PRURITUS

- Algorithm for Hemodialysis Patients
- Supplemental Summary
- Antipruritic Monographs

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**Assessment**

**General History**
- Generalized vs. localized pruritus
- Duration of pruritus
- Character of pruritus (e.g., paroxysmal, continuous)
- Exacerbating and relieving factors
- Detailed drug history

**Physical Examination**
(check for signs of severe pruritus):
- Physical findings of other primary skin eruptions (see possible etiologies)
- Excoriation marks
- Prurigo nodularis
- Lichenification of the skin

**Consider Etiology**

**Uremia Related:**
- Xerosis
- HD adequacy
- Anemia (CKD or iron-deficiency)
- Secondary hyperparathyroidism

**Uremia Unrelated:**
- Infestations (scabies, lice, etc.)
- Allergy
- Drug hypersensitivity
- Contact dermatitis (e.g., adhesive)
- Hypercalcemia
- Inflammation
- Neoplasm
- Hepatitis
- Hypothyroidism

**Consider and adjust PRN:**
- Heparin allergy → switch to NS flush or Citrasate dialysate and sodium citrate lock
- Ensure HD Adequacy → kt/V greater than 1.4
- Check LFTs/TSH/Ferritin
- Change dialyzer
- Change tubing
- Change dialysate → switch to ultrapure dialysate

**Non-Pharmacological Measures**
- Use gentle soap e.g. Dove
- Apply soap only to axillae and groin/perineum (except if other areas such as arms or legs are visibly dirty)
- Avoid excessive bathing or bathing with hot water – use only lukewarm water
- Eliminate wool or irritating clothing
- Keep finger nails trimmed
- For dry skin, apply moisturizing cream (NOT lotion) BID and after bathing, e.g. glaxal base, Uremol® cream, Nivea® Cream, Creamy Vaseline®

**Localized Itchiness**
(not recommended for large open areas)
- Topical steroids – apply BID PRN (use ointment on thick, lichenified lesions; low potency agents preferred on face and intertriginous areas)
  - Low potency – hydrocortisone 1% cream
  - Medium potency – betamethasone valerate 0.1% cream x 3 months or less
  - High potency – desoximetasone 0.25% cream x 3 months or less
  - Very high potency – clobetasol propionate 0.05% cream x 2-3 weeks only
- Capsaicin 0.025% cream – apply sparingly BID-QID [may take 2-4 weeks for onset of action]

**Generalized Itchiness**
- Oral antihistamine
  - Hydroxyzine 10 mg PO TID PRN; titrate by 10-25 mg weekly to a maximum of 25 mg PO QID as tolerated
  - Diphenhydramine 25 mg PO BID-TID PRN, titrate by 25 mg weekly to maximum of 25 mg PO QID as tolerated
  - Gabapentin 100 mg PO post HD (titrate by 100 mg weekly up to a maximum 300 mg PO HS as tolerated)

- If no contraindication, doxepin 10mg PO HS; titrate by 10-25 mg weekly to a maximum of 50 mg PO HS as tolerated
- Dermatology consult for differential diagnosis. Consider UVB light.

**Check Ca/PO_4/PTH**

**Correct abnormalities**

**Consider and adjust PRN:**
- Heparin allergy → switch to NS flush or Citrasate dialysate and sodium citrate lock
- Ensure HD Adequacy → kt/V greater than 1.4
- Check LFTs/TSH/Ferritin
- Change dialyzer
- Change tubing
- Change dialysate → switch to ultrapure dialysate

**Pruritus**

**Symptom Management Resources: Pruritus**

**Updated November 2012**
Pruritus Treatment Algorithm for Hemodialysis Patients

Supplemental Summary

In terms of non-pharmacological therapies, moisturizing cream should be considered for all hemodialysis patients as xerosis is prevalent in this population. Lotions are not recommended since the higher concentrations of emulsifiers and stabilizers and the lower concentration of lipid in lotions can further worsen the dry skin. Other non-drug measures, e.g. minimizing the use of soap and hot bath, should also be considered. The successful use of behavioral therapy or habit reversal techniques has been reported in patients with chronic pruritus; however, their utility in the hemodialysis population has not been studied. A dermatology consult should be considered early for other differential diagnosis or UVB phototherapy in severe or difficult-to-treat cases.

In terms of pharmacotherapies, available literature in hemodialysis patients is limited. Most studies are of small sample size, from single centre, have significant drop-outs or crossover design with a short washout period.

Although there are no studies confirming the efficacy of sedating antihistamines in the treatment of pruritus in hemodialysis patients, they have historically been used as first line agents for this indication. Non-sedating antihistamines have not been shown and are not considered to be effective by experts in alleviating pruritus in hemodialysis patients as they do not cross the blood brain barrier, and therefore unable to affect the perception of itch. Due to the lack of confirmatory studies, the agents listed under limited evidence are not included in the treatment algorithm but could be considered if other typical, more cost-effective agents fail.

POSITIVE STUDIES

Capsaicin (topical)

In a double-blind, placebo-controlled, crossover trial\(^1\) of 34 hemodialysis patients with uremic pruritus, capsaicin 0.03% was compared to placebo x 4 weeks with a 2-week washout. The mean pruritus score (maximum 18 points) was significantly reduced from 15.9 ± 6.3 to 2.5 ± 2.5 in the capsaicin treatment period vs. 15 ± 6.0 to 7.2 ± 5.5 in the placebo treatment period.

In another double-blind, placebo-controlled, crossover study\(^2\), capsaicin 0.025% cream was compared to placebo in 17 hemodialysis patients with moderate to severe pruritus. Fourteen had marked relief, of whom 5 had complete remission, with prolonged pruritic effect 8 weeks post capsaicin treatment. No serious adverse reactions were noted.

In an open-label uncontrolled trial and a double-blind, vehicle-controlled trial\(^3\) evaluating capsaicin 0.025% cream in hemodialysis patients. Eight of 9 evaluable patients in the open label trial reported marked relief or complete resolution; 12 patients were not evaluable. In the double-blind trial, 2 of 5 evaluable patients reported complete resolution and 2 were not evaluable. No serious adverse reactions were noted.

Doxepin

In a randomized, placebo-controlled, crossover trial\(^4\), doxepin 10 mg PO BID x 1 week was compared to placebo in 24 patients with pruritus resistant to conventional treatment. There was a 1-week washout between treatment periods. Mean age was 48 years. Complete resolution was reported in 58.3% patients with doxepin vs. 8.3% with placebo (p<0.001) with relative improvement in 29.2% vs. 16.7%, respectively. Drowsiness was reported in 50% of patients, which resolved in about 2 days. One patient refused doxepin.

Although there is only one study conducted with doxepin in the treatment of pruritus in hemodialysis patients, it has been successfully used in the treatment of intractable pruritus due to its strong anti-H, histaminic activity. If there is no contraindication to tricyclic antidepressants, doxepin may be tried after topical capsaicin and/or gabapentin.

Gabapentin

In a double-blind, placebo-controlled, crossover trial of 34 hemodialysis patients who failed antihistamines and moisturizers\(^5\), gabapentin 100 mg PO 3 times weekly post-hemodialysis x 4 weeks was compared to placebo with a one-week washout. Out of a maximum of 100 points, the mean pruritus scores were 6.44 ± 8.4 during gabapentin vs. 81.11 ± 11.07 during placebo period (p<0.001). Dizziness, drowsiness and fatigue were reported in 2 patients.
Pruritus Treatment Algorithm for Hemodialysis Patients

Supplemental Summary

In a randomized, double-blind, placebo-controlled trial, 34 hemodialysis patients were assigned either gabapentin 400 mg PO twice weekly post-HD vs. placebo x 4 weeks. On a 10 cm visual analogue scale, the mean reduction in pruritus score was 6.7 ± 2.6 vs. 1.5 ± 1.8 in gabapentin vs. placebo groups, respectively (p<0.001). No dropouts due to side effects.

In an open-label series, 5 consecutive HD patients unresponsive to antihistamines received gabapentin 100 mg PO 3 times weekly post-HD with dosage adjusted to clinical response. The mean visual analogue scale decreased from 8.4 to 1.6. Two patients received complete itch remission.

In another randomized, double-blind, placebo-controlled, crossover study, gabapentin 300 mg PO thrice weekly post-HD was compared to placebo x 4 weeks with a one-week washout in 25 patients who failed conventional therapy. The mean pruritus score reduced from 8.4 ± 0.94 to 1.2 ± 1.8 for gabapentin (p=0.0001) and to 7.6 ± 2.6 for placebo (p=0.098). Mild to moderate somnolence, dizziness and fatigue were reported.

In addition, activated charcoal may bind to and needs to be spaced apart from other medications during administration. Due to the significant pill burden and potential drug interactions, this option is not listed in the algorithm but may be used as a last resort.

**Gamma-linolenic acid (topical)**

A randomized, double-blind, placebo-controlled, crossover study compared gamma-linolenic acid 2.2% cream vs. placebo for 2 weeks with a 2-week washout in 16 dialysis patients with refractory uremic pruritus. Gamma-linolenic acid cream shows statistically significant change in visual analogue scale and pruritus score compared to placebo.

**Montelukast**

In a randomized, single-blind, placebo-controlled, crossover study in 5 hemodialysis centers, 16 patients were treated with montelukast 10 mg PO daily x 20 days vs. placebo with a 14-day washout. Pruritus was reduced by 35% (95% CI, 9.5% to 62.5%) with montelukast vs. 7% (95% CI, 0.5% to 15.9%) with placebo (p=0.002).

**Pregabalin**

An open-label series evaluated pregabalin 25 mg PO HS in 16 hemodialysis patients refractory to antihistamine for 2 months (hydroxyzine or desloratadine + levocetirizine). There was a statistically significant difference between the 10-point visual analogue scores before and one month after treatment, 7.44 ± 2.01 vs. 1.7 ± 1.31, respectively. Four patients discontinued treatment due to side effects.

**Naltrexone**

A randomized, double-blind, placebo-controlled, crossover study compared naltrexone 50 mg po daily x 7 days to be effective in 15 hemodialysis patients with persistent, treatment resistant pruritus. Seven patients did not complete the study. No statistically significant difference was found between the naltrexone and placebo treatment periods.

Although there is some limited evidence suggesting the efficacy of activated charcoal, the product is commercially available as 260 mg capsules and may be compounded as 360 mg capsules by compounding pharmacies. Therefore, it requires 17 to 23 capsules per day to make up a 6 g daily dose.

**LIMITED EVIDENCE**

**Activated Charcoal**

In an open-label case series, 23 hemodialysis patients were treated with activated charcoal 6 g PO daily (30 x 200 mg capsules) x 6 weeks. Ten single-blinded patients received placebo treatment prior to charcoal. Ten patients’ pruritus completely resolved, 10 had partial response while 3 were unresponsive. Four patients complained of nausea, weight gain or difficulty with pill burden.

In a double-blind, placebo-controlled, crossover study, activated charcoal 6 g PO daily x 8 weeks was shown to relieve pruritus in 10/11 hemodialysis patients with idiopathic generalized pruritus (p=0.01). Four patients were non-compliant. No adverse effects were noted.

Although there is some limited evidence suggesting the efficacy of activated charcoal, the product is commercially available as 260 mg capsules and may be compounded as 360 mg capsules by compounding pharmacies. Therefore, it requires 17 to 23 capsules per day to make up a 6 g daily dose.

**NEGATIVE STUDIES**

**Naltrexone**

A randomized, double-blind, placebo-controlled, crossover trial found naltrexone 50 mg PO daily x 7 days to be effective in 15 hemodialysis patients with persistent, treatment resistant pruritus. Seven patients did not complete the study. No statistically significant difference was found between the naltrexone and placebo treatment periods.

In addition, activated charcoal may bind to and needs to be spaced apart from other medications during administration. Due to the significant pill burden and potential drug interactions, this option is not listed in the algorithm but may be used as a last resort.

**Gamma-linolenic acid (topical)**

A randomized, double-blind, placebo-controlled, crossover study compared gamma-linolenic acid 2.2% cream vs. placebo for 2 weeks with a 2-week washout in 16 dialysis patients with refractory uremic pruritus. Gamma-linolenic acid cream shows statistically significant change in visual analogue scale and pruritus score compared to placebo.
Pruritus Treatment Algorithm for Hemodialysis Patients
Supplemental Summary

with severe resistant pruritus. The median pruritus scores were reduced from 9.9 (out of 10) to 2.1 for the naltrexone-placebo sequence and 1.0 for the placebo-naltrexone sequence at the end of the naltrexone treatment. Short-term efficacy was shown in this study.

Ondansetron
A randomized, double-blind, placebo-controlled study failed to demonstrate ondansetron 8 mg PO TID x 2 weeks to be more effective than placebo in 24 hemodialysis patients.

A prospective, placebo-controlled, double-blind, crossover study compared ondansetron 8 mg PO TID vs. placebo x 2 weeks in 16 hemodialysis patients with persistent pruritus. No statistically significant difference in daily pruritus score was reported between both treatment periods.

Tacrolimus 0.1% Ointment
A randomized, double-blind, vehicle-controlled study failed to demonstrate tacrolimus 0.1% ointment (n=12) to be more effective than vehicle (n=8) in relieving uremic pruritus.

STUDY REFERENCES


GENERAL REFERENCES


# Antipruritics

## ORAL

### Diphenhydramine (Benadryl®) *Covered by BCPRA*

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Shown to exert a significant antihistamine effect.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>Extensive hepatic metabolism to multiple metabolites, including cetirizine. Adult half-life: 20 hours; elderly: 29 hours.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Transient drowsiness, headache, somnolence, xerostomia and blurred vision. Use with caution in the elderly. May cause excessive sedation.</td>
</tr>
</tbody>
</table>

### Dosing Guidelines (Normal Renal Function)

- 25 mg PO BID-TID, may increase by 25 mg weekly as tolerated to 25 mg PO QID.

### Renal Dosing Guidelines GFR (mL/min)

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

### Supplemental Dose After

- IHD: None
- PD: None

### Pharmacare Coverage

- Yes

### Cost (30-day supply) without dispensing fee

- 25 mg PO TID - $23.40

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**SYMPTOM MANAGEMENT RESOURCES: PRURITUS**

**UPDATED NOVEMBER 2012**
## Antipruritics

### ORAL

**Doxepin (Sinequan®)**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Shown to exert a significant antihistamine effect.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>Extensive hepatic metabolism to an active metabolite, desmethyldoxepin. Renal excretion 0.5%. Only 7.6% of Doxepin and 13.9% of desmethyldoxepin is extracted by hemodialysis, none via peritoneal dialysis.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Sedation, dizziness, weight gain, bloating, constipation, xerostomia, blurred vision, urinary retention. In elderly: increased risk of confusion and oversedation.</td>
</tr>
<tr>
<td>Dosing Guidelines</td>
<td>10 mg PO HS, may increase by 10-25 mg weekly as tolerated to a maximum of 50 mg PO HS.</td>
</tr>
</tbody>
</table>

### Renal Dosing Guidelines

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
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### Supplemental Dose After

<table>
<thead>
<tr>
<th>DIF</th>
<th>IHD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

### Pharmacare Coverage

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
</tr>
</thead>
</table>

### Cost (30-day supply) without dispensing fee

<table>
<thead>
<tr>
<th></th>
<th>25 mg PO HS - $4.50</th>
</tr>
</thead>
</table>

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# Antipruritics

**ORAL**

| Gabapentin (Neurontin<sup>®</sup>) | *Covered by BCPRA*
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Not fully understood but thought to modulate various receptor sites (e.g. mu-receptors) and alter dopamine, serotonin, and norepinephrine release.</td>
</tr>
</tbody>
</table>
| **Pharmacokinetics** | Normal half-life 5-6.5 hours  
Saturable oral bioavailability [900 mg-60%; 1200 mg-47%; 2400 mg-34%]  
Limited hepatic metabolism, 70-80% excreted unchanged in the urine. |
| **Adverse Effects** | Sedation, confusion, incoordination, peripheral edema. |
| **Dosing Guidelines (Normal Renal Function)** | Start with 100 mg PO daily, then 100 mg TID, titrate gradually to effect and as tolerated to a max of 3600 mg per day (in 4 divided doses). |

<table>
<thead>
<tr>
<th>Renal Dosing Guidelines GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 mg PO TID</td>
<td>300 mg PO q12-24h</td>
<td>Usual max of 300 mg per day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplemental Dose After</th>
<th>IHD</th>
<th>PD</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>100 mg PO after HD</td>
<td>300 mg q2days</td>
</tr>
</tbody>
</table>

| Pharmacare Coverage | Yes |

| Cost (30-day supply) without dispensing fee | 300 mg PO HS - $11.40 |

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**SYMPTOM MANAGEMENT RESOURCES: PRURITUS**

**UPDATED NOVEMBER 2012**
# Antipruritics

## ORAL

<table>
<thead>
<tr>
<th>Hydroxyzine (Atarax®)</th>
<th>*Covered by BCPRA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Shown to exert a significant antihistamine effect.</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Extensive hepatic metabolism to an active metabolite, cetirizine. Normal half-life of hydroxyzine is 20 hours and cetirizine is 25 hours. Increases with age. May accumulate in ESRD.</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Transient drowsiness, headache, somnolence, xerostomia and blurred vision. Use with caution in the elderly. May cause excessive sedation in ESRD.</td>
</tr>
<tr>
<td><strong>Dosing Guidelines (Normal Renal Function)</strong></td>
<td>10 mg PO TID-QID PRN; may increase as tolerated to 25 mg PO QID.</td>
</tr>
<tr>
<td><strong>Renal Dosing Guidelines GFR (mL/min)</strong></td>
<td>&gt;50 (mL/min)</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
<tr>
<td><strong>Supplemental Dose After</strong></td>
<td>IHD</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td><strong>Pharmacare Coverage</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cost (30-day supply) without dispensing fee</strong></td>
<td>25 mg PO TID - $13.50</td>
</tr>
</tbody>
</table>

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## Antipruritics

### TOPICAL

**Capsaicin 0.25% Cream or Ointment (Zostrix®)**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Depletes substance P from peripheral sensory C-type neurons, which after repeated application, is presumed to reduce transmission of impulses to CNS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>Onset of action occurs after 14 to 28 days with peak effect after 4 to 6 weeks.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Local burning, stinging or erythema 44 to 81% (most prominent in the first week and diminishes with continued use). Coughing 5 to 12% due to inhalation of dried capsaicin residue (can be prevented by washing the treated skin 30 to 40 minutes after application).</td>
</tr>
<tr>
<td>Dosing Guidelines (Normal Renal Function)</td>
<td>Apply sparingly to affected area(s) TID to QID.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal Dosing Guidelines GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
</tr>
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<tr>
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<table>
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<tr>
<th>Supplemental Dose After</th>
<th>IHD</th>
<th>PD</th>
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<td></td>
<td>N/A</td>
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<table>
<thead>
<tr>
<th>Pharmacare Coverage</th>
<th>No</th>
</tr>
</thead>
</table>

| Cost (30-day supply) without dispensing fee | 60 g x 0.025% cream $18.00; 60 g x 0.075% cream $19.99 |

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**SYMPTOM MANAGEMENT RESOURCES: PRURITUS**

**UPDATED NOVEMBER 2012**
## Antipruritics

### Topical Steroid Cream or Ointment

**Low Potency:** desonide 0.05% (*Desocort®*); hydrocortisone 1% **(Cortate®)**

**Medium Potency:** betamethasone valerate 0.1% (*Betnovate®*); desoximetasone 0.05% (*Topicort Mild®*)

**High Potency:** desoximetasone 0.25% (*Topicort®*); fluocinonide 0.05% (*Lyderm®, Lidex®*)

**Very High Potency:** clobetasol propionate * (Dermovate®); halobetasol 0.05% * (Ultravate®)

*Covered by Pharmacare, **Covered by BCPRA, (no star= not covered)*

### Mechanism of Action

**Low to Medium Potency:** Usually effective for treating thin, acute, inflammatory skin lesions.

**High to Very High Potency:** Often required for treating chronic, hyperkeratotic or lichenified lesions.

**For face and intertriginous areas:** Use low potency agents; or limit higher potency agents for 2 weeks.

**For palms and soles:** Use high or very high potency agents.

**For infants and elderly:** Use low potency agents.

*Creams* are preferred for acute and subacute dermatoses; may be used on moist skin areas or intertriginous areas.

*Ointments* are preferred for thick, lichenified lesions to enhance drug penetration.

### Adverse Effects

Striae, skin atrophy; rarely the risk of adrenal suppression especially if applied to large open areas, with high potency agents +/- occlusive dressing, or in infants

### Dosing Guidelines (Normal Renal Function)

Apply once or twice daily. More frequent application may be necessary for palms or soles since the preparation is easily removed and penetration is poor due to a thick stratum corneum. Every other day or weekend only or intermittent application may be effective for treating chronic conditions.

**Medium Potency:** Limit use to 3 months or less.

**Very High Potency:** Limit use to less than 2-3 weeks and to a small body area.

<table>
<thead>
<tr>
<th>Renal Dosing Guidelines GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
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<table>
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<tr>
<th>Supplemental Dose After</th>
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<th>PD</th>
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<thead>
<tr>
<th>Pharmacare Coverage</th>
<th>Some (see title for more info)</th>
</tr>
</thead>
</table>

| Cost (30-day supply) without dispensing fee | For 60 g of cream/ointment: desonide 0.05% - $19.80 hydrocortisone 1% - $6 betamethasone 0.1% valerate - $6.60 desoximetasone 0.05% cream/gel - $30 desoximetasone 0.25% - $39 fluocinonide 0.05% - $19.80 clobetasol 0.05% - $16.80 halobetasol 0.05% - $55.80 |

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