Ivermectin Topical Cream 1% (SOOLANTRA)

National Drug Monograph

July 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information [1, 2]

Description/Mechanism of Action	Ivermectin is a macrocyclic lactone disaccharide antiparasitic agent which has been shown to have efficacy in the treatment of rosacea. The exact mechanism responsible for the drug's effectiveness in rosacea has not yet been determined; however, its anti-inflammatory activity is believed to result from down regulation of interleukin-1b and tumor necrosis factor-α.
Indication(s) Under Review:	Topical ivermectin is indicated for the treatment of inflammatory lesions of rosacea.
Dosage Form(s) Under Review	Cream, 1%
REMS	☐ REMS **X** No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Pregnancy Category C

Executive Summary

Efficacy

- Ivermectin 1% cream was FDA approved in December 2014 for the treatment of inflammatory lesions of rosacea based upon two pivotal phase III trials where ivermectin 1% cream, compared to a vehicle-control, was effective in the treatment of moderate or severe papulopustular rosacea as evidenced by the following significant changes: reductions in inflammatory lesion counts, improvements in Investigator Global Assessment (IGA) scores indicative of complete or near-complete clearing of rosacea, and improvements in assessment of healthcare-related quality of life (QoL).[2]
- In an additional phase III trial, ivermectin 1% cream applied once daily, compared to twice daily application of metronidazole 0.75% cream, resulted in a greater reduction in number of inflammatory lesions and an increased number of subjects with IGA scores indicative of complete or near-complete clearing of rosacea.[3] Patient satisfaction and QoL scores associated with ivermectin 1% cream were more improved versus those for metronidazole 0.75% cream; however, these assessments may have been impacted by the choice to trial twice daily metronidazole instead of an equally effective once daily regimen.
- There are no efficacy trials comparing ivermectin 1% cream to standard rosacea treatments including sodium sulfacetamide/sulfur lotion and azelaic acid 15% (both of which are considered to be more effective than metronidazole[4]), and no efficacy trials comparing ivermectin 1% cream to standard combinations of other topical agents (metronidazole, azelaic acid or sulfacetamide/sulfur lotion) with an oral antibiotic (doxycycline, or other).
- The application frequency of once daily is a favorable aspect of ivermectin 1% cream use which may improve adherence; however, it holds no application advantage over other topical rosacea treatments which may be applied with the same frequency with no loss of efficacy.[5,6]

Safety	• In vehicle-controlled phase III trials, ivermectin 1% cream was found to have a low potential for adverse effects. Small numbers of subjects experienced mild or moderate adverse reactions which most often consisted of skin burning, pruritus, and dry skin; there were no treatment-related serious adverse effects.[2] • Comparative studies have shown trends towards reduced adverse effects with ivermectin 1% cream versus azelaic acid 15% gel or metronidazole 0.75% cream. [3,7] • There are no contraindications for use of ivermectin 1% cream and no known drug-drug or drug-food interactions.[1]
Potential Impact	• Ivermectin 1% cream has proven efficacy in the management of papulopustular rosacea but it has unknown comparative efficacy relative to a variety of existing therapeutic approaches to this disorder. • Current evidence supports consideration of ivermectin 1% cream in instances where standard topical treatments and combinations of standard topical treatments with an oral antibiotic have been ineffective or poorly tolerated.

Background

Purpose for review

Ivermectin 1% cream was approved by the FDA (Dec 2014) for the treatment of rosacea; the purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to considering topical ivermectin for addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Also to be determined:

Is there evidence of need for ivermectin in the population to be treated?
Does topical ivermectin offer advantages to available alternatives for the treatment of rosacea?
Does topical ivermectin offer advantages over current VANF agents?
What safety issues need to be considered?
Does topical ivermectin have special characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives (topical unless otherwise noted)	Other Considerations
Metronidazole cream, gel	Non-drug therapeutic modalities include proper skin care and avoidance of known irritants and triggers including UV light
Sulfacetamide/ sulfur lotion	
Clindamycin lotion/ solution/swab	
Benzoyl peroxide gel, lotion	
Tretinoin cream, gel*	
Oral tetracyclines (doxycycline, minocycline)	
Isotretinoin oral*	

Non-formulary Alternative (if applicable)	Other Considerations
Azelaic acid gel	
Adapalene gel	
Of the topical agents, only metronidazole, sodium sulfacetamide, azelaic acid, and ivermectin 1% are FDA approved for the treatment of cutaneous rosacea **Use within VA limited to CFU*	

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (2011 to April 2015) using multiple search terms and combinations of terms including ivermectin, Soolantra, and rosacea. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials and all randomized controlled trials published in peer-reviewed journals are included in this review. Expert panel consensus recommendations regarding the treatment of rosacea and relevant practice standards (such as grading systems utilized in the classification and staging of rosacea) were also identified.

Review of Efficacy

- The 2014 FDA approval of ivermectin 1% cream was based on the results of two pivotal randomized, double-blind phase III studies of identical design in which ivermectin 1% cream or vehicle was applied once daily for 12 weeks to facial skin of subjects with papulopustular rosacea.[2] Investigators assessed efficacy related to disease severity and inflammatory lesion counts, in addition to assessing for safety and subject-reported outcomes [rosacea improvement and health-related quality of life (HRQoL)].
- The total population of study subjects was representative of a typical rosacea population: 67.5% were female, average age was 50 and approximately 85% were Caucasian; 1371 subjects were randomized 2:1 to receive ivermectin 1% cream or vehicle cream, 683 in Study 1a (451 to ivermectin; 232 to vehicle) and 688 in Study 2a (459 to ivermectin; 229 to vehicle) [*for the purposes of this monograph, these studies were given a suffix 'a' to differentiate them from the extension studies ('b') with similar titles*].
- There were no imbalances in the baseline characteristics of the two study populations; subjects had inflammatory lesion counts ranging from 15 to 70 [mean counts of 30.9 (Study 1a) and 32.9 (Study 2a)] and all patients had moderate or severe papulopustular rosacea as defined by an Investigator's Global Assessment (IGA) of Rosacea Severity scale (82.0% and 18.0%, respectively, in Study 1a; 75.9% and 24.1%, respectively, in Study 2a) [Table 1; also see Table 4: Assessment of Evidence Base].

Table 1. Investigator's Global Assessment (IGA) of Rosacea Severity* [2, 3, 7]

Grade	Description	Amount and size of inflammatory lesions present	Presence of erythema
0	Clear	None	None
1	Almost Clear	Very few, small papules /pustules	Very mild erythema
2	Mild	Few small papules/pustules	Mild erythema
3	Moderate	Several small or large papules/pustules	Moderate erythema
4	Severe	Numerous small and/or large papules/pustules	Severe erythema

* *The Investigator's Global Assessment (IGA) scoring system utilized in ivermectin clinical trials is a re-formatting of a Standardized Grading System used for grading of rosacea severity. The Standardized Grading System provides a basic framework for disease quantification; however, it has not yet been validated, and thus the statistical limitations of the grading system have not been established.* [8,9,10]

- Subjects were instructed to apply a thin film of study drug to the entire face once daily at bedtime. The entire face was considered to be comprised of 5 regions: right and left cheeks, forehead, chin, and nose. Subjects were advised to avoid application to upper and lower eyelids, lips eyes and mouth, and also to avoid rosacea triggers

such as sudden heat exposure, certain food and excessive UV light exposure. Following an initial screening, study visits were conducted at baseline and at weeks 2, 4, 8, and 12.

- There were 2 primary efficacy measures: the IGA scale was used at each visit to assess efficacy of study treatment on disease severity and inflammatory lesion counts on the 5 facial regions. The secondary efficacy endpoint was percent change in inflammatory lesion counts from baseline to week 12. Also at week 12, subject evaluation of their rosacea improvement compared to baseline was recorded as well as HRQoL [assessed through subject responses to the Dermatology Life Quality Index (DLQI) and the Rosacea Quality of Life Index (RosaQoL)]. Safety assessments were conducted at each visit and severity of adverse event was graded on a scale of 0 (none) to 3 (severe).
- The DLQI has been extensively validated and is the most commonly used HRQoL dermatological assessment tool in clinical practice and in randomized controlled trials; it consists of a 10-item (max score 30) questionnaire which assesses the impact of skin disease from the patients' point of view regarding symptoms and feelings, daily activities, leisure, work, personal relationships and treatment. The RosaQoL is also a validated QoL assessment instrument which partly consists of rosacea-specific questions: 21questions are grouped into 3 subscales (symptoms, emotions and function) which are scored from 1 (never) to 5 (all the time). Scores of the subscales and total scores are averaged and also range from 1 to 5. Higher scores for both the DLQI and the RosaQoL indicate a worse HRQoL.[11]
- Greater than 90% of subjects in each treatment group in both studies completed the 12 week trial. Primary and secondary efficacy outcomes are summarized in Table 2. In both studies, at 12 weeks, compared to application of vehicle alone, ivermectin 1% cream significantly lessened rosacea severity and reduced inflammatory lesion counts. IGA ratings of 'clear" or 'almost clear' were achieved in 38.4% and 40.1% of ivermectin 1% treated Study 1a and Study 2a subjects, respectively, compared to 11.6% and 18.8% of subjects receiving vehicle only.
- In studies 1a and 2a, patient reported outcomes were respectively rated 'excellent or good' in 69% and 66.2% of ivermectin 1% cream recipients, whereas only 38.4% and 34.4% those receiving vehicle reported those levels of improvement (all $p < 0.001$). The rate of subjects reporting an 'excellent' outcome was 4 times greater in ivermectin 1% cream treated patients compared to those given vehicle ($p < 0.001$). Compared to baseline scores, DLQI was significantly improved in subjects receiving ivermectin 1% cream compared to vehicle alone (53% *versus* 35%, both studies, $p < 0.001$) as was RosaQoL (-0.64 ± 0.7 *versus* -0.60 ± 0.6; both studies, $p < 0.001$).

Table 2. Primary and secondary outcome measures, ivermectin 1% cream compared to vehicle applied for 12 weeks in patients with moderate to severe papulopustular rosacea.[2]

Efficacy Measures	**Study 1a (n = 683)**			**Study 2a (n = 688)**		
Primary	**Ivermectin n = 451**	**Vehicle n = 232**	**p value**	**Ivermectin n= 459**	**Vehicle n = 229**	**p value**
Disease severity (% clear or almost clear)	38.4%	11.6%	< 0.001	40.1%	18.8%	< 0.001
Lesion Counts [difference in lesions vs. vehicle, baseline to week 12 (95% CI)]	-8.13 (-10.12, -6.13)			-8.22 (-10.18, -6.25)		
Secondary						
Inflammatory lesion counts (reduction from baseline)	76%	50%	< 0.001	75%	50%	< 0.001

- There were no serious adverse events in either study. The incidence of adverse events was similar in subjects receiving ivermectin 1% cream or vehicle in studies 1a and 2a (40.5% and 39.4% for ivermectin 1%, respectively; 36.5% for vehicle in both studies). The most common related adverse events were skin burning in study 1a and

pruritus and dry skin in study 2a, but the incidence of these adverse effects was typically less with ivermectin 1% cream than with vehicle (Study 1a: 1.8% incidence of skin burning with ivermectin 1%, 2.6% with vehicle; Study 2a: 0.7% incidence of pruritus or dry skin with ivermectin 1%, 0% pruritus and 0.9% dry skin with vehicle). Hematology and biochemical testing did not show clinically significant abnormalities in any treatment group in either study.

Comparative Trials

Ivermectin 1% Cream *versus* Azelaic Acid 15% Gel[7]

- Stein-Gold et al. (2014b) reported results from two 40-week extension studies of the vehicle-controlled phase III trials previously detailed (Study 1a and Study 2a).[7] *For the purposes of this monograph, these extension studies are referred to as Study 1b and Study 2b.*
- Subjects originally treated with ivermectin 1% cream applied once daily continued the same therapy; subjects initially treated with vehicle cream were switched to azelaic acid 15% gel applied twice daily. Study visits were conducted from week 12 of the initial study and every 4 weeks thereafter to the 40th week. Efficacy was assessed with the IGA tool at each study visit (see Table 4: Assessment of Evidence Base). Safety assessments included adverse events, local tolerability signs and symptoms [graded on a scale of 0 (none) to 3 (severe)], and assessment of hematology and chemistry parameters.
- Enrollment in Study 1b and Study 2b was comprised of 622 and 636 subjects, respectively. In Study 1b and 2b, 85.2% and 82.5% of ivermectin 1% treated subjects completed the 40 week trial. Completion rates for subjects given azelaic acid 15% gel were marginally lower (83.3% and 76.4%, respectively).
- IGA scores for ivermectin 1% cream and azelaic acid gel 15% gel treated subjects in both studies who completed 40 weeks' treatment are detailed in Table 3; the investigators noted that the scores between treatment groups could not be directly compared because the ivermectin 1% groups had received an additional 12 weeks of active treatment.

Table 3: IGA scores for subjects with papulopustular rosacea who applied ivermectin 1% daily for 52 weeks or azelaic acid 15% gel twice daily for 40 weeks;[7] also see Table 4: Assessment of Evidence Base

IGA Scores	Study 1b (n = 683)		Study 2b (n = 688)	
	Ivermectin x 52 weeks n = 349	Azelaic Acid x 40 weeks n = 175	Ivermectin x 52 weeks n= 358	Azelaic Acid x 40 weeks n = 164
Grades 0 and 1 (% clear or almost clear)	71.1	59.4	76.0	57.9
Grade 2 (% with mild severity)	20.9	28.6	17.9	23.8
Grade 3 (% with moderate severity)	7.2	10.3	5.6	17.1
Grade 4 (% with severe disease)	0.9	1.7	0.6	1.2

- Subjects receiving an additional 40 weeks of ivermectin 1% cream experienced improvement in IGA scores compared to 12 weeks' treatment (IGA score of 0 or 1 in 71.1% or 76% of subjects versus 38.4% or 40.1%, respectively).
- Subjects receiving 40 weeks of azelaic acid 15% gel achieved Grade 0 or 1 improvement in approximately 58% of cases.
- The incidences of related adverse events were 1.9% and 2.1% for ivermectin 1% cream in Studies 1b and 2b, respectively. Typically, this was a burning sensation, skin irritation or dry skin occurring on the area of

application. No severe or serious adverse events were considered to have been related to ivermectin 1% cream in either study.

- Adverse events related to azelaic acid occurred in 6.7% of Study 1b subjects and 5.8% of Study 2b subjects. Most complaints were of a sensation of skin pain or discomfort, sensation of skin burning, skin irritation, dry skin, or pruritus, all on the area of application. While no serious adverse events could be contributed to azelaic acid in either study; one subject in Study 2b had severe skin irritation considered related to azelaic acid use.

Ivermectin Cream 1% *versus* Metronidazole 0.75% Cream[3]

- Ivermectin 1% cream applied once daily was compared to twice-daily application of metronidazole 0.75% cream in 962 subjects with papulopustular rosacea in a 16 week, phase III, multicenter and multinational, investigator-blinded, randomized, parallel-group study.[3]
- Subjects were randomized 1:1; study drugs were applied in the same fashion and patients were cautioned to avoid rosacea triggers as occurred in the pivotal phase III vehicle-controlled 12 week trials and in the 40 week extension. Following a screening visit, subjects were assessed at baseline, and at weeks 3, 6, 9, 12 and 16.
- Primary efficacy assessments were comprised of inflammatory lesion counts and IGA scores at week 16; the same IGA scoring system was utilized for the ivermectin 1% and metronidazole 0.75% comparison as in the previously described trials (see Table 4: Assessment of Evidence Base). Subject evaluation of rosacea improvement at 16 weeks compared to baseline was determined on a 5 point scale (worse, no improvement, moderate, good, or excellent); in addition, subject satisfaction with study drug and DLQI (see page 4) were assessed.
- Safety assessments included recording of adverse events throughout the study, grading of local tolerance parameters as in the previously described trials, and laboratory screening at baseline, and at weeks 9 and 16.
- Study subjects demographics were representative of a typical rosacea population: 65.2% were female, mean age was 51.5 years and all but 3 of the 962 subjects were Caucasian. There were no imbalances in the baseline characteristics of the two treatment groups; subjects had an average number of 32 inflammatory lesions and the majority (83.3%) had IGA scoring consistent with moderate rosacea.

Table 4: Primary efficacy outcome measures, ivermectin 1% cream compared to metronidazole 0.75% cream applied for 16 weeks, in subjects with moderate to severe papulopustular rosacea; [3] also see Table 4: Assessment of Evidence Base.

Interval	Week 3	Week 6	Week 9	Week 12	Week 16
Mean percentage Change from Baseline in Inflammatory Lesion Counts					
Ivermectin 1% (n= 478)	-32.5*	-55.6**	-66.3**	-75.7**	-83**
Metronidazole 0.75% (n= 484)	-30.5	-49.2	-59.8	-67.1	-73.7
Percentage of Subjects with IGA Score 0 or 1					
Ivermectin 1%	7.9	28.2*	43.9*	64.9**	84.9**
Metronidazole 0.75%	5.6	21.5	36.0	50.0	75.4

* $p < 0.04$; ** $p < 0.001$

- Primary efficacy outcomes are summarized in Table 4; greater than 93% of each treatment group completed the 16 week trial. At 16 weeks, ivermectin 1% cream reduced inflammatory lesion sites to an greater extent than metronidazole 0.75% (83% versus 73.7%, respectively; $p < 0.001$). A significant difference was noted starting in week 3. Percentage of subjects with IGA score 0 or 1 was similarly affected by ivermectin 1% cream versus metronidazole 0.75% cream.
- Subject evaluation of global improvement and satisfaction with study drug trended towards a superior response with ivermectin 1% cream; in addition, subjects treated with ivermectin 1% had a greater numerical

reduction in the DLQI scores than those treated with metronidazole 0.75% (-5.18 versus -3.92; $p < 0.01$), indicating an improved HRQoL with ivermectin 1% cream.

- Overall incidence of adverse events was comparable between ivermectin 1% and metronidazole 0.75% creams; however, local tolerance adverse events trended higher for metronidazole 0.75% cream. Three subjects (0.6%) withdraw from the study due to adverse events with ivermectin 1% versus 10 (2.1%) with metronidazole 0.75%. The most common related adverse event was skin irritation for both agents. There were no clinically significant abnormalities in laboratory tests attributable to study drugs.
- Once- and twice-daily regimens of metronidazole have been shown to be essentially equivalent in the treatment of rosacea;[5] the choice to trial a twice-daily regime (versus once-daily) may have negatively impacted the measures of subject satisfaction and DLQI for metronidazole.

Table 4: Assessment of Evidence Base

Category	Summary
Overall Quality of Studies (GRADE) (Internal validity or risk of bias)	GRADE: the pivotal trials considered in the FDA approval of ivermectin 1% cream are considered to be MODERATE in overall quality. These studies were randomized, double-blind, and vehicle-controlled, 12 weeks in length, and included adequate numbers of active treatment patients and controls (total enrollment, both trials, 1,371); however, the Investigator's Global Assessment (IGA) scoring system has not been fully validated as a rosacea efficacy assessment tool. [2, 8, 9] The safety comparisons of ivermectin 1% cream and azelaic acid 15% gel were controlled, investigator blinded 40-week extensions of the above described 12 week trials.[7] They are deemed to be of MODERATE overall quality due to use of the same IGA scoring system. The randomized and investigator-blinded efficacy and safety comparison of ivermectin 1% cream and metronidazole 0.75% cream[3] is considered to be of MODERATE overall quality. In addition to use of the same IGA scoring system – metronidazole 0.75% cream was utilized at a twice daily frequency instead of an equally effective once daily schedule. This choice of application frequency may have negatively impacted secondary measures of subject satisfaction and healthcare-related quality of life (DLQI).
Consistency of Results (Within and among studies)	Each of the studies showed significant benefit in reducing the inflammatory lesions and erythema due to papulopustular rosacea. The 40 week extension trials demonstrated not only durability of reduction in rosacea severity but also higher percentages of subjects achieving 'clear' or 'almost clear' response to ivermectin 1% cream compared to response observed in the 12 week trials.
Directness of Evidence	All studies used the same clinician assessment of rosacea severity for efficacy outcomes. The 12 week pivotal comparisons with vehicle and the 16 week comparison with metronidazole 0.75% cream each contained patient reported outcomes (global improvement and QOL assessment) which were consistently improved with ivermectin 1% cream.
Precision of Results	No deficiencies noted

All studies were funded by the manufacturer of ivermectin 1% cream (Galderma). Each of the 3 publications listed one or two authors identified as employees of Galderma R&D.[2, 3, 7]

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

There do not appear to be any proposed, ongoing, or completed trials for ivermectin 1% cream relating to unlabeled indications (reference www.clinicaltrials.gov, accessed April 16, 2015).

There are multiple proposed, ongoing, and completed trials for varying formulations of topical ivermectin 0.5% for treatment of head lice.

Safety[1]	
(additional information may be found in the product package insert)	
	Comments
Boxed Warning	• None
Contraindications	• None
Warnings/Precautions	• None

Safety Considerations

During clinical trials, 2047 subjects with inflammatory lesions of rosacea received ivermectin 1% cream once daily. A total of 1555 subjects were treated once daily for > 12 weeks and 519 for approximately one year.

Adverse reactions reported in subjects treated with ivermectin 1% cream for 12 weeks in vehicle-controlled clinical trials are as follows:

- Skin burning [8 of 451 (1.8%) ivermectin subjects versus 6 of 232 (2.6%) vehicle-control subjects]
- Pruritus [3 of 459 (0.7%) ivermectin subjects versus 0 (0%) vehicle-control subjects]
- Dry skin [3 of 459 (0.7%) ivermectin subjects and 2 of 229 (0.9%) vehicle-control subjects]

Adverse Reactions [1, 2]	
Common adverse reactions	Incidence ≥ 1%: skin burning; incidence ≥ 0.5%: pruritus, dry skin, skin irritation
Death/Serious adverse reactions	There were no serious or severe adverse reactions attributed to ivermectin 1% cream in controlled clinical trials
Discontinuations due to adverse reactions	The percentage of subjects using ivermectin 1% cream that discontinued treatment due to an adverse reaction was ≤ 1.3% in the pivotal phase III trials leading to product approval

Drug Interactions

Drug-Drug Interactions[1]

- In vitro studies have shown that topical ivermectin cream, applied to achieve therapeutic concentrations, neither inhibited nor induced cytochrome P450 (CYP450) enzymes.

Drug-food Interactions and Drug-Lab Interactions have not been reported to occur concerning topical ivermectin.

Risk Evaluation

As of February 26, 2015:

	Comments				
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC				
Look-alike/sound-alike error potentials	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment

Ivermectin 1% cream	None	None	None	Ivermectin tablets Ivermectin lotion Ivacaftor
Soolantra	None	None	None	Sonata Survanta Sufenta

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations [1, 4, 5, 6]

Both sodium sulfacetamide/sulfur lotion and azelaic acid gel have been shown to have superior efficacy compared to topical metronidazole. [4]

The efficacy of once-daily versus twice-daily application has been shown to be essentially equal for both metronidazole and azelaic acid 15% gel. [5, 6]

Ivermectin cream 1% is a hydrophilic formulation containing the following inactive ingredients: carbomer copolymer type B, cetyl alcohol, citric acid monohydrate, dimethicone, edetate disodium, glycerin, isopropyl palmitate, methylparaben, oleyl alcohol, phenoxyethanol, polyoxyl 20 cetostearyl ether, propylene glycol, propylparaben, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol.[1]

Ivermectin 1% cream should be stored at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F).[1]

Dosing and Administration[1]

The recommended frequency of application of ivermectin 1% cream is once daily; a pea-size amount should be applied to each area of the face (forehead, chin, nose, each cheek) that is affected and spread as a thin layer, avoiding the eyes and lips.

Special Populations (Adults)[1]

	Comments
Elderly	• Of the 1371 subject in randomized controlled vehicle-controlled comparisons, 170 (12.4%) were 65 and over, while 37 (2.7%) were 75 and over. No overall differences in safety or efficacy were noted between these subjects and younger subjects. Other reported clinical experiences have not identified differences in response between elderly and younger patients.
Pregnancy	• Ivermectin 1% cream has been categorized as Pregnancy Category C. There are no adequate and well-controlled studies of its use in pregnant women; thus, ivermectin 1% cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	• Excretion of ivermectin in human milk following topical administration has not been evaluated; however, it is known that ivermectin is excreted in human milk in low concentrations following oral administration.
Renal Impairment	• No data identified
Hepatic Impairment	• No data identified
Pharmacogenetics/genomics	• There are no data identified in the FDA approved labeling http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm (accessed February 26, 2015).

Projected Place in Therapy [2, 4, 7, 12]

- Rosacea is a common, chronic inflammatory disorder, primarily affecting the skin of the face. The cause of rosacea is unknown and its pathogenesis is complex and poorly understood.
- Conservative estimates suggest that rosacea affects 13-14 million individuals in the US, reflecting a prevalence rate of approximately 5%. It affects both sexes but is more common in women than in men. Rosacea is most frequently observed in individuals with fair skin but has also been diagnosed in Asians and African Americans. In FY14, 36,579 VA patients had ICD-9 coding for rosacea, a general diagnostic classification which includes four clinical subtypes: erythematotelangietatic, papulopustular, phymatous, and ocular.
- Patients may progress from one rosacea subtype to another and can have more than one subtype at the same time. Patients affected with papulopustular rosacea have persistent central facial erythema in addition to papules and/or pustules and possibly burning and stinging of the affected skin. Like all manifestations of rosacea, the papulopustular subtype is treatable but not curable and, because of typical localization to the face, there can be psychosocial consequences for the affected patient leading to a decreased quality of life.
- Topical ivermectin is FDA-approved for the treatment of inflammatory lesions of rosacea. In clinical trials of moderate overall quality, ivermectin 1% cream, compared to vehicle-controls, was shown to be effective in the treatment of moderate or severe papulopustular rosacea as evidenced by significant reductions in inflammatory lesion counts and improvements in IGA scores indicative of complete or near-complete clearing. These same trials also showed significant improvement in indexes of healthcare-related quality of life (DLQI and RosaQoL) resulting from use of ivermectin 1% cream.
- The IGA system has not been validated as a rosacea severity assessment tool; however, it is based upon a standard method of assessment utilized in dermatology and is effective in the quantification of disease improvement.
- Ivermectin 1% cream applied once daily, compared to twice daily application of metronidazole 0.75% cream, resulted in a greater reduction in number of inflammatory lesions and an increased number of subjects with IGA scores indicative of complete or near-complete clearing of rosacea lesions and inflammation. Patient satisfaction and DLQI scores associated with ivermectin 1% cream were more improved versus those for metronidazole 0.75% cream; however, these secondary assessments may have been impacted by the choice to trial twice daily metronidazole instead of an equally effective once daily regimen.
- Ivermectin 1% cream has a low potential for adverse effects; clinical trials reported very small numbers of subjects who experienced adverse reactions which most often consisted of skin burning, pruritus, and dry skin. Studies have shown trends towards reduced adverse effects with ivermectin 1% cream when compared to azelaic acid 15% gel or metronidazole 0.75% cream.
- Recommendations exist for the treatment of papulopustular rosacea based upon guidance issued by the Rosacea International Expert Group, Consensus Recommendations from the American Acne and Rosacea Society, and current literature. These recommendations list ivermectin as an antimicrobial agent:
  - Mild papulopustular rosacea: use topical antimicrobials (metronidazole, clindamycin, sulfacetamide/sulfur, and ivermectin), azelaic acid, or retinoids
  - Moderate papulopustular rosacea: continue topical agent and add an oral antimicrobial [low-dose doxycycline, macrolide, or ivermectin]
  - Severe papulopustular rosacea: continue topical agent and add high-dose tetracycline OR low-dose isotretinoin.

  These recommendations allow for use of ivermectin 1% cream for mild, moderate or severe papulopustular rosacea and are in concurrence with the evidence summarized in this monograph.
- There are no efficacy trials comparing ivermectin 1% cream to standard rosacea treatments including sodium sulfacetamide/sulfur lotion and azelaic acid 15% (both of which are considered to be more effective than metronidazole [4]), and no efficacy trials comparing ivermectin 1% cream to commonly used combinations of other topical agents (metronidazole, azelaic acid or sulfacetamide/sulfur lotion) with an oral antibiotic (doxycycline, or other).
- Current evidence supports consideration of ivermectin 1% cream in the treatment of papulopustular rosacea where standard topical treatments and combinations of standard topical treatments with an oral antibiotic have been ineffective or poorly tolerated.

- The use of ivermectin 1% cream, relative to alternative treatments, may be most appropriately determined by dermatologists or other providers with specialized experience in the management of rosacea.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010; 153:194-199.