

Fludrocortisone (Florinef®) Shortage

05 Jul 2019

Fludrocortisone 0.1 mg tablets are currently in short supply and may become shorted.

Suppliers of fludrocortisone¹

Product	Strength	DIN	MFR
Florinef	0.1 mg	02086026	PAL

Health Canada approved indications of fludrocortisone²:

- partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease
- treatment of salt losing adrenogenital syndrome.

Off-label uses of fludrocortisone³:

- increase blood pressure in patients with orthostatic hypotension

Status as of 05 Jul 2019:

- Allocation
 - Paladin has limited stock available that is being placed on allocation and distributed to requesting wholesalers, who will then be responsible for allocation among their customers. **Be sure to inform your wholesaler of fludrocortisone needs as soon as possible.** Paladin anticipates supply to be re-established in September, 2019.⁴
 - **Consider giving priority to infants and children** (see PEDIATRICS below).

Management Options in the Event of Manufacturer Shortage

Pharmaceutical Alternatives

- Compounding
 - Compounding pharmacies currently have access to fludrocortisone to compound.
 - Medisca has a limited supply of bulk fludrocortisone that pharmacies can order.⁵
 - Acquisition cost of the powder may be quite expensive (>\$150 per gram)
 - The Saskatchewan Drug Plan needs to be contacted in advance for approval of the compounded products, which are only covered when no manufactured product is available.
 - Bill NIHB claims with the pDIN 99505004, the extemporaneous DIN for backorder products; document the reason for the claim for auditing purposes.

Therapeutic Alternatives

Chronic adrenocortical insufficiency (e.g. Addison's Disease) and Congenital Adrenal Hyperplasia (Salt Losing Adrenogenital Syndrome)

Fludrocortisone is a potent mineralocorticoid agent and there are no alternatives with the same therapeutic effects. Individualized treatment will be necessary. Patients, especially pediatric patients, should seek consultation with their endocrinologist (either directly or via their primary care provider).

Background⁶⁻⁸

- Patients with primary chronic adrenocortical insufficiency (i.e. Addison's disease, post-operative adrenalectomy, other) need supplementation with corticosteroids for glucocorticoid and mineralocorticoid activity.

- Congenital adrenal hyperplasia (CAH) is a genetic enzyme deficiency disorder that most often presents in infancy; more than 75% of those with CAH have mineralocorticoid deficiency.⁹
- Fludrocortisone is a potent mineralocorticoid corticosteroid that is sometimes added to glucocorticoid-dominant corticosteroids such as prednisone, dexamethasone or hydrocortisone to prevent hyponatremia, hypotension and hyperkalemia. Requirements for aldosterone/fludrocortisone vary individually and some patients do not require daily or any supplementation.
- The most common doses of fludrocortisone are 0.05-0.1 mg once daily, although doses vary depending on patient response.
- IV glucocorticoids given at stress doses (i.e. hydrocortisone 100 mg IV q6-8 hrs) provide mineralocorticoid and additional overlapping with oral fludrocortisone is not required.
- Glucocorticoid-dominant corticosteroids may have some mineralocorticoid activity, though considerably less than that provided by fludrocortisone.
 - Relative mineralocorticoid potency: fludrocortisone >>>> hydrocortisone > prednisone > dexamethasone (no mineralocorticoid activity)
 - Estimates of doses resulting in equivalent mineralocorticoid activity among the corticosteroids vary as they are not well-established. The table below is intended to give an indication of the *relative* activity.

Table 1: Approximate doses resulting in equivalent MINERALOCORTICOID activity

Corticosteroid	Approximate Equivalent Dose
Fludrocortisone	0.1 mg
Hydrocortisone	20 mg ^{6,10,11} to 40 mg ⁸
Prednisone	50 mg ^{6,10,11}
Dexamethasone	No mineralocorticoid activity at replacement doses

Therapeutic Management

PEDIATRICS

- Consult pediatric endocrinologist – the strategies used in adults may be ineffective or unsafe in infants and children.

ADULTS (potentially adolescents)

- **Consider reducing dose to conserve tablets;** adults often do well on twice weekly dosing.
- **Patients on prednisone or dexamethasone** can be switched to hydrocortisone for maximal mineralocorticoid activity. Hydrocortisone is given in 2 or 3 divided doses with a larger dose in the morning.^{6,12} Use Table 2 below to find the dose that provides approximately equivalent **glucocorticoid** activity. This may be sufficient but patients may need to increase fluid/sodium and will need to be monitored.

Table 2: Approximate doses resulting in equivalent GLUCOCORTICOID activity

Corticosteroid	Approximate Equivalent Dose ¹⁰
Hydrocortisone	20 mg
Prednisone	5 mg
Dexamethasone	0.75 mg
Cortisone	25 mg
Methylprednisolone	4 mg

- **For patients already taking hydrocortisone,** emphasize increased sodium and fluid intake and close monitoring.
- Pickles are a good source of sodium.
- **Monitoring parameters** include salt cravings and postural hypotension; electrolytes may be necessary in some patients.

Orthostatic Hypotension (OH)¹³⁻¹⁵

- Remind/encourage patients to adopt non-pharmacological practices such as:
 - getting up gradually
 - avoiding: large meals; alcohol intake; warm environments/hot baths; and heavy exertion
 - raising the head of the bed using blocks or bricks, if tolerated
 - increasing salt and fluid intake if appropriate
 - physical maneuvers such as leg crossing when standing, bending forward, squatting
 - compression stockings (waist-high) or abdominal binders
- Check profile for exacerbating medications and discontinue/reduce dose if possible.

Therapeutic alternatives

- All pharmacological agents used for OH have limitations.
- Most commonly used agents in Canada are fludrocortisone and midodrine.
 - midodrine 2.5 mg TID, increasing to effect up to 10 mg TID
- Other agents with less evidence and/or specific situations:
 - caffeine, clonidine, desmopressin acetate, erythropoietin, NSAIDs, octreotide, pyridostigmine
- See the RxFiles Chart [Orthostatic hypotension \(OH\): considerations for management](#) for more details.

Prepared by Carmen Bell BSP, medSask | Posted 28 Jun 2019 | Updated 05 Jul 2019

Endocrinology Reviewers:

Dr. Terra Arnason MD PhD FRCPC Adult Endocrinology, Associate Professor, UofS

Dr. Mark Inman MD, FRCPC, Pediatric Endocrinology, Assistant Professor, UofS

Internal reviewers:

Kirsten Bazylak BSP; Kelly Kizlyk BSP; Dorothy Sanderson BSP



References:

1. Health Canada. Drug Product Database Online Query. Ottawa, ON: Health Canada; [cited 25 Jun 2019]. Available from: <http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>
2. Product monograph for Florinef. Paladin Labs Inc. St-Laurent QC, H4M 2P2. 27 Feb 2019
3. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2019. CPS online: Corticosteroids: systemic. CPhA Monograph; [updated Aug 2018; cited 24 Jun 2019]. Available from: <https://www.e-therapeutics.ca>
4. Personal phone communication with Paladin, 1-866-340-1112; 28 Jun 2019
5. Personal phone communication with Medisca Canada, 1.800.665.6334; 24 Jun 2019
6. Nieman L. Treatment of adrenal insufficiency in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. <https://www.uptodate.com> (Accessed 26 Jun 2019)
7. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - 2019. Record No. T116703, Adrenal insufficiency in adults; [updated 30 Nov 2018, cited 25 Jun 2019]. Available from <https://www.dynamed.com/topics/dmp~AN~T116703>. Registration and login required.
8. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101(2):364–389.
9. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - 2019. Record No. T114916, Congenital adrenal hyperplasia; [updated 30 Nov 2018, cited 27 Jun 2019]. Available from <https://www.dynamed.com/topics/dmp~AN~T114916>. Registration and login required.
10. Corticosteroids Systemic Equivalencies. In: Lexi-Comp Online Database [database on the Internet]. Hudson, Ohio: Lexi-Comp, Inc.; 2019; [updated 16 Jan 2019; cited 25 Jun 2019]. Available from: <http://online.lexi.com>
11. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30.
12. Hydrocortisone (Systemic). In: Lexi-Comp Online Database [database on the Internet]. Hudson, Ohio: Lexi-Comp, Inc.; 2019; [updated 25 Jun 2019; cited 28 Jun 2019]. Available from: <http://online.lexi.com>
13. RxTx[Internet]. Ottawa (ON): Canadian Pharmacists Association; 2019. Solbiati M, Sheldon M. Syncope; [updated Feb 2018; cited 26 Jun 2019]. Available from: <https://www.e-therapeutics.ca/>.
14. Kaufmann H. Treatment of orthostatic and postprandial hypotension. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. <https://www.uptodate.com> (Accessed 26 Jun 2019)
15. Lu L, Stone S, Regier L. Orthostatic hypotension (OH): Considerations for management. RxFiles drug comparison charts. Saskatoon, SK: Saskatoon Health Region. [updated Jun 2014; accessed 26 Jun 2019]. Available from: www.RxFiles.ca