FLUDROCORTISONE
for Orthostatic Hypotension

Nottinghamshire Area Prescribing Committee

Traffic light classification- Amber 2
Information sheet for Primary Care Prescribers

Key points/interactions

- Fludrocortisone should only be considered when non-pharmacological strategies have failed to alleviate the patient's symptoms, unless otherwise considered clinically appropriate by the specialist.
- The most common side effects are fluid retention/oedema, hypokalaemia, headache and supine hypertension.
- Fludrocortisone interacts with CYP3A substrates and digoxin (increasing toxicity)

Licensed Indications

Fludrocortisone does not have a marketing authorisation in the UK for treating postural hypotension, so the use for this indication is *unlicensed*.

Exclusions

Children under 18 years, pregnancy, and lactation. Active infection unless on specific treatment. Patients for whom rise in BP or increase in fluid retention will cause known risks or worsening of comorbidity.

Medicines Initiation

Fludrocortisone should be initiated by a consultant geriatrician/cardiologist/neurologist or other specialist experienced in the management of neurocardiovascular instability. ***Fludrocortisone should only be considered when non-pharmacological strategies have failed to alleviate the patient's symptoms,*** unless otherwise deemed clinically appropriate by the specialist. A diagnostic and management algorithm is included at Appendix II.

Dose Regiment and Route of Administration

Initial dose: 50-100 micrograms once daily in the morning.
The dose may be increased ***weekly*** up to 400 micrograms a day, in divided doses if necessary, depending on the supine and standing blood pressure results. No specific dose adjustment is needed in renal disease, but fludrocortisone may not be appropriate in view of sodium and fluid retention. Although fludrocortisone acetate 50 micrograms tablets are now available, the 100 microgram tablets are more cost effective, and many brands are scored and can be halved as per their product licence.

Duration of Treatment

Duration of treatment should be determined on an individual basis. For some, treatment can be weaned and stopped as fluid status or morbidity changes. For others, treatment is likely to be required long term (e.g. Parkinson's disease contributing to orthostatic hypotension).

Monitoring Requirements and Responsibilities

- The initiating prescriber is responsible for ensuring the monitoring is continued until care can safely be transferred to Primary Care.
- The initiating specialist will be responsible for assessing risk factors or pre-existing conditions that may be exacerbated by mineralocorticoid therapy (U&E's, fluid status, lying and standing BP, assessment of fracture risk in the context of any falls).
- A medication review should be conducted before starting fludrocortisone, assessing any drugs that may cause or contribute to orthostatic hypotension, such as antihypertensives, and ensure this is clearly documented in all correspondence.
- On-going Primary Care requirements should include monitoring for hypokalaemia, excessive fluid retention and response to treatment. Additional specific advice should be clearly documented in any correspondence.

	U & E's	Signs & Symptoms of fluid overload or heart failure	Blood Pressure (Lying & Standing)
Initiation	✓ Weekly (first month) or until stable	✓	✓ Weekly (first month) or until stable
After any dose increase	✓	✓	✓
Minimum 6 monthly or if symptoms recur	✓	✓	✓

- In addition to absolute values for haematological or biochemical indices, a rapid fall or rise or consistent downward or upward trend in any value should prompt caution and extra vigilance.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Systemic infections unless specific anti-infective therapy is employed.
  Avoid live virus vaccines in patients receiving immunosuppressive doses of systemic corticosteroids. Please refer to the Green Book Chapter 6 for current guidance on the use of live vaccines in patients taking corticosteroids. If a live vaccine is required and a non-live vaccine is unsuitable, consult an immunologist for further advice.

Explicit Criteria for Review and Discontinuation*	Action
Symptoms that may indicate supine hypertension such as chest pain, palpitations, shortness of breath, headache, blurred vision, and pounding in the ears	Check lying and standing blood pressure. If supine hypertension present, see below.
Supine hypertension (systolic BP>160mmHg)	Usually dose related but check if the last dose is taken at least 4 hours before bedtime. Consider dose reduction or withhold and discuss with the specialist. If persistent despite dose reductions, consider discontinuation in consultation with the specialist.
Lying or standing Blood pressure increases above 180/100 mmHg or is considered clinically significant.	Reduce / withhold and discuss with the specialist team.
Acute or severe renal impairment	Withhold until discussed with the specialist team. Likely to contribute to fluid retention.
Signs and symptoms of heart failure	Withhold and discuss with the specialist team.
Hypokalaemia	Correct with supplements. Discuss with the specialist team if severe or persistent.
Persistently labile blood pressure after the initial titration	Discuss with the specialist team.

* Glucocorticoid effects are expected to be minimal at recommended doses but as a precaution withdrawal after prolonged therapy should be gradual. Seek specialist advice if withdrawal is considered urgent.

Precautions (for a full list, see manufacturer's guidance available here)

- Hypokalaemia may be additive with other medicines and may pose concerns with those that predispose to cardiac dysrhythmias.
- Sodium and fluid retention may precipitate or exacerbate heart failure.
- Corticosteroid effects can be minimised by using the lowest possible dose.
- Glucocorticoid related side effects are considered very rare and generally well tolerated at therapeutic doses.
- A patient steroid treatment card should be supplied at the point of dispensing to every patient. This gives a clear guidance on the precautions to be taken to minimise risk of potential infection and adrenal suppression, and provides details of prescriber, medication, dosage and the duration of treatment.

Key Medication Interactions (for a full list, see manufacturer's guidance available here)

Antihypertensive, including diuretics	**Fludrocortisone antagonises the effects of antihypertensive and diuretics. The hypokalaemic effect of diuretics, including acetazolamide, is enhanced**
Anticoagulants	Response to anticoagulants may be altered by corticosteroids (but this may be less pronounced with the small doses used)
CYP3A inhibitors	Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects.
Digitalis glycosides (e.g. Digoxin)	Co-administration may enhance the possibility of digitalis toxicity.
Hepatic Enzyme Inducers (e.g. barbiturates, carbamazepine, phenytoin, primidone, rifabutin, rifampicin)	There may be increased metabolic clearance of Fludrocortisone. Patients should be carefully observed for possible diminished effects, and the dosage should be adjusted accordingly.
NSAIDS	Corticosteroids may increase GI bleeding and ulceration associated with NSAIDS. They can reduce serum salicylate levels. Stopping corticosteroids when on high-dose NSAIDS may result in salicylate toxicity and additive fluid retention.
Thyroid medications	Metabolic clearance of adrenocorticoids is ***decreased*** in hypothyroid patients and ***increased*** in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustments in adrenocorticoid dosage.

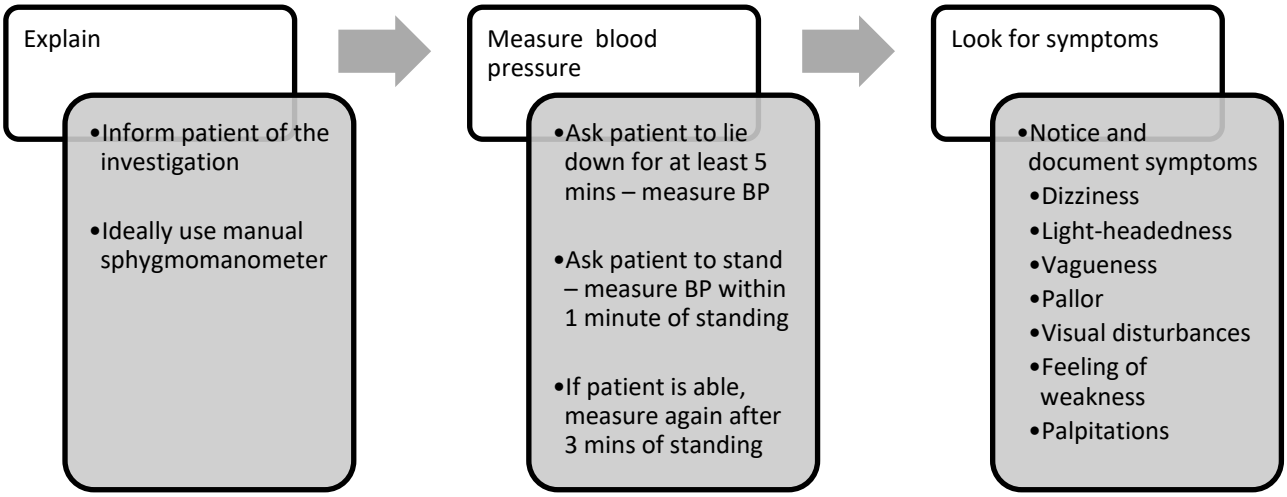
For advice and queries please contact the original prescriber. For a more complex patient review (e.g. comorbidities and very frail patient), consider referral to a local community geriatrician via the appropriate pathway.

References

1. APC. Midodrine Information Sheet. . [Online]. Available at: https://www.nottsapc.nhs.uk/. Last updated on July 2022. Accessed 26/06/2024.
2. Lanier J B et al (2011): Evaluation and Management of Orthostatic Hypotension *Am Fam Physician.* Sep 1; 84(5):527-536.
3. Martindale: The complete reference. Fludrocortisone. [Online]. Available at: www.medicinescomplete.com. Last revised on 24/06/2010.
4. NICE Evidence summary [ESUOM20]. Postural hypotension in adults: fludrocortisone. 2013. [Online]. Available at: https://www.nice.org.uk/advice/esuom20/chapter/Key-points-from-the-evidence. October 2013. Accessed 26/06/2024.
5. The Renal Drug Database. [Online]. Available at: FLUDROCORTISONE ACETATE. Last reviewed on 19/11/2024.
6. Summary of Product Characteristics. Fludrocortisone Acetate, Aspen. [Online]. Available at: www.medicines.org.uk. Last updated on 10/06/2024. Accessed 26/06/2024.
7. BNF. Fludrocortisone.[Online] Available at: Fludrocortisone acetate | Drugs | BNF | NICE Last revised on 29/05/2024. Accessed on 26/06/2024.

Appendix I – Lying and Standing Blood Pressure Measurement

Automated equipment can be used but where measurements are difficult it will be necessary to use a manual sphygmomanometer. Ascertain if the patient is able and safe to stand. Illness may impair their ability to bear weight and severe symptoms resulting from a profound fall in blood pressure on standing could lead to a fall. Sitting blood pressure can be taken however this can reduce the sensitivity of the test.



- Ask or assist the patient to stand up or sit on the edge of the bed if the patient is unable to stand
- Stop if the patient is unable to stand/sit unsupported or is at risk of falling
- Keep the patient standing/sitting for the full 3 minutes

Postural hypotension is said to be present if:

- Systolic Blood Pressure falls (SBP) by ≥ 20mmHg on standing (with or without symptoms)
- SBP falls to below 90mmHg on standing (even if the drop is less than 20mmHg with or without symptoms)
- Diastolic Blood Pressure falls by ≥10mmHg on standing with symptoms (although clinically much less significant than a drop in systolic BP)

Appendix II – Management of Orthostatic Hypotension Algorithm

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- Symptomatic
- Orthostatic Hypotension
- Neurally-mediated vasodepressor syncope

- Secondary (and otherwise treatable) causes excluded and medications reviewed

Hydration advice:

- Increase fluid intake between 08:00 and 18:00
- No more than 4 caffeinated drinks per 24 hours
- >65 years and no systemic hypertension – Additional table salt in diet

NB: Caution in heart failure or volume overload

Venous compression:

Graded compression hosiery (If tolerated and practicable) – **NOT** TEDS

NB – not to be used in the presence of significant peripheral vascular disease or in patients with broken skin or ulceration.

Volume Expansion:

Fludrocortisone 100 micrograms in the morning initially
(50 micrograms if >65 years)
Titrate dose according to response to a maximum of 400 micrograms daily in 2 or 3 divided doses.

Monitor:

- Symptoms (abolition or improvement in presyncopal symptoms or no episodes of syncope)
- Lying/standing BP

Midodrine*:

2.5mg three times a day.

NB: - The third dose of the day should be by (or before) 17:00 to avoid supine hypertension.
Example: Midodrine 2.5mg at 7:00, 12:00 and 17:00.

Depending on the results of supine and standing blood pressure recordings and tolerability, this dose may be increased weekly up to a dose of 10mg three times a day. Fludrocortisone may also be continued in combination.

* Refer to APC Midodrine Information Sheet

Monitor electrolytes weekly until stable and after any dose change, minimum 6 monthly thereafter. Monitor for signs of developing heart failure or volume overload.
Salt restriction and/or Potassium supplements may be necessary.
Withdraw slowly to avoid the effects of adrenal suppression.