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Drug Class Literature Scan: Topical Antipsoriatics

Date of Review: September 2017

Date of Last Review: January 2015
Literature Search: 01/01/15 – 04/30/17

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- Since the last review additional evidence has become available with the publication of 1 systematic review. One new combination vitamin D analogue/corticosteroid product has been approved by the Food and Drug Administration (FDA).
- There is insufficient comparative evidence to support differences in safety or efficacy among non-steroidal topical antipsoriatics.
- For scalp psoriasis clearance, one systematic review found that combinations of topical corticosteroids plus vitamin D are more effective than topical vitamin D monotherapy with a NNT of 6.
- For scalp psoriasis clearance, one systematic review found that topical corticosteroid monotherapy is more effective than topical vitamin D monotherapy with a NNT of 4.

Recommendations:
- No changes are recommended to the OHP PDL based on the review of current evidence.
- Assign coal tar preparations to antipsoriatic class as non-preferred products.
- After review of comparative drug costs in the executive session, no PDL changes were recommended.

Previous Conclusions:
- First line therapy for psoriasis remains traditional topical therapies, including corticosteroids, vitamin D and vitamin D analogues, dithranol (anthralin), and tar preparations.
- There is no evidence of a significant difference in efficacy/effectiveness or harms between the different vitamin D analogues.
- Combination therapy with a vitamin D analogue and corticosteroid has proved to be more effective than either component alone.
- Calcipotriene is recommended first line in childhood psoriasis.
- There is lower strength of evidence for the efficacy of anthralin and it should be used as alternative therapy after vitamin D analogues and/or corticosteroids.

Previous Recommendations:
- No further review or research needed. Evaluate comparative costs in executive session.

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Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Cochrane: Topical Treatments for Scalp Psoriasis
A 2016 Cochrane Collaboration systematic review evaluated the efficacy and safety of topical treatments for scalp psoriasis.[1] Main comparators included topical steroids, vitamin D3 analogues, and corticosteroid plus vitamin D combination products. Other comparators included corticosteroid plus salicylic acid combination products, tar-based preparations, anthralin, and salicylic acid monotherapy. Fifty-nine randomized controlled trials in 11,561 participants were included. Data on age of participants were available in 38 of the studies (n=9051) with a mean age of 45.2 years.[1] Few studies included children. Follow-up lasted for a median duration of 2.4 weeks (range: 1-8 weeks).[1] Primary outcomes included either lesion clearance or clinical response as measured by the 5-point Investigator's Global Assessment (IGA) scale.[1] The 5-point IGA scale has been used in evaluation of psoriasis severity in clinical trials and correlates with other common psoriasis assessment tools but is not as well validated.[2] Additional primary outcomes assessed were quality of life improvements and adverse events leading to treatment withdrawal.

Six studies assessed combination vitamin D/steroid preparations versus vitamin D monotherapy for topical psoriatic lesion clearance.[1] Four of the 6 studies (n=2008) addressed IGA clearance as the primary outcome measure.[1] Combinations of topical steroids plus vitamin D were more effective than vitamin D alone (Relative Risk (RR) 2.28; 95% Confidence Interval (CI) 1.87 to 2.78; Absolute Risk Reduction (ARR) = 19%, Number Needed to Treat (NNT) = 6; high quality evidence).[1] However, in three studies (n=1827), overall treatment response favored corticosteroid monotherapy over vitamin D monotherapy (RR 2.09; 95% CI 1.80 to 2.41; ARR = 28%, NNT = 4; high quality evidence).[1] Meta-analysis of 4 studies (n=2291) indicated more participants withdrew due to adverse events for treatment with vitamin D monotherapy versus steroid monotherapy (5% vs. 1%, respectively; Absolute Risk Increase (ARI) = 4%, Number Needed to Harm (NNH) = 25) although no study reported on the nature of the adverse event requiring withdrawal.[1] Data from 4 studies (n=2180) demonstrated that topical steroids improved psoriatic lesion clearance in 29% of patients compared to 16% of patients on calcitriol as measured with the IGA scale (RR 1.82; 95% CI 1.52 to 2.18; ARR = 13%; NNT = 8).[1] All four studies had unclear allocation concealment and 3 of the 4 studies had unclear blinding of outcome assessments which resulted in the quality of evidence downgraded to moderate risk of bias by the authors. There was insufficient evidence to assess efficacy and safety of additional topical agents such as salicylic acid, tar- or anthralin-based treatments.[1]

New Guidelines:
None identified.

New Formulations:
In 2015, the FDA approved Enstilar® (calcipotriene 0.005%/betamethasone dipropionate 0.064%) topical foam for the treatment of plaque psoriasis in patients 18 years and older.[3] Enstilar® is applied to affected areas once daily for up to 4 weeks.[3] Approval for the foam was based on one phase 2 and one phase 3 multicenter, randomized, double-blind trial (n=728) in subjects with mild to severe psoriasis.[4] Disease severity was graded using a 5-point Investigator's Global Assessment (IGA) and at least 75% of subjects in each study were classified with "moderate" psoriasis at baseline.[4] Successful treatment outcomes were defined as the proportion of subjects at week 4 who were "Clear" to "Almost Clear" of psoriatic lesions.[4] Trial 1 (n=302) compared three treatment groups: Enstilar Foam, betamethasone dipropionate in vehicle, or calcipotriene hydrate in vehicle. The difference in proportion of subjects with successful clearance was higher for Enstilar Foam compared to calcipotriene monotherapy (45% vs. 15%, respectively; p<0.001; ARR = 30%, NNT=4) and versus betamethasone dipropionate alone (45% vs. 31%; p=0.047; ARR = 14%, NNT = 8).[4] Trial 2 (n=426) compared Enstilar Foam to vehicle. For trial 2, the proportion of subjects with treatment success was 53% for Enstilar foam versus 5% for vehicle (p<0.001; ARR = 48%, NNT = 3).[4,5] The most commonly reported adverse events for those treated with Enstilar were nasopharyngitis (2%), increased blood pressure (1%), as well as application site pain (2%), pruritus (1%), and irritation (1%).[5]

New FDA Safety Alerts:
None identified.

References:

1. Schlager JG, Rosumeck S, Werner RN, et al. Topical treatments for scalp psoriasis. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2016. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD009687.pub2/abstract. Accessed April 11, 2017.
2. Langley RGB, Feldman SR, Nyirady J, Kerkhof P van de, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. Journal of Dermatological Treatment. 2015;26(1):23-31. doi:10.3109/09546634.2013.865009. Accessed June 16, 2017.
3. Enstilar® (calcipotriene 0.005%/betamethasone dipropionate 0.064%) Prescribing Information. LEO Pharma Inc. 1 Sylvan Way, Parsippany, NJ 07054. Oct 2015 https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207589s000lbl.pdf. Accessed June 1, 2017.
4. CDER Evaluation of Enstilar® https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207589Orig1s000ClinPharmR.pdf. Accessed June 1, 2017.
5. Leonardi C, Bagel J, Yamauchi P, et al. Efficacy and Safety of Calcipotriene Plus Betamethasone Dipropionate Aerosol Foam in Patients With Psoriasis Vulgaris--a Randomized Phase III Study (PSO-FAST). Journal of Drugs in Dermatology. 2015;14(12):1468-1477.

Appendix 1: Current Preferred Drug List

Antipsoriatic Agents

Formulation	Brand	Generic	PDL
CREAM (G)	CALCIPOTRIENE	CALCIPOTRIENE	Y
SOLUTION	CALCIPOTRIENE	CALCIPOTRIENE	Y
OINT. (G)	CALCIPOTRIENE-BETAMETHASONE DP	CALCIPOTRIENE/BETAMETHASONE	Y
CREAM (G)	DOVONEX	CALCIPOTRIENE	Y
OINT. (G)	TACLONEX	CALCIPOTRIENE/BETAMETHASONE	Y
CREAM (G)	TAZAROTENE	TAZAROTENE	Y
CREAM (G)	TAZORAC	TAZAROTENE	Y
GEL (GRAM)	TAZORAC	TAZAROTENE	Y
CREAM (G)	DRITHOCREME HP	ANTHRALIN	N
CREAM (G)	ANTHRALIN	ANTHRALIN	N
SHAMPOO(G)	ZITHRANOL	ANTHRALIN MICRONIZED	N
OINT. (G)	CALCIPOTRIENE	CALCIPOTRIENE	N
OINT. (G)	CALCITRENE	CALCIPOTRIENE	N
FOAM	SORILUX	CALCIPOTRIENE	N
SUSPENSION	TACLONEX	CALCIPOTRIENE/BETAMETHASONE	N
FOAM	ENSTILAR	CALCIPOTRIENE/BETAMETHASONE	N
OINT. (G)	CALCITRIOL	CALCITRIOL	N
OINT. (G)	VECTICAL	CALCITRIOL	N
FOAM	PSORIATAR	COAL TAR	N
FOAM	SCYTERA	COAL TAR	N
OINT. (G)	MG217 PSORIASIS	COAL TAR	N
CREAM (G)	SORBOLENE	GLYCERN/MIN OIL/PETROLAT/C.ALC	N
CREAM (G)	AVAGE	TAZAROTENE	N

Coal Tar Products

FormDesc	Brand	Generic	PDL
SHAMPOO	ANTI-DANDRUFF	COAL TAR	
SHAMPOO	BETATAR	COAL TAR	
SOLUTION	COAL TAR	COAL TAR	
EMULSION	CUTAR	COAL TAR	
SHAMPOO	DHS TAR	COAL TAR	

SHAMPOO	DHS TAR GEL	COAL TAR
SHAMPOO	DUPLEX T	COAL TAR
SHAMPOO	IONIL T	COAL TAR
LOTION	OXIPOR VHC	COAL TAR
SHAMPOO	PC TAR	COAL TAR
SHAMPOO	PENTRAX	COAL TAR
SHAMPOO	PENTRAX GOLD	COAL TAR
SHAMPOO	POLYTAR	COAL TAR
GEL (GRAM)	PSORIASIN	COAL TAR
LOTION	TEGRIN PSORIASIS	COAL TAR
SHAMPOO	TERA-GEL TAR	COAL TAR
SHAMPOO	T-GEL	COAL TAR
SHAMPOO	THERA-GEL	COAL TAR
SHAMPOO	THERAPEUTIC SHAMPOO	COAL TAR
SHAMPOO	T-PLUS	COAL TAR
SHAMPOO	X-SEB T PLUS	COAL TAR

Appendix 2: New Comparative Clinical Trials

A total of 28 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), data collection methods (eg, unblinded), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April Week 4 2017
1 calcipotriene.mp. 773
2 calcipotriene and betamethasone.mp. 194
3 tazarotene.mp. 479
4 Calcitriol/ or calcitriol.mp. 12630
5 anthralin.mp 327
6 coal tar 701
7 psoriasis.mp. or Psoriasis/ 23589
8 1 or 2 or 3 or 4 or 5 or 6 14104
9 7 and 8 1202
limit 9 to (yr="2015 -Current" and english and humans and (clinical study or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or systematic reviews)) 28

Topical Antipsoriasis Drugs

Goal(s):

Restrict topical antipsoriasis drugs only for funded OHP diagnoses. Moderate/Severe psoriasis treatments are funded on the OHP. Treatments for mild psoriasis (L400-404, L408-418, L448), seborrheic dermatitis (L2083, L210-219, L303), keroderma (L110, L83, L850-852, L870-872, L900-902, L906, L940, L943) and other hypertrophic and atrophic conditions of skin (L119, L572, L574, L664, L908-909, L918-919, L922, L985) are not funded.

Length of Authorization:

- Up to 12 months

Requires PA:

Non-preferred drugs
STC = 92 and HIC = L1A, L5F, L9D, T0A

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for seborrheic dermatitis (L2083, L210-219, L303), keroderma (L110, L83, L850-852, L870-872, L900-902, L906, L940, L943) or other hypertrophic and atrophic conditions of skin (L119, L572, L574, L664, L908-909, L918-919, L922, L985)?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the diagnosis Psoriasis? (ICD-10 L400-404,L408-418, L448)	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Is the Psoriasis Moderate/Severe? Moderate/Severe psoriasis is defined as: • At least 10% body surface area involved or with functional impairment • Hand, foot or mucous membrane involvement	**Yes:** Go to #5	**No:** Pass to RPh; deny, not funded by the OHP.
5. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #6
6. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No:** Approve for length of treatment; maximum 1 year.
7. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.	**If funded, or clinic provides supporting literature:** Approve for length of treatment.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *7/17 (DE); 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *10/15; 8/15; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*