (SD) | 88 (11) | 76 (4) | p<0.05 |
| Mean supine DBP versus mean tilted position DBP | No statistically significant difference between mean supine and tilted position DBP with fludrocortisone (p value not reported) | Statistically significant difference between mean supine and tilted position DBP with placebo (p<0.02) | |
| Supine heart rate, beats per minute, mean (SD) | 76 (12) | 78 (10) | NS, p value not reported |

| | | | |
|---|---|---|---|
| Tilted position heart rate, beats per minute, mean (SD) | 86 (20) | 97 (18) | p<0.001 |
| **Safety** | | | |
| Discontinuation or withdrawal from study | n=1/6 | n=0/6 | 1 person is reported to have 'defaulted' while taking fludrocortisone. No further information is provided. |
| AE: pitting ankle oedema | n=2/5 (within 1 week of starting treatment) | n=0/5 | Both people had intermittent proteinuria and low plasma albumin |
| AE: self-reported frontal headache and breathlessness | n=1/5 | n=0/5 | The person had intermittent proteinuria and low plasma albumin |
| Serum sodium, mmol/litre, mean (SD) | 142.6 (2.2) | 140.6 (1.3) | p<0.02 |
| Serum potassium, mmol/litre, mean (SD) | 3.6 (0.4) | 4.3 (0.2) | p<0.01 |
| Body weight, kg (SD) | 71.6 (9.3) | 68.9 (9.3) | p<0.001 |
| Total plasma volume, ml (SD) | 3286 (234) | 2957 (171) | p<0.02 |

Abbreviations: AE, adverse event(s); DBP, diastolic blood pressure n, number of patients; NS, non-significant; SBP, systolic blood pressure; SD, standard deviation.

**Table 2 Summary of Schoffer et al. (2007) (adults with Parkinson's disease and postural hypotension)**

| | Fludrocortisone plus non-pharmacological treatment | Domperidone plus non-pharmacological treatment | Non-pharmacological treatment alone |
|---|---|---|---|
| Schoffer et al. (2007): double-blind randomised crossover trial | | | |
| Dose | 100 micrograms daily | 10 mg 3 times daily | |
| Randomised | n=17 | | |
| **Efficacy** | | | |
| Analysed | n=13 | | |
| **Primary outcome measures** | | | |
| COMPASS-OD score[a] expressed as mean (SD) (median; range) | 6 (3)<br>(6; 1 to 10)<br>Statistically significant improvement compared with non-pharmacological treatment alone (p=0.02) | 7 (2)<br>(6; 3 to 11)<br>Statistically significant improvement compared with non-pharmacological treatment alone (p=0.04) | 9 (3)<br>(9; 5 to 15) |

| | | | |
|---|---|---|---|
| CGI score[b] expressed as mean (SD)<br>(median; range) | 0.6 (1.2)<br>(1; −1 to 2)<br>No statistical analysis reported for this outcome measure | 0.9 (1.2)<br>(1; −2 to 2)<br>No statistical analysis reported for this outcome measure | 0.4 (1)<br>(0; −2 to 2) |
| Drop in SBP, mmHg, at 3 minutes of tilt table, expressed as mean (SD) (median; range) | 18 (24)<br>(8; −8 to 64)<br>No statistical analysis reported for tilt-table testing | 18 (23)<br>(5; −4 to 57)<br>No statistical analysis reported for tilt-table testing | 21 (20)<br>(17; −15 to 48) |
| Maximal drop in SBP, mmHg, during 5 minutes of tilt table, expressed as mean (SD) (median; range) | 30 (23)<br>(24; −2 to 64)<br>No statistical analysis reported for tilt-table testing | 28 (21)<br>(19; 5 to 61)<br>No statistical analysis reported for tilt-table testing | 35 (23)<br>(32; 6 to 68) |
| Drop in DBP, mmHg, at 3 minutes of tilt table, expressed as mean (SD) (median; range) | 8 (13)<br>(8; −11 to 33)<br>No statistical analysis reported for tilt-table testing | 7 (15)<br>(0; −10 to 36)<br>No statistical analysis reported for tilt-table testing | 7 (7)<br>(8; −4 to 18) |
| Maximal drop in DBP, mmHg during 5 minutes of tilt table, expressed as mean (SD) (median; range) | 18 (12)<br>(20; 0 to 35)<br>No statistical analysis reported for tilt-table testing | 14 (15)<br>(6; −1 to 40)<br>No statistical analysis reported for tilt-table testing | 17 (10)<br>(20; 3 to 37) |

| | | | |
|---|---|---|---|
| Supine SBP, mmHg, expressed as mean (SD) (median; range) | 134 (24)<br>(137; 100 to 165)<br>No statistical analysis reported for tilt-table testing | 138 (27)<br>(125; 107 to 189)<br>No statistical analysis reported for tilt-table testing | 138 (23)<br>(139; 107 to 175) |
| **Safety** (n=17) | | | |
| Discontinuation or withdrawal from study | n=1 | n=3 | |
| Total patients reporting AEs | n=6<br>No statistical analysis reported | n=5<br>No statistical analysis reported | |
| Abbreviations: AE, adverse event(s); CGI, clinical global impression of change; COMPASS-OD, orthostatic domain of the Composite Autonomic Symptom Scale; DBP, diastolic blood pressure; n, number of patients; SBP, systolic blood pressure; SD, standard deviation.<br>[a] COMPASS-OD: a series of weighted questions relating specifically to orthostatic hypotension. Maximum score is 16, with higher scores indicating more severe symptoms.<br>[b] CGI: Global impression of change score that focuses on orthostatic symptoms (+3=very much improved, +2=much improved, +1=minimally improved, 0=no change, −1=minimally worse, −2=much worse, −3=very much worse). | | | |

**Table 3 Summary of Rowe et al. (2001) (people with chronic fatigue syndrome and neurally mediated hypotension)**

| | Fludrocortisone | Placebo | Analysis |
|---|---|---|---|
| Rowe et al. (2001): double-blind randomised trial | | | |

| | | | |
|---|---|---|---|
| Dose | Week 1:<br>25 micrograms daily<br>Week 2:<br>50 micrograms daily<br>Week 3 to end of week 9:<br>100 micrograms daily | Dose titrated as per the intervention dose | |
| Randomised | n=50 | n=50 | |
| **Efficacy** | | | |
| **Primary outcome** | | | |
| Global wellness score 15-point improvement | 14% (7/50) | 10% (5/50) | p=0.76 using ITT analysis |
| **Selected secondary and additional outcomes** | | | |
| **Tilt-table outcomes**[a] | | | |
| Analysed | n=50 for baseline tilt test, n=33 for second tilt test during treatment | n=50 for baseline tilt test, n=41 for second tilt test during treatment | |
| Supine SBP, mmHg, mean (SD) | Baseline: 115.8 (11.9) | Baseline: 117.7 (13.1) | p=0.46 |
| | During treatment: 117.5 (9.6) | During treatment: 113.7 (10.0) | p=0.11 |
| Supine DBP, mmHg, mean (SD) | Baseline: 72.4 (6.7) | Baseline: 75.0 (7.2) | p=0.06 |
| | During treatment: 73.3 (6.6) | During treatment: 73.4 (7.4) | p=0.93 |
| HR, beats/minute Mean (SD) | Baseline: 70.7 (8.4) | Baseline: 69.8 (9.8) | p=0.64 |
| | During treatment: 69.0 (8.8) | During treatment: 69.3 (9.2) | p=0.90 |

| | | | |
|---|---|---|---|
| Number of people who had NMH provoked in stage 1 of tilt test | Baseline: 34 | Baseline: 33 | p=0.83 |
| | During treatment: 20 | During treatment: 17 | p=0.16 |
| Number of people who had NMH provoked in stage 2 of tilt test | Baseline: 16 | Baseline: 17 | No p value given |
| | During treatment: 6 | During treatment: 14 | No p value given |
| Tilt test normal in both stages | Baseline: 0 | Baseline: 0 | No p values given |
| | During treatment: 4 | During treatment: 9 | |
| Refused stage 2 of tilt test | Baseline: 0 | Baseline: 0 | No p values given |
| | During treatment: 3 | During treatment: 1 | |
| No follow-up tilt test during treatment | 5 | 1 | No p value given |
| **Safety** | | | |
| Discontinuation or withdrawal from study | n=13 (12 people withdrew before week 5) | n=8 (5 people withdrew before week 5) | No statistical analysis reported |
| Participants reporting at least 1 AE | 61% | 71% | No statistical analysis reported. |
| Mean serum sodium concentration during treatment, mEq/litre (SD) | 141.9 (2.0) | 140.3 (2.3) | p=0.003 |
| Mean serum potassium concentration during treatment, mEq/litre (SD) | NR | NR | Reported as no difference between groups, no p value given |
| Mean weight increase kg (SD) | 1.1 (1.6) | 1.2 (1.6) | No p value given |

Abbreviations: AE, adverse event; DBP, diastolic blood pressure; HR, heart rate; ITT, intention to treat; n, number of patients; NMH, neurally mediated hypotension; NR, not reported; SBP, systolic blood pressure; SD, standard deviation.

[a] Tilt-table testing was performed at baseline 2 weeks before treatment started and then again during the 9th week of treatment.

## Safety

The summary of product characteristics for Florinef (100 microgram tablets) reports that because fludrocortisone is a potent mineralocorticoid, dosage and salt intake should be monitored to avoid the development of hypertension, oedema or weight gain and that monitoring of serum electrolytes is advisable during prolonged therapy (prolonged therapy not further defined). Fludrocortisone is contraindicated for people with systemic infections (unless anti-infective therapy is used) and for people with hypersensitivity to any of the ingredients. Withdrawal after prolonged use must be gradual to avoid acute adrenal insufficiency and should involve tapering off over weeks or months depending on the treatment dose and duration. The summary of product characteristics reports that when adverse effects occur with fludrocortisone, they are usually reversible after stopping treatment and that the incidence of predictable adverse effects is dependent on the dosage, frequency and duration of treatment. The common adverse effects of systemic corticosteroids may be associated with more serious consequences in older adults.

In Campbell et al. (1975), there was an increase in mean supine SBP with fludrocortisone compared with placebo. However, in Rowe et al. (2001), mean supine SBP was similar between fludrocortisone and placebo and in Schoffer et al. (2007), mean supine SBP with fludrocortisone was similar to the mean supine SBP before treatment.

In Campbell et al. (1975), 2 people, both with known intermittent proteinuria and low plasma albumin, developed pitting ankle oedema within 1 week of starting fludrocortisone. One of these people also reported frontal headache and breathlessness. Adverse effects were said to rapidly subside after completing treatment. There was an increase in mean body weight and total plasma volume with fludrocortisone compared with placebo. There was also an increase in serum sodium concentration and a reduction in serum potassium concentration with fludrocortisone compared with placebo.

In the crossover RCT of 17 people with Parkinson's disease (Schoffer et al. 2007), there were fewer withdrawals in the fludrocortisone group (1 person) compared with

domperidone (3 people). Six people reported adverse effects while receiving fludrocortisone compared with 5 people receiving domperidone. Adverse effects reported with fludrocortisone were: nausea (2 reports), with single reports of chest discomfort, morning headache, light-headedness and dizziness. No testing of statistical significance between groups was reported.

In the RCT of people with chronic fatigue syndrome (Rowe et al. 2001), study withdrawals were more common in the fludrocortisone group (13 of 50) compared with placebo (8 of 50); statistical analysis was not reported. At least 1 adverse effect was reported during treatment by 61% of people receiving fludrocortisone compared with 71% receiving placebo. No important adverse effects were reported by the study authors as lasting long after treatment discontinuation. Overall mean weight increased by 1.1 kg in the fludrocortisone group and by 1.2 kg in the placebo group. Mean serum sodium concentration was higher with fludrocortisone compared with placebo.

Longer-term safety data for fludrocortisone in treating postural hypotension are limited. One prospective observational study (Hussain et al. 1996) provided information on older adults receiving the drug over an average follow-up of 12 months (range 2–21 months). The study included 64 people (mean age 80 years) with 1 or more hypotensive disorders. Adverse events were reported in 38 of 64 people (59.4%) and 17 stopped treatment because of adverse effects at a mean of 5 months. Reasons for drug withdrawal were: cardiac failure (n=7), systolic hypertension (n=4), depression (n=3), lack of benefit (n=2) and stroke (n=1). Hypokalaemia developed in 8 participants but there were no withdrawals for this reason. However, the observational nature of this study in a mixed population with people with 1 or more hypotensive disorders and the lack of a control arm limit the conclusions that can be drawn.

## Cost effectiveness and cost

No studies on the cost effectiveness of fludrocortisone in treating postural hypotension were identified.

According to the NHS electronic drug tariff (September 2013), the cost of Florinef (100 microgram tablets; fludrocortisone acetate) is £5.05 for 100 tablets.

# Relevance to NICE guidance programmes

This off-label use of fludrocortisone for postural hypotension is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme. No NICE guidance specifically on postural hypotension was identified.

Other NICE guidance related to postural hypotension includes:

- Transient loss of consciousness ('blackouts') management in adults and young people (NICE clinical guideline 109). This guideline includes recommendations on assessment and referral for suspected postural hypotension and safety advice for people with the condition.
- Parkinson's disease: diagnosis and management in primary and secondary care (NICE clinical guideline 35). This guideline includes a recommendation on managing autonomic disturbances, including postural hypotension.
- Falls: the assessment and prevention of falls in older people (NICE clinical guideline 161). This guideline does not specifically refer to managing postural hypotension, but is included as a related guideline because having a fall is a possible outcome of postural hypotension.

One of the RCT's included in this evidence summary was carried out in a population with chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME). NICE has published a clinical guideline on Chronic fatigue syndrome / myalgic encephalomyelitis (or encephalopathy): diagnosis and management of CFS/ME in adults and children (NICE clinical guideline 53). The guideline recommends that mineralocorticoids, such as fludrocortisone, should not be used for treating CFS/ME.

This is discussed in more detail in the intervention and alternatives section.

# Intervention and alternatives

This evidence summary addresses the use of oral fludrocortisone acetate tablets (Florinef; E.R. Squibb & Sons) for treating postural hypotension in adults.

Fludrocortisone is a synthetic mineralocorticoid that acts by increasing plasma volume as a result of its sodium-retaining effects, thus increasing cardiac output. It also acts by

potentially increasing sensitivity to sympathetic nerve stimulation, leading to an increase in peripheral vascular resistance (Ong et al. 2013).

# Condition

Postural (or orthostatic) hypotension is a condition in which standing leads to an abnormally large drop in blood pressure, which can result in symptoms such as light-headedness, dizziness, blurring of vision, fainting and falls (Lahrmann et al. 2011). Symptoms resolve as blood pressure returns to normal (for example, on returning to a seated position). Not all people with postural hypotension experience symptoms.

On standing, gravity causes blood to pool in the lower extremities. The autonomic nervous system usually counteracts this by increasing heart rate, cardiac contractility and vascular tone (Freeman et al. 2011). The skeletal muscle in the lower body also contracts to prevent excessive pooling.

The definition of postural hypotension endorsed by the European Federation of Autonomic Societies is a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing, or of tilting the body (with the head up) to at least a 60° angle on a tilt table (Freeman et al. 2011). Acute, unexpected, episodic falls in blood pressure while standing, such as those seen in vasovagal syncope, do not satisfy criteria for postural hypotension (Goldstein and Sharabi 2009). The use of fludrocortisone for vasovagal syncope was not the focus of this evidence summary, although the trial by Rowe et al. (2001) included people with neurally mediated hypotension (NMH), which the authors report is also known as vasovagal hypotension, delayed orthostatic hypotension, neurocardiogenic syncope or vasodepressor syncope. Safety data from fludrocortisone use over a mean of 12 months in an observational study of a mixed population are also included. The study included people with 1 or more hypotensive disorders (postural hypotension, vasodepressor carotid sinus syncope and/or vasodepressor neurocardiogenic syncope).

Postural hypotension may be idiopathic or may arise as a result of disorders affecting the autonomic nervous system (for example, Parkinson's disease, multiple system atrophy or diabetic autonomic neuropathy), from a loss of blood volume or dehydration, or because of certain medications such as antihypertensives (Gibbons et al. 2010).

Postural hypotension is more common in older people, and estimates of prevalence range from 5% to 30% of people aged over 65 years (in the general population), up to 60% of

people with Parkinson's disease, and up to 70% of people living in nursing homes (Freeman et al. 2011; Lahrmann et al. 2011). It is estimated that about 0.2% of people over 75 years are admitted to hospital with problems relating to postural hypotension (Gibbons et al. 2010).

NICE guidance on transient loss of consciousness in adults and young people advises that, if postural hypotension is suspected after an initial assessment, when the history is typical and there are no features suggesting an alternative diagnosis, then the person should have their blood pressure measured lying and standing (with repeated measurements while standing for 3 minutes). The guidance advises that if postural hypotension is confirmed, the likely causes should be considered and the condition should be managed appropriately. NICE clinical guideline on Parkinson's disease recommends that people with Parkinson's disease should have postural hypotension treated appropriately. Specific management options are not discussed in these guidelines.

NICE guidance on chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) recommends that the head-up tilt test should not be done routinely to aid CFS/ME diagnosis. It also recommends that mineralocorticoids such as fludrocortisone should not be used for treating CFS/ME.

# Alternative treatment options

A number of drug and non-pharmacological approaches have been used to treat postural hypotension (Logan and Witham 2012). Non-pharmacological treatments include increasing water and salt intake, or using compression garments or bandages and physical manoeuvres to counter the drop in blood pressure (Gibbons et al. 2010; Logan and Witham 2012).

There are no drugs with marketing authorisation for use in postural hypotension in the UK. Many drugs have been considered or studied for potential use in postural hypotension, including drugs that target the autonomic nervous system (such as midodrine, phenylephrine, ephedrine, pseudoephedrine, droxidopa and phenylpropanolamine), pyridostigmine, domperidone, non-steroidal anti-inflammatory drugs and erythropoietin (Gibbons et al. 2010; Logan and Witham 2012).

Some of these drugs, such as domperidone and pyridostigmine (as well as fludrocortisone) have licences for other indications in the UK, but their use in postural hypotension is off label.

Midodrine does not have UK marketing authorisation for postural hypotension or any other indication. NICE has published an evidence summary on the unlicensed or off-label use of midodrine for treating postural hypotension in adults.

One systematic review concluded that many commonly used interventions for postural hypotension have a limited evidence base to support their use (Logan and Witham 2012).

# Evidence review: efficacy

One 2013 systematic review of 2 randomised controlled trials (RCTs) and 1 additional RCT not included in the systematic review were identified that met inclusion criteria.

## Systematic review

One systematic review was identified (Ong et al. 2013) that included double-blind RCTs evaluating the efficacy of drug treatments for orthostatic (postural) hypotension in adults. It included trials assessing efficacy of short-term (less than 24 hours) and long-term use (more than 24 hours and with blood pressure measurements taken over at least 48 hours).

The review included 3 RCTs that assessed the long-term effects (24 hours or more) of fludrocortisone. One of these RCTs compared midodrine plus fludrocortisone with placebo plus fludrocortisone (Kaufmann et al. 1988). Because both trial arms in this study received fludrocortisone, its efficacy cannot be determined, so the study has not been further described. The other 2 RCTs (Campbell et al. 1975 and Schoffer et al. 2007) included in the systematic review are summarised below.

## Randomised controlled trial by Campbell et al. (1975)

Campbell et al. (1975) performed a double-blind, placebo-controlled, crossover RCT that included 6 adult males (mean age 52 years) with symptomatic postural hypotension (with a fall of systolic blood pressure of 30 mmHg or more) as a result of diabetic autonomic neuropathy. None of the included participants had ischaemic heart disease or cardiac failure. Two had intermittent proteinuria and a reduced serum albumin. Four participants are reported to have been receiving insulin and 2 as receiving an oral antidiabetic drug (not further specified).

Participants completed a 3-week observation period and were then randomised to 3 weeks of oral 100 micrograms fludrocortisone tablets twice daily or placebo. This was followed by a 3-week washout period, then crossover to 3 weeks of the alternative treatment. A total of 5 participants were evaluated, with 1 excluded because of 'default' while taking fludrocortisone. No further information is provided about why this participant dropped out.

Measurements were carried out at the end of each 3-week period during a physical examination. Systolic and diastolic blood pressure (SBP and DBP) were measured during standardised tilt-table testing. Mean values for SBP, DBP and heart rate in the supine position were compared with mean values in the tilted position.

After 3 weeks of treatment, there was a statistically significant increase in mean supine and tilted SBP with fludrocortisone compared with placebo:

- Mean supine SBP was 180 mmHg (±26) with fludrocortisone compared with 149 mmHg (±21) with placebo, $p<0.05$.
- Mean tilted SBP was 154 mmHg (±29) with fludrocortisone compared with 110 mmHg (±16) with placebo, $p<0.005$.

There was a statistically significant difference between mean supine and tilted position SBP with placebo ($p<0.001$). However, there was no statistically significant difference between mean supine and tilted position SBP with fludrocortisone ($p<0.10$).

After 3 weeks of treatment, there was a statistically significant increase in tilted position DBP with fludrocortisone compared with placebo. There was no statistically significant difference between fludrocortisone and placebo for mean supine DBP:

- Mean supine DBP was 95 mmHg (±17) with fludrocortisone compared with 87 mmHg (±10) with placebo; reported as non-significant, p value not reported.
- Mean tilted DBP was 88 mmHg (±11) with fludrocortisone compared with 76 mmHg (±4) with placebo, $p<0.05$.

There was a statistically significant difference between mean supine and tilted position DBP with placebo ($p<0.02$). However, there was no significant difference between mean supine and tilted position DBP with fludrocortisone (p value not reported).

There was no statistically significant difference between fludrocortisone and placebo for

supine heart rate. However, there was a statistically significant reduction in heart rate in the tilted position with fludrocortisone compared with placebo (86 beats/min [±20] with fludrocortisone compared with 97 beats/min [±18] with placebo, p<0.001). Participant-reported symptoms of postural hypotension were assessed regularly during the trial, and 4 out of 5 participants evaluated reportedly noticed 'a marked improvement' in symptoms while on fludrocortisone. However, it is not reported how this was assessed and no symptom scores or between-group comparisons were reported.

# Randomised controlled trial by Schoffer et al. (2007)

Schoffer et al. (2007) was a double-blind, crossover RCT that included 17 adults (mean age 69 years; 76% male) with symptomatic postural hypotension (postural drop of at least 20 mmHg in SBP and/or 10 mmHg in DBP) and idiopathic Parkinson's disease. Participants with SBP more than 200 mmHg or DBP more than 100 mmHg were excluded as were participants with acute coronary syndrome or other causes of autonomic failure. At baseline, 1 of the 17 participants did not show a postural blood pressure drop that would fit the description of postural hypotension described above; however, they were still included in the study because they had a previous history of confirmed postural hypotension. Participants had an average time since Parkinson's diagnosis of 6 years. The study was carried out in 2 phases: phase 1 evaluated non-pharmacological treatment for postural hypotension and phase 2 evaluated drug treatment (fludrocortisone and domperidone).

The 3 primary outcome measures were: the orthostatic domain of the Composite Autonomic Symptom Scale (COMPASS-OD; maximum score of 16, with higher scores indicating more severe symptoms); clinical global impression of change (CGI) score focusing on orthostatic symptoms (+3=very much improved, +2=much improved; +1=minimally improved, 0=no change; −1=minimally worse, −2=much worse, −3=very much worse) and postural blood pressure. Comparisons were made between baseline and non-pharmacological treatment and between non-pharmacological treatment alone and non-pharmacological treatment plus the designated drug treatment. No direct comparisons between fludrocortisone and domperidone were made.

At baseline, COMPASS-OD score and supine and standing blood pressure were obtained. Participants were then asked to comply with 12 non-pharmacological treatments (including increasing dietary salt intake, elevating the head of the bed and wearing thigh-high pressure stockings) for 3 weeks. At the end of the 3-week period, COMPASS-OD score and blood pressure testing were repeated and the CGI score was obtained.

Participants then entered into phase 2 of the study; postural blood pressure was assessed by tilt-table testing. Participants lay supine for at least 15 minutes, then had blood pressure and heart rate changes recorded during 5 minutes lying supine; during 5 minutes at an 80° head-up tilt; and during a further 5 minutes of lying supine. Maximal drop in SBP and DBP over 5 minutes and drop in SBP and DBP at 3 minutes were calculated.

Participants were then randomised to receive either 3 weeks of 100 micrograms once-daily fludrocortisone tablets plus 2 placebo tablets (given at lunch and dinner) or 10 mg 3 times daily domperidone tablets. This was followed by a 1-week washout period, then crossover to 3 weeks of the alternative treatment. Participants were instructed to continue with the 12 non-pharmacological treatments throughout the study. At the end of each 3-week treatment period, COMPASS-OD, CGI and tilt-table testing were repeated.

There was no significant change in postural blood pressure or COMPASS-OD score after 3 weeks of non-pharmacological treatment.

Withdrawal from the study was higher while receiving domperidone, with 3 people withdrawing in the first week of treatment compared with 1 withdrawal in the first week with fludrocortisone. Therefore, in phase 2, a total of 13 of 17 participants were evaluated in a per protocol analysis.

The mean COMPASS-OD score after non-pharmacological treatment was 9±3 (median 9; range of scores 5 to 15). The mean CGI score after non-pharmacological treatment was 0.4±1 (median 0; range of scores −2 to 2).

The mean COMPASS-OD score with fludrocortisone plus non-pharmacological treatment was 6±3 (median 6; range 1 to 10). This was a statistically significant improvement compared with non-pharmacological treatment alone (p=0.02). The mean CGI score was 0.6±1.2 (median 1; range −1 to 2) after fludrocortisone treatment; no p value reported.

The mean COMPASS-OD score with domperidone plus non-pharmacological treatment was 7±2 (median 6; range 3 to 11). Again, this was a statistically significant improvement compared with non-pharmacological treatment alone (p=0.04). The mean CGI score was 0.9±1.2 (median 1; range −2 to 2) after domperidone treatment; no p value reported.

There were inconsistencies in the reporting of SBP and DBP in the figures and in the narrative text of the study. Findings reported here are taken from the figures, because this included results for all 3 treatment periods, whereas the narrative text only reported

results for baseline. The authors concluded that there was a trend towards reduced blood pressure drop on tilt-table testing with fludrocortisone and domperidone. No statistical analysis is reported for the tilt-table test results. The results below are expressed as mean±standard deviation (SD) (median; range):

- Drop in SBP mmHg at 3 minutes: before treatment 21±20 (17; −15 to 48), after fludrocortisone 18±24 (8, −8 to 64), after domperidone 18±23 (5; −4 to 57)
- Maximal drop in SBP mmHg over 5 minutes: before treatment 35±23 (32; 6 to 68), after fludrocortisone 30±23 (24; −2 to 64), after domperidone 28±21 (19; 5 to 61)
- Drop in DBP mmHg at 3 minutes: before treatment 7±7 (8; −4 to 18), after fludrocortisone 8±13 (8, −11 to 33), after domperidone 7±15 (0, −10 to 36)
- Maximal drop in DBP mmHg over 5 minutes: before treatment 17±10 (20; 3 to 37), after fludrocortisone 18±12 (20, 0 to 35), after domperidone 14±15 (6; −1 to 40).

Mean supine SBP before drug treatment was 138 (±23) mmHg compared with 134 (±24) mmHg after fludrocortisone, and 138 (±27) mmHg after domperidone.

## Randomised controlled trial by Rowe et al. (2001)

Rowe et al. (2001) performed a double-blind, placebo-controlled RCT that included 100 adults aged 18–50 years with chronic fatigue syndrome (CFS) and neurally mediated hypotension (NMH) diagnosed during a 2-stage tilt-table test. NHM was defined as a drop of 25 mmHg in SBP from baseline supine values, sustained for at least 1 minute, accompanied by symptoms of presyncope (defined as the presence of premonitory symptoms and signs of imminent syncope, such as severe weakness, light-headedness, nausea or diaphoresis [sweating]), with no increase in heart rate.

The study aimed to assess whether treatment with fludrocortisone would improve general wellbeing and orthostatic intolerance among people with CFS and NMH. It has been included in this evidence summary as part of the review of evidence on the use of fludrocortisone to treat postural hypotension.

To be included, participants had to have at least moderate severity of illness as determined by a score of 65 or less (out of 100) on a global wellness scale, with higher scores indicating greater wellness.

Participants were randomised in equal numbers to fludrocortisone titrated to 100 micrograms daily or placebo for 9 weeks with follow-up for a further 2 weeks after stopping treatment. If adverse effects occurred, participants were advised to reduce the dosage to the most recently tolerated dose. Both groups received potassium chloride tablets from the onset of treatment.

Tilt-table testing was performed in 2 stages. Participants lay supine for 15 minutes followed by head-up tilt to 70° for up to 45 minutes. Blood pressure and heart rate were recorded every 5 minutes while supine, 1 minute after head-up tilt and then every 5 minutes. If NMH was not provoked at stage 1, participants were returned to the supine position, received an infusion of 2 microgram/min isoproterenol hydrochloride for 10 minutes, followed by head-up tilt to 70° for a maximum of 15 minutes. Baseline tilt-table testing was performed 2 weeks before the start of treatment and again in the 9th week of treatment, while participants were still taking the study medication.

Total dropout from the study was higher in the fludrocortisone group (26%, n=13) than in the placebo group (16%; n=8), but no statistical comparison was reported. Dropout was reported up until the end of week 8, although treatment lasted for 9 weeks.

There was no statistically significant difference between fludrocortisone and placebo for the main primary outcome of the study, the proportion of participants with at least a 15-point improvement on global wellness scores over the course of the study (7/50 compared with 5/50; p=0.76). This analysis was reported to be by intention to treat and appeared to include all 100 participants; however, only 83 of 100 participants were reported to have adequate outcome data for analysis, so it is unclear if this analysis was in fact performed by intention to treat.

Tilt-table testing found no statistically significant differences for mean supine SBP, DBP or heart rate between the fludrocortisone and placebo groups:

- Mean supine SBP was 117.5 (SD 9.6) while on fludrocortisone compared with 113.7 (SD 10.0) on placebo, p=0.11.
- Mean supine DBP was 73.3 (SD 6.6) while on fludrocortisone compared with 73.4 (SD 7.4) on placebo, p=0.93.

At baseline, 67% of participants had NMH provoked during stage 1 of the tilt test. The remaining 33% had NMH provoked during stage 2. At the second tilt test, which was carried out in the 9th week of treatment, there was no statistically significant difference

between fludrocortisone and placebo for the number of participants who had NMH provoked during stage 1 (20/33 compared with 17/41; p=0.16). Nine participants in the placebo group had a normal tilt test in both stages of the second tilt test compared with 4 in the fludrocortisone group (no p value reported). However, this is not based on the whole population because complete results from the second tilt test are not available for 20 participants in the fludrocortisone group and 10 participants in the placebo group.

# Evidence review: safety

The summary of product characteristics for Florinef (100 microgram tablets; fludrocortisone acetate) reports that fludrocortisone is contraindicated for people with systemic infections, unless specific anti-infective therapy is used, and in people with hypersensitivity to any of the ingredients.

Suppression of the inflammatory response and immune function by fludrocortisone increases susceptibility to infections and their severity; chicken pox, shingles and measles are of particular concern. Patients should be advised to avoid exposure to these diseases and seek medical advice without delay if exposure occurs. The summary of product characteristics reports that because fludrocortisone is a potent mineralocorticoid, dosage and salt intake should be monitored to avoid hypertension, oedema or weight gain, and that monitoring of serum electrolyte levels is advisable during prolonged therapy ('prolonged' not further defined).

The summary of product characteristics reports that adrenal cortical atrophy develops with prolonged use and may persist for years after stopping treatment. It says that withdrawal after prolonged use must be gradual to avoid acute adrenal insufficiency and fludrocortisone should be tapered off over weeks or months depending on the treatment dose and duration.

The summary of product characteristics reports that people should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting the treatment. The summary of product characteristics reports that when adverse effects occur with fludrocortisone, they are usually reversible after stopping treatment and that the incidence of predictable adverse effects is dependent on the dosage, frequency and duration of treatment. It says that people receiving fludrocortisone should have close monitoring for adverse effects associated with corticosteroid therapy. The common adverse effects of systemic corticosteroids may be associated with more serious consequences in older

adults.

In Campbell et al. (1975), there was a statistically significant increase in supine systolic blood pressure (SBP) with fludrocortisone compared with placebo. However in Rowe et al. (2001), mean supine SBP was similar between fludrocortisone and placebo, and it was reported that no participants had a change in SBP of more than 40 mmHg while receiving treatment. In Schoffer et al. (2007), mean supine SBP with fludrocortisone was similar to the mean supine SBP before treatment.

In Campbell et al. (1975), 2 people, both with known intermittent proteinuria and low plasma albumin, developed pitting ankle oedema within 1 week of starting fludrocortisone; 1 of these people also reported frontal headache and breathlessness. Both participants were reported to have completed the 3-week intervention period, and the adverse effects were said to rapidly subside after completing treatment. The other 3 participants who completed the study are reported not to have experienced any side effects while taking fludrocortisone.

There was an increase in mean body weight (mean difference 2.7 kg, $p<0.001$) and total plasma volume (mean difference 329 ml, $p<0.02$) with fludrocortisone compared with placebo. There was a statistically significant rise in serum sodium (142.6 mmol/litre [±2.2] versus 140.6 mmol/litre [±1.3], $p<0.02$) and a statistically significant reduction in serum potassium (3.6 mmol/litre [±0.4] versus 4.3 mmol/litre [±0.2], $p<0.01$) with fludrocortisone compared with placebo. There were no significant differences between fludrocortisone and placebo for urinary electrolyte concentrations, plasma and urine osmolality and creatinine clearance (no p values given).

Schoffer et al. (2007) found that withdrawal from the study was lower in the fludrocortisone group (1 of 17 [5.9%]) than the domperidone group (3 of 17 [17.6%]). These withdrawals all occurred within the 1st week of treatment. Six people reported side effects while receiving fludrocortisone (including 2 reports of nausea and single reports of chest discomfort, morning headache, light-headedness and dizziness) compared with 5 people receiving domperidone (2 reports of nausea and single reports of chest pain, abdominal pain, palpitations and headache); statistical significance of between-group comparison not reported. On the basis of unused medication in returned pill bottles, adherence to treatments was reported as excellent, with an average missed dosage of 1 tablet of fludrocortisone and 3 tablets of domperidone.

Rowe et al. (2001) found that withdrawal from the study was higher in the fludrocortisone

group (13 of 50 [26%]) than in the placebo group (8 of 50 [16%]); statistical analysis not reported. In the fludrocortisone group, 4 people withdrew because they developed depression, 2 for worsening symptoms, 2 for abdominal discomfort, 1 for worsening headache, 1 who was randomised but did not receive treatment because of major depression, and 1 because of unrelated medical illness. In the placebo group, 3 people dropped out because of no improvement, 1 for panic symptoms and tachycardia, 1 for increased fatigue and 1 stopped taking the medication because of severe light-headedness, fatigue and sweating. One person from each group withdrew because of hypertension and 1 person withdrew from each group because of unwillingness to continue with the study.

At least 1 adverse effect was reported during treatment by 61% of people receiving fludrocortisone compared with 71% receiving placebo; data for these adverse events are not reported. No important adverse effects were reported by the study authors as lasting long after treatment was stopped. Mean weight increased by 1.1 kg in the fludrocortisone group and by 1.2 kg in the placebo group. Mean serum sodium concentration was higher during the treatment period in the fludrocortisone group (141.9 mEq/litre [±2.0]) compared with the placebo group (140.3 mEq/litre [±2.3], p=0.003).

Limited data on longer-term safety with fludrocortisone are available from a prospective observational study in 64 adults (mean age 80 years, range 58–98 years) with 1 or more hypotensive disorders with an average follow-up of 12 months (range 2–21 months) (Hussain et al. 1996). There were inconsistencies in the reporting of the doses of fludrocortisone between the abstract and in the full text of the publication, which were corrected in a later edition of the journal (Hussain et al. 1996; erratum). Of 64 people, 13 died of causes unrelated to hypotension. Adverse events were reported in 38 of 64 people (59.4%) with 17 stopping treatment.

There were inconsistencies in the reporting of reasons for drug withdrawal between figures reported in the abstract and figures reported in the table. Figures for drug withdrawal reported here are taken from the table, because it contains other additional information about adverse events. Reasons for drug withdrawal were: cardiac failure (n=7), systolic hypertension (n=4), depression (n=3), no benefit (n=2) and stroke (n=1). Hypokalaemia developed in 8 participants but there were no withdrawals for this reason. However, the observational nature of this study, its mixed population, with people with postural hypotension (n=17), vasodepressor carotid sinus syndrome (n=19), mixed vasodepressor carotid sinus syndrome and postural hypotension (n=14) and other hypotensive disorders (n=14), and the lack of a control arm limit the conclusions that can

be drawn.

# Evidence review: economic issues

## Cost effectiveness

No studies on the cost effectiveness of fludrocortisone in postural hypotension were identified.

## Cost

According to the NHS electronic drug tariff (September 2013), the cost of Florinef (100 microgram tablets; fludrocortisone acetate) is £5.05 for 100 tablets.

## Current drug usage

Prescription cost analysis for England (2012) showed there were 323,300 prescription items of 100 microgram Florinef tablets at a net cost of £600,300. However, the prescription cost analysis does not include information on the indications for which the drug was prescribed. There are liquid forms of the drug, but these are much less commonly used, with fewer than 1000 prescriptions in 2012.

# Evidence strengths and limitations

The main limitations of the 2 trials in people with autonomic diabetic neuropathy (Campbell et al. 1975) and people with Parkinson's disease (Schoffer et al. 2007) are the small study sizes (n=6 and n=17 respectively). Campbell et al. (1975) also focused on disease-orientated outcomes (change in standing blood pressure performed using tilt-table testing), as opposed to patient-orientated outcomes, such as light-headedness, fainting or falls. Only the trial in people with chronic fatigue syndrome (CFS; Rowe et al. 2001) had a reasonable sample size (100 people). This study did assess patient-orientated outcomes; however, these were of more relevance to a population with CFS rather than postural hypotension. Schoffer et al. (2007) did include clinical outcomes of relevance to postural hypotension – the orthostatic domain of the Composite Autonomic Symptom Scale (COMPASS-OD) and a global impression of change score focusing on orthostatic

symptoms. However, Schoffer et al. (2007) did not report any statistical analysis for 2 out of the 3 primary outcome measures.

Two of the trials appeared to have attempted allocation concealment (Schoffer et al. 2007 and Rowe et al. 2001).

The trials by Campbell et al. (1975) and Schoffer et al. (2007) included people with postural hypotension as a result of autonomic diabetic neuropathy and Parkinson's disease, and the trial by Rowe et al. (2001) included people with CFS who had neurally mediated hypotension provoked during tilt testing. Results from these trials may not apply to people with postural hypotension from other causes or conditions.

In Rowe et al. (2001), the largest of the trials, there was a higher level of withdrawals from the fludrocortisone group (26%) compared with placebo (16%). Rowe et al. (2001) reported using an intention-to-treat analysis for reporting of the primary outcome (change in global wellness score of more than 15 points). However, the study authors reported that only 83 of the 100 participants had adequate outcome data for analysis, so it is unclear if the analysis was in fact performed by intention to treat. Complete outcome data for the second tilt-table test that was performed in the 9th week of treatment were not available for 20 people in the fludrocortisone group and 10 people in the placebo group. Campbell et al. (1975) and Schoffer et al. (2007) did not use an intention-to-treat analysis.

Another limitation of the trials was that blood pressure was recorded on a single assessment, and this may miss significant changes (Schoffer et al. 2007).

The RCTs included in this evidence summary were all of short-term duration and therefore do not provide information about the longer-term safety and efficacy of fludrocortisone.

An observational study by Hussain et al. (1996) did examine safety of fludrocortisone prospectively over an average follow-up of 12 months. However, the observational nature of this study and the lack of a control arm limit the interpretations that can be drawn.

# Summary for patients

A summary written for patients is available.

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# 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.

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# Declarations of interest

No relevant interests declared.

# Appendix: Search strategy and evidence selection

# Search strategy

## General background, guidelines and technology assessments:

Broad internet search: allintitle: Florinef OR Fludrocortisone or fluorocortisol or fluorohydrocortisone filetype:pdf

- Trip Database

**MEDLINE (via Ovid)**

1. Hypotension, Orthostatic/

2. ((Postural or orthostatic) adj3 hypotension).ti,ab.

3. 1 or 2

4. Fludrocortisone/

5. (florinef or Fludrocortisone).tw.

6. (fluorocortisol or fluorohydrocortisone).tw.

7. 4 or 5 or 6

8. 3 and 7

9. limit 8 to english language

**Embase (via Ovid)**

1. Hypotension, Orthostatic/

2. ((Postural or orthostatic) adj3 hypotension).ti,ab.

3. 1 or 2

4. Fludrocortisone/

5. (florinef or Fludrocortisone).tw.

6. (fluorocortisol or fluorohydrocortisone).tw.

7. 4 or 5 or 6

8. 3 and 7

9. limit 8 to (english language and exclude medline journals) (77)

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

#1 MeSH descriptor: [Hypotension, Orthostatic] explode all trees

#2 ((Postural or orthostatic) next hypotension):ti,ab,kw

#3 #1 or #2

#4 MeSH descriptor: [Fludrocortisone] explode all trees

#5 (florinef or Fludrocortisone):ti,ab,kw

#6 (fluorocortisol or fluorohydrocortisone):ti,ab,kw

#7 #4 or #5 or #6

#8 #3 and #7

**CRD HTA, DARE and EED database**

1. MeSH DESCRIPTOR Fludrocortisone EXPLODE ALL TREES

2. (((Postural or orthostatic) and hypotension)) AND ((florinef or Fludrocortisone or fluorocortisol or fluorohydrocortisone))

3. 1 OR 2

**Grey literature and ongoing trials**

- NICE Evidence
- Health Canada – Clinical Trials Search
- metaRegister of Controlled Trials (mRCT)
- ClinicalTrials.gov

**Manufacturers' websites**

Bristol-Myers Squibb

Evidence selection

This evidence summary has included randomised controlled trials (RCTs) that have investigated the efficacy and safety of oral fludrocortisone for treating postural hypotension in adults. Cohort studies, case series or case reports identified by the initial search were excluded.

Two relevant double-blind, crossover RCTs were identified: 1 in people with postural hypotension and autonomic diabetic neuropathy; and 1 in adults with postural hypotension and Parkinson's disease. One additional placebo-controlled RCT was identified in adults with chronic fatigue syndrome who had neurally mediated hypotension (NMH) provoked during a 2-stage tilt-table test. This study was included in this evidence summary because the definition for NMH was similar to that used for postural hypotension in the other included RCTs (25 mmHg drop in systolic blood pressure sustained at least for 1 minute) despite NMH being provoked during 2-stage tilt-table testing.

The initial search identified 1 study (Testani et al. 1994) that had a title of 'Clozapine induced orthostatic hypotension treated with fludrocortisone'. Extensive efforts were made to locate the full text of this study to determine if it was an RCT, but it could not be located. Because no abstract or contact details for the authors were available, the study was excluded from this evidence summary.

# 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.

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