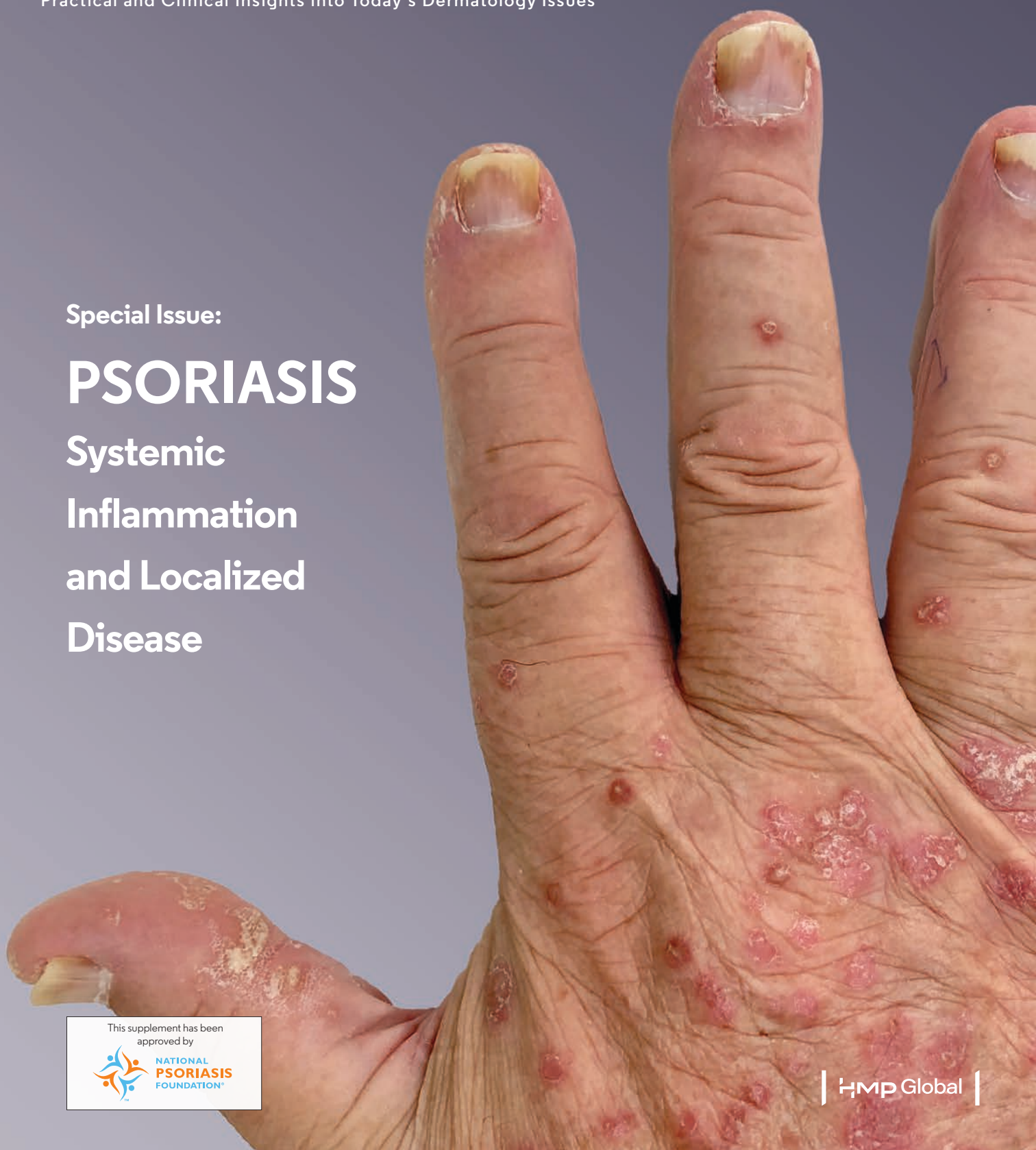
September 2021 | Supplement

the dermatologist®

Practical and Clinical Insights into Today's Dermatology Issues



Special Issue:

PSORIASIS

Systemic Inflammation and Localized Disease

This supplement has been approved by NATIONAL PSORIASIS FOUNDATION®

HMP Global

SKYRIZI IS NOW AVAILABLE AS A SINGLE 150 mg INJECTION

For adults with moderate to severe plaque psoriasis

1 INJECTION 4 TIMES A YEAR[1]

After Week 0 and 4 Injections

Skyrizi®

risankizumab-rzaa

SKYRIZI is the only 4-dose-a-year biologic in psoriasis that offers a single-dose pen[1]

- **Same SKYRIZI you know and trust, now in a single 150 mg/mL injection[1]***
- **Consistent efficacy and safety profile[1-2]**
- **In-office or at-home administration after proper training[1]**

SKYRIZI is also available in a 150 mg/mL prefilled syringe

*Bioequivalence was demonstrated between a single 150 mg/mL injection and two 75 mg/0.83 mL injections in a prefilled syringe. Bioequivalence was also demonstrated between 150 mg/mL prefilled syringe and prefilled pen.[3]

ADMINISTRATION INSTRUCTIONS[1]

SKYRIZI is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject SKYRIZI after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of SKYRIZI according to the Instructions for Use.

INDICATION[1]

SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

IMPORTANT SAFETY INFORMATION[1]

Infection

- SKYRIZI® (risankizumab-rzaa) may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.
- In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

Pre-Treatment Evaluation for Tuberculosis (TB)

- Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Administration of Vaccines

- Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating SKYRIZI, complete all age appropriate vaccinations according to current immunization guidelines.

Adverse Reactions

- Most common (≥1%) adverse reactions associated with SKYRIZI include upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections.

SKYRIZI is available in a 150 mg/mL prefilled syringe and pen.

Please see the Brief Summary of the Full Prescribing Information on the following page.

References: 1. SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **2.** Data on file, ABVRRTI71470. AbbVie Inc. **3.** Lon HK, Cheng L, Nudurupati S, et al. Pharmacokinetic comparability of risankizumab formulations in prefilled syringe and auto-injector for subcutaneous injection. *Clin Ther.* 2021;43(3):629-636. doi:10.1016/j.clinthera.2021.01.009

 North Chicago, IL 60064 US-SKZ-210068 May 2021 Printed in U.S.A.

SKYRIZI® (sky-RIZZ-ee) (risankizumab-rzaa) injection, for subcutaneous use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

SKYRIZI® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infections

SKYRIZI may increase the risk of infections. In clinical studies, infections occurred in 22.1% of the SKYRIZI group compared to 14.7% of the placebo group through 16 weeks of treatment. Upper respiratory tract infections and tinea infections occurred more frequently in the SKYRIZI group than in the placebo group. Subjects with known chronic or acute infections were not enrolled in clinical studies *[see Adverse Reactions]*.

The rate of serious infections for the SKYRIZI group and the placebo group was ≤ 0.4%. Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the IMMHANCE study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with SKYRIZI, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Infections *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse drug reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 2234 subjects were treated with SKYRIZI in clinical development trials in plaque psoriasis. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled trials were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group.

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical trials.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

Adverse Drug Reactions	SKYRIZI N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	15 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 were folliculitis and urticaria.

Specific Adverse Drug Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared to 14.7% of the placebo group (56.5 events per 100 subject-years) and did not lead to discontinuation of SKYRIZI. The rates of serious infections for the SKYRIZI group and the placebo group were ≤0.4%. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis, and herpes zoster. In ULTIMMA-1 and ULTIMMA-2, through Week 52, the rate of infections (73.9 events per 100 subject-years) was similar to the rate observed during the first 16 weeks of treatment.

Safety Through Week 52

Through Week 52, no new adverse reactions were identified, and the rates of the adverse reactions were similar to those observed during the first 16 weeks of treatment. During this period, serious infections that led to study discontinuation included pneumonia.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products, including other risankizumab products, may be misleading.

By Week 52, approximately 24% (263/1079) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, approximately 57% (14% of all subjects treated with SKYRIZI) had antibodies that were classified as neutralizing. Higher antibody titers in approximately 1% of subjects treated with SKYRIZI were associated with lower risankizumab-rzaa concentrations and reduced clinical response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women with plaque psoriasis who become pregnant while treated with SKYRIZI. Patients should be encouraged to enroll by calling 1-877-302-2161.

Risk Summary

Limited available data with SKYRIZI use in pregnant women are insufficient to evaluate a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Human IgG is known to cross the placental barrier; therefore, SKYRIZI may be transmitted from the mother to the developing fetus.

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 and 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. At the 50 mg/kg dose [20 times the maximum recommended human dose (MRHD); 2.5 mg/kg based on administration of a 150 mg dose to a 60 kg individual], increased fetal/infant loss was noted in pregnant monkeys *(see Data)*. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared to the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg (20 times the MRHD, based on mg/kg comparison) and the NOAEL for developmental toxicity was identified as 5 mg/kg (2 times the MRHD, based on mg/kg comparison). In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

Lactation

Risk Summary

There are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYRIZI and any potential adverse effects on the breastfed infant from SKYRIZI or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of SKYRIZI in pediatric patients less than 18 years of age have not yet been established.

Geriatric Use

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 subjects were 65 years or older and 24 subjects were 75 years or older. No overall differences in risankizumab-rzaa exposure, safety or effectiveness were observed between older and younger subjects who received SKYRIZI. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects.

OVERDOSAGE

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with SKYRIZI.

No effects on male fertility parameters were observed in sexually mature male cynomolgus monkeys subcutaneously treated with 50 mg/kg risankizumab-rzaa (at 20 times the clinical exposure at the MRHD, based on mg/kg comparison) once weekly for 26 weeks.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that SKYRIZI may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions]*.

Administration of Vaccines

Advise patients that vaccination with live vaccines is not recommended during SKYRIZI treatment and immediately prior to or after SKYRIZI treatment. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Instruct patients to inform the healthcare practitioner that they are taking SKYRIZI prior to a potential vaccination *[see Warnings and Precautions]*.

Administration Instruction

Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified healthcare professional for training in preparation and administration of SKYRIZI, including choosing anatomical sites for administration, and proper subcutaneous injection technique.

If using SKYRIZI 75 mg/0.83 mL, instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the full 150 mg dose of SKYRIZI.

Instruct patients or caregivers in the technique of pen or syringe disposal.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women with plaque psoriasis exposed to SKYRIZI during pregnancy and patients can call 1-877-302-2161 *[see Use in Specific Populations]*.

Manufactured by:
AbbVie Inc.
North Chicago, IL 60064, USA
US License Number 1889

Ref: 20067753-R2 Revised: April, 2021

LAB-4850 **MASTER**

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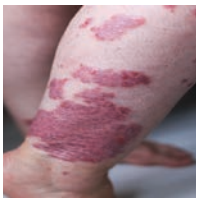

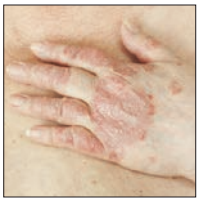

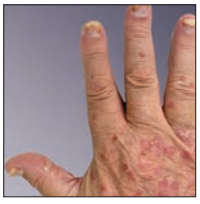

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Editorial correspondence should be addressed to Lauren Mateja, Managing Editor, *The Dermatologist*®, HMP Global, 70 E Swedesford Road, Suite 100, Malvern, PA 19355. Telephone: 800-237-7285 or 610-560-0500, Ext. 4135. E-mail: lmateja@hmpglobal.com.

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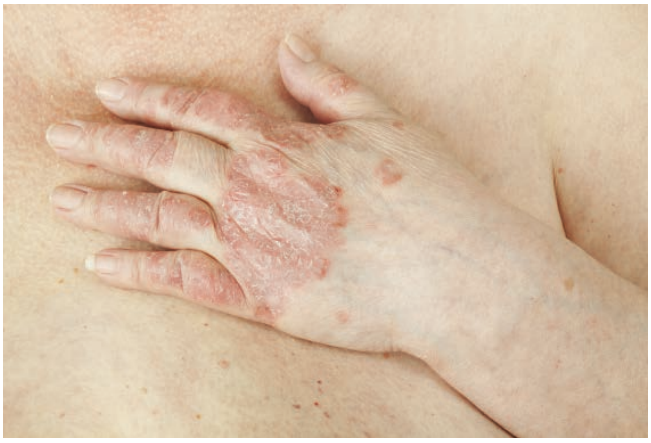
Psoriasis Burden is Mild in Early PsA But Impacts HRQoL

The majority of patients with psoriatic arthritis (PsA) have mild psoriasis during the first year of follow-up, but psoriasis impacts health-related quality of life (HRQoL) when measured using a dermatology-specific HRQoL questionnaire.

"Therefore, in order to assess the burden of psoriasis in early PsA and whether more attention from rheumatologists is warranted, the aim of this study is (1) to quantify the degree of psoriasis evolution in patients with early psoriatic arthritis during the first year of follow up and (2) to evaluate whether the impact of psoriasis on HRQoL in PsA can be adequately measured with a dermatology-specific HRQoL questionnaire," wrote the study authors.

Researchers used data from patients with PsA in the Dutch south west Early Psoriatic Arthritis cohort and measured severity with the Psoriasis Area and Severity Index (PASI). The evolution of psoriasis during the first year of follow-up and the association between the severity and symptoms and psychosocial subscale was assessed. In total, 644 patients were included: 109 with no (PASI = 0) psoriasis, 456 with mild (PASI <7) psoriasis, 56 with moderate (PASI 7-12) psoriasis, and 23 with severe (PASI >12) psoriasis.

Results showed that psoriasis severity in patients with PsA is mild with minor fluctuations during the first year and remained in this category. In addition, a dermatology-specific HRQoL questionnaire measured the impact of psoriasis severity.



"Psoriasis severity in patients [with PsA] is mostly mild but impacts HRQoL when measured using a dermatology-specific HRQoL questionnaire," concluded the study authors. The recommended that patients are screened for skin burden with a HRQoL questionnaire. ■

Reference

Kasiem FR, Kok MR, Luime JJ, et al. The burden of psoriasis in patients with early psoriatic arthritis. *Rheumatology (Oxford)*. Published online July 24, 2021. doi:10.1093/rheumatology/keab606

Work Absenteeism, Disability Higher in Patients With PsA and Psoriasis

Patients with psoriatic arthritis (PsA) and psoriasis have higher work absence costs, sick leaves, and more frequent short-term disability compared with a control group, according to a recent study published in *Clinical Rheumatology*.

Researchers aimed to compared work absenteeism and short-term disability among adults with psoriasis or PsA by screening adults eligible for work absenteeism and/or short-term disability benefits. Controls were matched to the patients with psoriasis and PsA. Costs associated with each type of work absence were evaluated.

Nonrecreational work absence costs were an average of $1681 and $1657 for the PsA and psoriasis group, respectively, compared with $1217 for the control group. A higher percentage of patients with PsA compared with patients with psoriasis and the control group had sick leaves after 1 year (56.2% vs 55.6% and 41.5%; *P*<.0001), more frequent short-term disability (8.8% vs 5.6% and 4.7%; *P*<.0001), and higher average corresponding costs ($605 vs $406 and $335; *P*<.0001).

"Annual work absenteeism and short-term disability were consistently greater among patients with PsA and psoriasis than

controls, highlighting the substantial economic burden of psoriatic disease," concluded the study authors. ■

Reference

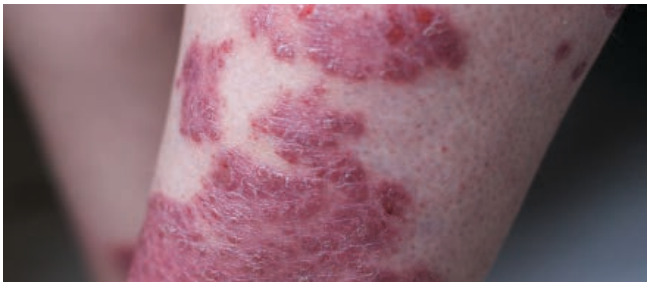
Orbai AM, Reddy SM, Dennis N, et al. Work absenteeism and disability associated with psoriasis and psoriatic arthritis in the USA-a retrospective study of claims data from 2009 to 2020. *Clin Rheumatol*. Published online July 21, 2021. doi:10.1007/s10067-021-05839-9

Oxylipin Profiles Differ in Patients With Psoriasis vs PsA

Proinflammatory oxylipins were lower in both patients with psoriasis or with psoriatic arthritis (PsA) with higher skin scores, but arachidonic acid (AA)-derived oxylipins were increased in patients with PsA with enthesitis.

The authors compared the serum oxylipin profiles in patients with PsA and with psoriasis without inflammatory arthritis to examine the specific disease manifestations and identify new biomarkers. They recruited patients with PsA or with psoriasis from a rheumatology outpatient clinic and performed a thorough clinical examination, which included entheseal and joint involvement. Pain and global disease activity was evaluated on a visual analog scale, and they also calculated disease activity scores (Disease Activity Index for Psoriatic Arthritis [cDAPSA], Psoriasis Area and Severity Index [PASI]).

The study included 20 patients with psoriasis only and 19 patients with PsA. Higher PASI scores correlated with lower serum concentrations of proinflammatory oxylipins, most of which were AA-derived. However, several AA-derived oxylipins were increased in patients with PsA with enthesitis compared with those without. cDAPSA was not associated with oxylipin profiling.



"The AA-derived proinflammatory oxylipins were lower in both [patients with psoriasis] and PsA with higher skin scores," concluded the study authors. They added that joint disease activity was not associated with the concentrations of oxylipins, though enthesitis was associated with increased AA-derived proinflammatory oxylipins in patients with PsA. ■

Reference

Coras R, Kavanaugh A, Kluzniak A, et al. Differences in oxylipin profile in psoriasis versus psoriatic arthritis. *Arthritis Res Ther*. 2021;23(1):200. doi:10.1186/s13075-021-02575-y

Adherence and Persistence Rates Highest Among Psoriasis and PsA Treated With Guselkumab and Ustekinumab

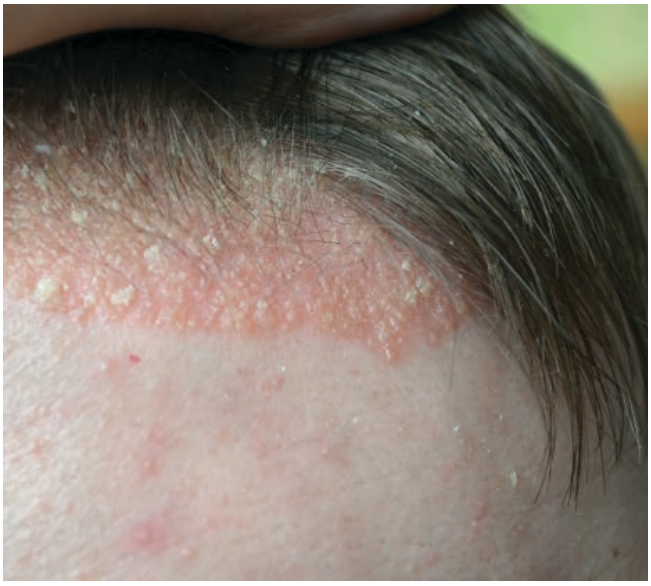
Psoriasis and psoriatic arthritis (PsA) patient adherence and persistence was highest among those treated with guselkumab and ustekinumab, followed by secukinumab, ixekizumab, adalimumab, etanercept, and certolizumab pegol. The results of the review were published in *Journal of Dermatological Treatment*.

"We examined adherence and persistence among patients [with psoriasis and] with comorbid PsA who initiated treatment with any of these biologics," wrote the study authors.

Researchers analyzed seven study cohorts during fixed follow-up periods (3, 6, 9, and 12 months), looking at adherence and persistence rates during these periods. Participants in the study were adult patients with at least one pharmacy/medical claim for any of the seven biologics (adalimumab, certolizumab pegol, etanercept, guselkumab, ixekizumab, secukinumab, and ustekinumab).

During the 9-month follow-up period, adherence rates were highest among those treated with guselkumab (59.5%) and ustekinumab (57.0%), followed by secukinumab (47.9%), ixekizumab (47.6%), adalimumab (46.8%), etanercept (37.4%), and certolizumab pegol (22.0%). Persistence rates were also numerically highest among those treated with guselkumab (65.9%) and ustekinumab (65.7%).

"Adherence and persistence rates were numerically highest among patients who initiated guselkumab and ustekinumab," concluded the study authors. ■



Reference

Xu C, Teeple A, Wu B, Fitzgerald T, Feldman SR. Treatment adherence and persistence of seven commonly prescribed biologics for moderate to severe psoriasis and psoriatic arthritis in a U.S. commercially insured population. *J Dermatolog Treat*. Published July 15, 2021. doi:10.1080/09546634.2021.1950600

Risk of IBD With IL-17 Inhibitors Higher Than Apremilast, Lower Than Etanercept for Psoriasis, PsA, and AS

Risk of developing inflammatory bowel disease (IBD) is greater in IL-17 inhibitors new-users than in apremilast new-users, but not in etanercept new-users, for patients with psoriasis, psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Researchers investigated whether IL-17 inhibitor initiation in real life is associated with a higher risk of IBD in patients with psoraisis, PsA, or AS in a nationwide cohort study involving the French national health data system database. They conducted a nationwide cohort study using data from a French national health data system, from which the demographics and health information of all adults with psoriasis, PsA, and AS who were new-users of IL-17 inhibitors between 2016 to 2019 were collected and analyzed. Also included were two nonexposed psoriasis and PsA/AS populations of new-users of apremilast and new-users of etanercept. The study's primary endpoint was an occurrence of IBD in a time-to-even analysis.

In total, 16,793 patients starting an IL-17 inhibitor, 20,556 starting apremilast, and 10,245 starting etanercept were included. IBD occurred in 132 cases, of which 72 (0.43%) were in IL-17 new-users, 11 (0.05%) in apremilast new-users, and 49 (0.48%) in etanercept new-users. Thus, the risk of IBD was significantly greater with IL-17 than apremilast, but not etanercept new-users. Further, most IBD cases occurred 6 months postexposure.

"Compared with patients initiating etanercept that displayed the same severity of the underlying disease, IL17i new-users did not present a higher risk of IBD," concluded the study authors. "These results need to be confirmed in other large databases," they added. ■

Reference

Penso L, Bergqvist C, Meyer A, et al. Risk of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis initiating interleukin 17 inhibitors: a nationwide population-based study using the French national health data system. Arthritis Rheumatol. Published online July 19, 2021. doi:10.1002/art.41923

Patients With PsA Have Higher Risk of Cardiovascular Disease Due to Risk of Developing Thrombotic Complications

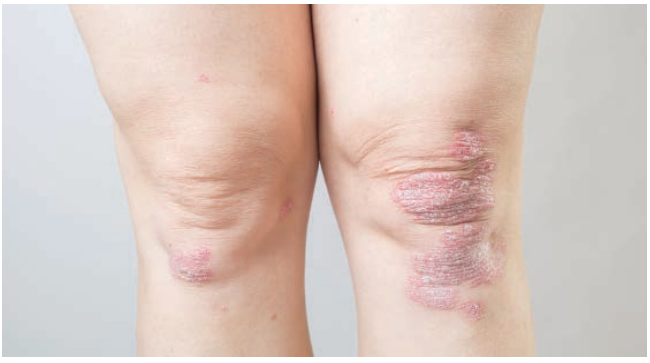
Psoriatic arthritis (PsA) is associated with inflammation, endothelial activation, and altered hemostatic function, according to a recent study published in Scientific Reports.

In a cross-sectional study, researchers investigated whether a hypercoagulable state is present in patients with PsA, evaluated whole blood (WB) coagulation efficiency, characterized the fibrin network architecture, and measured the levels of biomarkers indicative of inflammation, endothelial dysfunction, and platelet activation.

Results showed elevated levels of circulating inflammatory molecules in patients with PsA compared with healthy patients. The presence of disease was also associated with an increased tendency towards thrombus formation. Patients with PsA showed an increased tendency towards thrombus formation and had denser fibrin clots.

These results add to the accumulating evidence of the systemic nature of psoriatic disease and risk of cardiovascular comorbidities in these patients due to an acquired hypercoagulability.

"We suggest that haemostatic function should be monitored carefully in psoriatic patients that present with severe disease, due to the pre-eminent risk of developing thrombotic complications," concluded the study authors. ■



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NATIONAL PSORIASIS FOUNDATION®

Challenges and Opportunities in Psoriasis: Making the Diagnosis and Evaluating Severity

The following has been adapted from transcripts of Expert Insights in Psoriasis and Psoriatic Arthritis: Challenges and Opportunities, a multimedia content series tackling some of the most important topics in psoriasis care.

Abby Van Voorhees, MD, professor and chair of dermatology, Eastern Virginia Medical School, Norfolk, VA.

Making the Diagnosis

Understanding Systemic Inflammation, featuring Abby Van Voorhees, MD

We used to think of psoriasis as a disease that was limited to the skin. Certainly, that is what our patients see—it is why they come to us for care. But in the last decade, we have come to understand that psoriasis is associated with systemic inflammation and that it is really a whole-body disease.

We knew patients who have psoriasis frequently had issues with psoriatic arthritis (PsA). We have come to understand that the same inflammation that is causing difficulty in a patient's joints is also causing difficulty in their cardiovascular system and in their liver. This is very much a disease that profoundly affects our patients, and there is sometimes involvement of areas that are very sensitive for patients, where a small amount of psoriasis can cause a huge amount of disability.

There also is a rise in variant forms of psoriasis that are very severe and potentially life-threatening. Erythrodermic psoriasis and generalized pustular psoriasis come to mind. These kinds of psoriasis have so much inflammation that they can cause what is called *high-output failure*, which may be fatal, especially if the patient has any kind of underlying heart disease. This degree of inflammation can be problematic, and it is important that these patients are treated with the appropriate care and get the therapeutic intervention that they need right away so that we do not put them at further risk.

Understanding the disease and outcomes of our patients who have psoriasis may become more complicated as we understand the impact of these various metabolic conditions and other systemic associations that our patients may have. Learning more about the disease will help us potentially judge how to treat people and how to get our patients to that goal that we all need to be striving toward, which is clear or almost clear skin.

Psoriasis in Skin of Color, featuring Seemal R. Desai, MD, FAAD

Psoriasis in patients with skin of color (SOC) can be a challenge. We know that psoriasis is a chronic papulosquamous disease, and one of the hallmarks that we tend to think about is the classic erythematous or pink, bright red scaly patches or plaque typically on the elbows, knees, sometimes the scalp, and other familiar anatomical areas.

One of the key challenges in patients with SOC is that the redness or erythema may be more difficult to distinguish. It often looks more like a brownish-purplish discoloration, and the scaling that we see in psoriasis in SOC is not as common as the thick, silver, micaceous scale that we see in lighter skin tones.

When we examine patients from different racial and ethnic backgrounds, particularly those dealing with conditions like psoriasis or other inflammatory skin disease, cultural competency is a key component of what we need to be aware of for

Seemal R Desai, MD, FAAD, president and medical director, Innovative Dermatology, PA, Plano, TX; and clinical assistant professor of dermatology, University of Texas Southwestern, Dallas.

these populations. We need to think about everything, from what the patient's cultural beliefs are when coming to see a doctor to how the family unit potentially interacts in terms of care. For example, someone with SOC who is African American and has psoriasis may not feel comfortable with a doctor prescribing a medicated shampoo for daily use, because they are used to shampooing only once a week. We also need to keep in mind that there are skin care practices related to homeopathic and natural products, oils, and botanicals as well as hair care products. All of those things are critically important.

One of the things that I find most impactful is trying to develop an understanding of the patient's viewpoint. Dermatologists should not be afraid to ask questions such as:

- *How often do you wash your hair?*
- *Do you use oils?*
- *Do you use any special ethnic products?*
- *Do you use anything different than a prescription?*
- *Also, in terms of your body skin, have you been told that your skin looks or feels a certain way?*
- *Are there family history or family barriers to you coming to see a board-certified dermatologist?*

We also need to recognize that there often is a stigma associated with skin disease in many cultures. All of those things play an important role in what we do to make sure these patients have the best possible outcome.

One of the most challenging things we need to keep in mind is that the medical literature and our dermatologic literature still needs more work in terms of images and standardized photography for patients with darker skin tones. Much of the work that has been done by organizations such as the Skin of Color Society and the American Academy of Dermatology has been designed to make sure that SOC dermatology remains relevant and at the forefront of our educational efforts and patient-based needs. We still need more images in our image banks, databases, and learning sets for residents, as well as in published studies. I really hope that board-certified dermatologists can unite as a community to help tackle that, so that we can provide better care for our patients with psoriasis and other inflammatory skin diseases.

Differential Diagnoses of Psoriasis, featuring Dr Van Voorhees

Sometimes psoriasis is quite classic in its appearance, and it is always nice when the patient's presentation is clear. Other times, psoriasis can be much more nebulous, and there are other diseases that often trip us up.

Atopic dermatitis (AD) sometimes can look a whole lot like psoriasis. For example, we tend to think of AD as involving the antecubital fossa, as opposed to the elbows like we see in psoriasis, but sometimes patients can have eczema that involves the elbows too. Especially for people who have very thin plaque, sometimes we can get confused between psoriasis and eczema. It can also be harder in patients with SOC to make that distinction.

Psoriasis can also be confusing to distinguish from seborrheic dermatitis (SD). In general, psoriasis tends to be a little more focal and so a little more isolated. You get a single spot; it can get thick and scaly, but immediately adjacent normal skin may also be present. In contrast, SD has a more classical greasy scale that is more diffuse and without such clear margins. Those two diseases can certainly overlap and be a little confusing. We especially see that confusion when we label a disease as sebopsoriasis, where we have some features of seborrhea and some features of psoriasis.

Mycosis fungoides (MF) is another possible differential diagnosis for psoriasis. While typically we see lesions of MF on the buttocks, that is not always the case; MF can also be seen on the trunk, proximal extremities, and mammary regions. It is critical to start the appropriate therapy as soon as possible, given the malignant nature of MF vs the systemic inflammation of psoriasis.

We may see suspicious scaling with lichen planus. There typically are not polygonal papules in lichen planus, but I find that these two things can be a little confusing to distinguish when the patient has an extensive presentation. Similarly, pityriasis rubra pilaris (PRP) can be a little tricky. The classic stigmata of PRP are those yellow-orange palms and soles with thick hyperkeratosis. Nail changes also occur, and sometimes when patients come in with nail changes, it can be very difficult to say whether this is early PRP or psoriasis.

As we list them out, there are quite a few circumstances in which psoriasis can be challenging to distinguish from other inflammatory situations. Fortunately, most of the time that is not true and we can recognize psoriasis. I do believe that

when there is any doubt, it is important to take a biopsy. These different entities can usually be distinguished histologically, which allows for that clarity.

Barriers to an Accurate Diagnosis of PsA, featuring Dr Van Voorhees

The trickiest part of psoriasis is determining whether patients have PsA. Obviously, patients may come into our offices with various complaints. Sometimes, they tell us that their joints hurt, but it is hard to know whether that knee pain is a result of, for example, a prior athletics injury they had when they were 20 years old or whether it may represent PsA. We have to dig a bit deeper and often over a long period to discern whether a patient's compliant may be related to their psoriasis.

One of the biggest problems we have in psoriatic disease is that there is no formal test for PsA. It would help us all if there were a definitive testing tool with which we could say to patients, "Aha! You do have early psoriatic arthritis," or "No, this doesn't look like that at all; rather, this is probably a little osteoarthritis, fibromyalgia, or some other kind of discomfort that needs to be addressed in a different way."

The National Psoriasis Foundation (NPF) has invested a huge amount of research dollars in trying to develop a tool that will enable us to have a more definitive test, so that we can make the diagnosis sooner and get our patients the appropriate care. This diagnostic test grant currently supports the work of multiple groups exploring various tools to use in our practices. I am very excited about the opportunity that lies ahead, and I am really hoping that this funding effort will result in a highly rewarding product that will ultimately lead to better patient care and outcomes.

Assessing Severity, fearuing Elizabeth B Wallace, MD, FAAD

Measuring Severity Beyond the Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) is one measure to determine psoriasis severity. The PASI has a role in clinical trials to determine the severity of psoriasis at the initiation of a trial and then track patient improvement with regards to disease severity over time. There are different elements in the PASI, including the degree of erythema, induration, and the amount of scaling of individual plaques, all of which go into the calculation of the PASI score along with the percentage area affected by psoriasis in four regions (head-neck, upper limbs, trunk, and lower limbs).

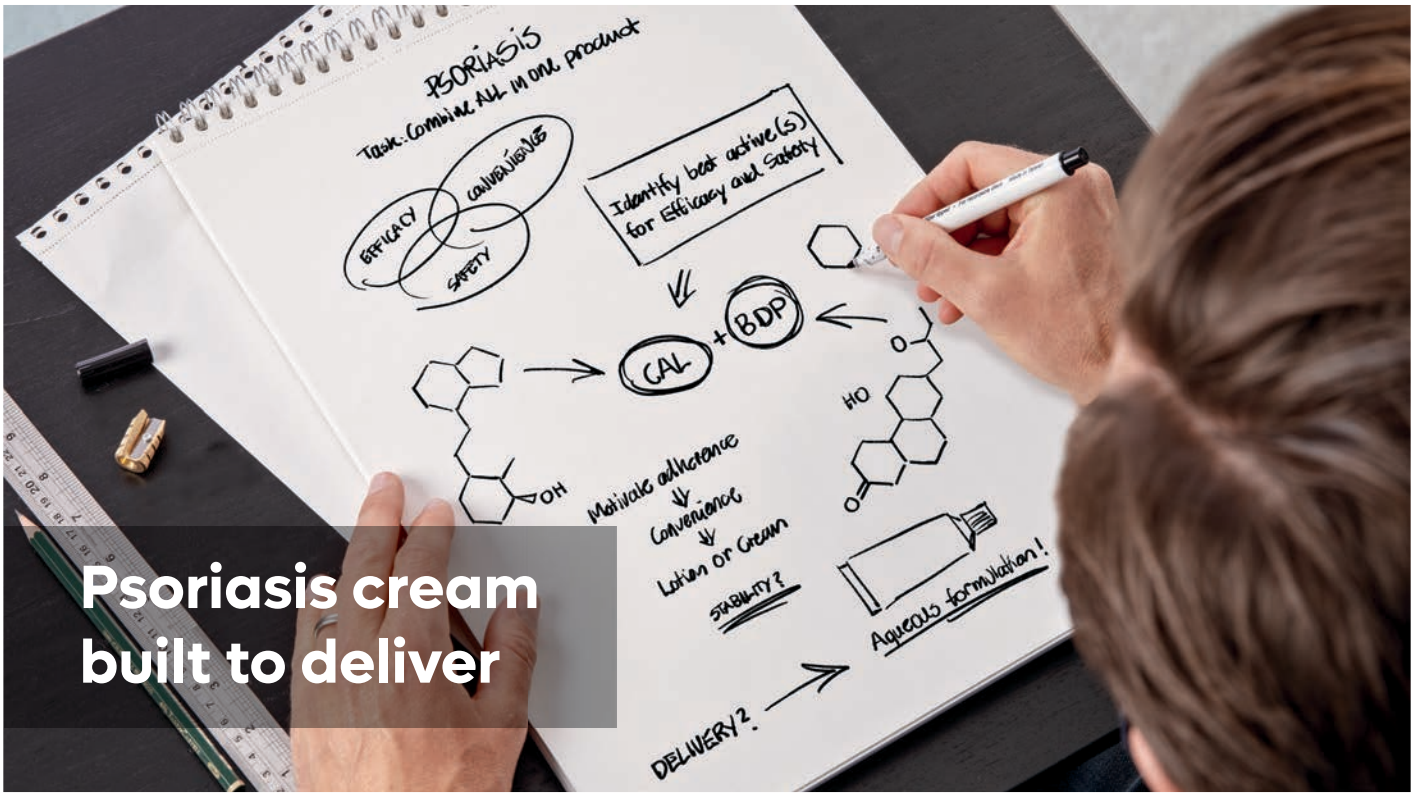
Determining disease severity in clinic using the PASI can have value because it is a validated tool, and we can track improvement over time, just as we do in clinical trials to demonstrate the efficacy of new therapies. There is certainly a range of severities—mild, moderate, and severe disease—but this range also needs to consider the patient's quality of life. For example, with the PASI, even if someone has a mild disease severity, does that severity also reflect the impact of the psoriasis on their quality of life? We may even want to consider the systemic inflammation our patients with psoriasis have in our definition of their overall severity. I believe both disease severity and quality of life should be taken into account when evaluating the patient, determining how we want to treat the patient, and measuring patient improvement.

While the PASI is a validated tool for evaluating severity in clinical trials, there are other tools that we can use in our daily practice. I routinely use body surface area and the Investigator Global Assessment is another severity measure, both of which allow us to track improvement over time and we can show patients how they are doing on their current care plan. Logistically, it can help us with insurance approval for certain medications or therapies. It is also important to have a very open and honest conversation with patients about how they perceive their progress and how they are feeling. The Dermatology Life Quality Index is another validated measure to specifically track quality of life over the time, and it can be a complement to our traditional severity measures for evaluating psoriasis.

Framing Severity by Impact on Quality of Life

We know that psoriasis is no longer just a skin condition; it goes beyond the skin, and its inflammation affects other organ systems, including the cardiovascular system, the gastrointestinal system, and mental health, as well as the joints. Selecting therapies to treat patients with psoriasis needs to take into

Elizabeth B Wallace, MD, FAAD, assistant professor of dermatology, department of dermatology; codirector, Connective Tissue Disease Program; cofounder, Rheumatology-Dermatology Clinic; and assistant director of Clinical Trials, University of Colorado School of Medicine and Anschutz Medical Campus, Aurora, CO.



Psoriasis cream built to deliver

Efficacy | **Safety** | **Convenience** ... by design[1,2]

Wynzora Cream is designed to optimize treatment of plaque psoriasis and increase treatment satisfaction.[1-3] Visit **wynzora.com** today or scan the QR code to see what makes Wynzora different.

Wynzora®
(calcipotriene and betamethasone dipropionate)
Cream, 0.005%/0.064%

Cal BDP

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INDICATION AND USE
Wynzora® (calcipotriene and betamethasone dipropionate) Cream is indicated for plaque psoriasis in adults. It is not known if Wynzora Cream is safe and effective in children.

IMPORTANT SAFETY INFORMATION
- Wynzora Cream is for topical use only.
- Patients should not use more than 100g of Wynzora Cream per week.
- Wynzora Cream should not be used near or in the mouth, eyes, or intravaginally.
- Patients should avoid using Wynzora Cream on the face, groin, or armpits, or if they have atrophy at the treatment site.
- Patients should apply Wynzora Cream to the affected areas of the skin once a day for up to 8 weeks.
- Patients should discontinue use once the plaque psoriasis is under control.
- Patients should not use with occlusive dressings.
- Hypercalcemia and hypercalciuria have been observed with use of topical calcipotriene.
- Wynzora Cream can cause reversible HPA axis suppression with the potential for clinical glucocorticosteroid insufficiency during and after withdrawal of treatment.
- Wynzora Cream may cause vision problems, including increasing the risk of cataracts and glaucoma.
- It is not known whether Wynzora Cream may harm your unborn baby.
- Breastfeeding women should not apply Wynzora Cream directly to the nipple and areola.
- It is not known whether topically administered calcipotriene and betamethasone dipropionate is absorbed in human milk.

Please see accompanying Brief Summary and visit wynzora.com to obtain the FDA-approved full Prescribing Information for Wynzora Cream.

You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

References: 1. Wynzora® Cream [package insert]. MC2 Therapeutics; 2020. **2.** Præstegaard M, Vestbjerg B, Selmer J, et al. Phase 3 trial demonstrates superior patient treatment convenience of MC2-01 calcipotriene plus betamethasone dipropionate cream compared to current topical suspension. *J of Skin*. 2020;4(5):s62. doi:10.25251/skin.4.supp.61. **3.** US Department of Health and Human Services. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*. 41st ed. US Government Publishing Office; 2021. Accessed March 16, 2021. https://www.fda.gov/media/71474/download.

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WYNZORA® (calcipotriene and betamethasone dipropionate)

BRIEF SUMMARY- PLEASE SEE THE WYNZORA® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

WYNZORA Cream is a combination of calcipotriene, a vitamin D analog, and betamethasone dipropionate, a corticosteroid, indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older.

DOSAGE AND ADMINISTRATION

For topical use only. Not for oral, ophthalmic, or intravaginal use.

Apply WYNZORA Cream to affected areas once daily for up to 8 weeks. Rub in gently to ensure that the plaques are saturated with the cream.

Do not use more than 100 g per week.

Discontinue therapy when control is achieved.

Do not use with occlusive dressings unless directed by a healthcare provider or on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

DOSAGE FORMS AND STRENGTHS

Cream: 0.005%/0.064%

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Potential to cause hypercalcemia and hypercalciuria

Hypercalcemia and hypercalciuria have been observed with use of topical calcipotriene. If either occurs, discontinue until parameters of calcium metabolism normalize.

Potential effects on Endocrine System

Wynzora can cause reversible hypothalamicpituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of treatment. Risk factors include the use of high-potency topical corticosteroid, use over a large surface area, or to areas under occlusion, prolonged use, altered skin barrier, liver failure, and young age. Modify use should HPA axis suppression develop.

Ophthalmic Adverse Reactions

Wynzora may increase the risk of cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The rates of adverse reactions given below were reported in a randomized, multicenter, prospective, vehicle and active controlled clinical trial in adult subjects with plaque psoriasis. Subjects applied WYNZORA Cream, 0.005%/0.064% or vehicle once daily for 8 weeks. The mean weekly dose of WYNZORA Cream was 33.8 g. A total of 342 subjects were treated with WYNZORA Cream, 337 with calcipotriene/betamethasone dipropionate topical suspension, 0.005%/0.064% and 115 with vehicle. The majority of subjects were White (87%) and male (62%). Approximately 72% were non-Hispanic/Latino. The mean age was 52 years and ages ranged from 18 to 89 years.

The most common adverse reactions reported by ≥1% of subjects treated with WYNZORA Cream and more frequently than vehicle are presented in Table 1.

Table 1: Adverse Reactions Through Week 8

Preferred Term	WYNZORA Cream (N=342)	Vehicle Cream (N=115)
Upper Respiratory Infection (URI) [a]	7%	5%
Headache	2%	0%
Application site irritation	1%	0%

[a] Includes nasopharyngitis, upper respiratory tract infection (URTI), and viral URTI

Post Marketing Experience

The following adverse reactions have been identified during post-approval use of topical corticosteroids. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Post marketing reports for local adverse reactions to topical corticosteroids included: atrophy, striae, telangiectasias, itching, dryness, hypopigmentation, perioral dermatitis, secondary infection, and miliaria.

Ophthalmic adverse reactions of cataracts, glaucoma, and increased intraocular pressure, have been reported during use of topical corticosteroids, including topical betamethasone products.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available data with WYNZORA Cream are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes. Although there are no available data on use of the calcipotriene component in pregnant women, systemic exposure to calcipotriene after topical administration is likely to be low. Observational studies suggest an increased risk of having low birthweight infants with the maternal use of potent or very potent topical corticosteroids. Advise pregnant women that WYNZORA Cream may increase the potential risk of having a low-birth-weight infant and to use WYNZORA Cream on the smallest area of skin and for the shortest duration possible.

In animal reproduction studies, oral administration of calcipotriene to pregnant rats during the period of organogenesis resulted in an increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs. Oral administration of calcipotriene to pregnant rabbits during the period of organogenesis had no apparent effects on embryo-fetal development. Subcutaneous administration of betamethasone dipropionate to pregnant rats and rabbits during the period of organogenesis resulted in fetal toxicity, including fetal deaths, reduced fetal weight, and fetal malformations (cleft palate and crooked or short tail) *(see Data)*. The available data do not allow the calculation of relevant comparisons between the systemic exposures of calcipotriene and betamethasone dipropionate observed in animal studies to the systemic exposures that would be expected in humans after topical use of WYNZORA Cream.

The background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Lactation

Risk Summary

There is no information regarding the presence of topically administered calcipotriene and betamethasone dipropionate in human milk, the effects on the breastfed infant, or the effects on milk production. Concentrations of calcipotriene in plasma are low after topical administration, and therefore, concentrations in human milk are likely to be low.

It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WYNZORA Cream and any potential adverse effects on the breastfed child from WYNZORA Cream or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use WYNZORA Cream on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply WYNZORA Cream directly to the nipple and areola to avoid direct infant exposure.

Pediatric Use

Safety and effectiveness of the use of WYNZORA Cream in adolescents and pediatric patients under the age of 18 years have not been established.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical corticosteroids. Pediatric patients are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency with the use of topical corticosteroids including WYNZORA Cream.

Systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids. Local adverse reactions including striae have also been reported with use of topical corticosteroids in pediatric patients.

Geriatric Use

The trial included 66 subjects ≥ 65 years of age treated with WYNZORA Cream. No overall differences in safety or effectiveness of WYNZORA Cream were observed between these subjects and younger subjects. All other reported clinical experience has not identified any differences in response between elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

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account these other comorbidities, both to make sure that you are prescribing one that is safe but also effective and compatible with those other conditions. For example, not all psoriasis medications also treat PsA. We have to be aware of a patient's different domains of disease, so that we can pick a treatment that not only matches their severity but also takes into account the whole person—their skin, joints, and overall health.

The National Psoriasis Foundation has conducted several surveys to better understand the impact the disease has on the patient community. We know that psoriasis affects the emotional well-being of nearly 90% of the psoriasis population. It is important to keep that in the back of our mind and let patients know that they are not alone and to normalize these feelings. Patients can have diminished quality of life for many reasons, including:

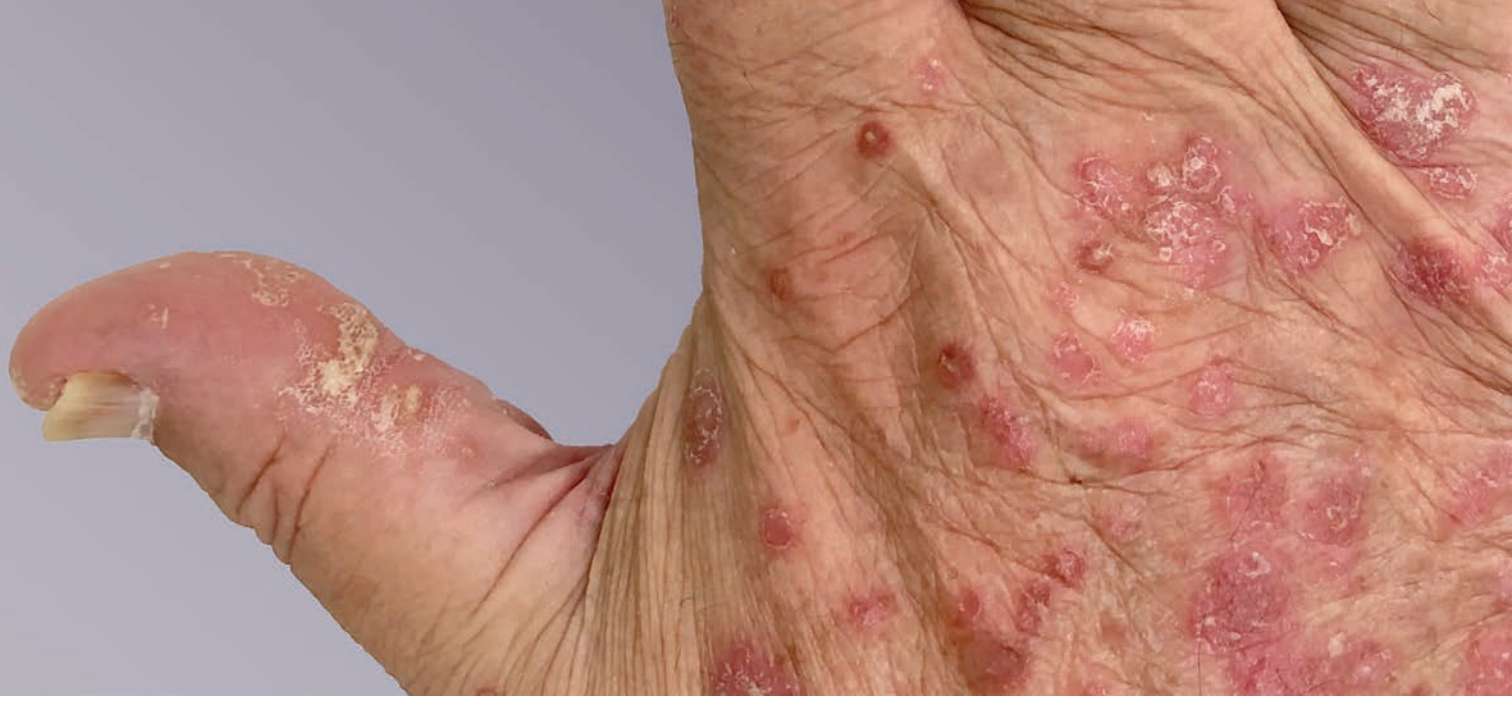
- Feeling frustrated with their disease
- Delayed diagnosis
- Fears of flares
- Social embarrassment

We need to take the time to understand the psoriasis patient's perspective of what is preventing them from going about their day-to-day life, functioning optimally at work, and maintaining strong, healthy relationships. We should take that perspective into consideration along with their disease severity to come up with a personalized and tailored treatment plan. We can then set expectations for what the patient can hope to accomplish with that treatment plan.

In addition, the visibility of the disease can be a factor that heavily influences quality of life, thereby affecting the patient's perspective of their severity. For example, nail psoriasis can be an embarrassing presentation of the disease. When psoriasis is on the trunk or on the extremities, you can throw on a long-sleeve shirt to cover the plaques. But when the psoriasis is on your fingernails and you have to interact with people at work or you are out with a group of friends, it is really hard, especially for men who do not use nail polish, to hide that. A number of patients have come to me distressed about having nail psoriasis but have mild or no disease elsewhere. Other areas that might be more visible include the ears or the scalp, which can be difficult to cover and visibly flaky.

Having psoriasis in those areas can have a major impact on patient quality of life, demonstrating the need to consider psoriasis severity by more than just the traditional definitions. ■

Want to learn more from thought leaders in psoriasis care? Visit the Expert Insights series online at the-dermatologist.com for full access to the videos.



The Evidence for Biologics for Localized, Difficult-to-Treat Psoriasis

The definitions of severity are changing for psoriasis, thereby changing how dermatologists approach the disease with advanced therapies. Though FDA indications are limited, biologics may be a useful tool for treating patients who present with difficult-to-treat, limited areas of psoriasis.

Seymour Rand, MD

Multiple biologic therapies have been approved for the treatment of psoriatic arthritis and moderate to severe plaque psoriasis. These products fall into one of three general categories—tumor necrosis factor (TNF), interleukin (IL) 17, and IL-23 (including IL-12/23)—and have been found to be effective and safe in clinical trials for plaque psoriasis requiring phototherapy or a systemic therapy such as methotrexate, cyclosporine, and acitretin. These therapies have provided tremendous advances in the treatment of plaque psoriasis to date with a high level of safety for most patients.

There have been recent calls[1] in the dermatology community for a wider "off-label" use of biologic medication to include mild to moderate disease, including treatment for limited localized areas of involvement. In this regard, some dermatologists may begin to question whether the admission criteria for these advanced therapeutics underestimated disease severity and impact on patient quality of life.[2] Some specific localized areas that psoriasis affects can result in resistant disease, such as the nails, scalp, intertriginous areas (armpits, groin, under the breasts, other areas of skin folds), and palms and soles. The article herein discusses the evidence of biologic efficacy in difficult to treat areas and shares insight as to what dermatologists should consider when prescribing a biologic for localized disease.

Brief FDA History of Psoriasis Treatments

In the mid 1990s, the regulatory criteria for treatment success in plaque psoriasis clinical trials was related to a reduction in the Psoriasis Area and Severity Index (PASI) scores. Cyclosporine was approved as a therapy for severe widespread plaque psoriasis in 1997 by demonstrating statistically significant reductions in PASI scores as well as providing an acceptable safety profile for this drug.[3] Patients enrolled in these studies were required to have widespread plaque psoriasis affecting greater than 5% body surface area (BSA).

The efficacy and safety of nonbiologic systemic therapies have been detailed in previous reports.[4,5] These generally include methotrexate, cyclosporine, acitretin, and phototherapy. Mycophenolate mofetil and azathioprine are amongst additional treatment modalities for this degree of disease. Efficacy results are treatment-specific, but many times are not successful enough to satisfy the patient who requests additional therapeutic choices.

At the 1998 FDA Dermatology Advisory Committee[6] on plaque psoriasis, additional treatment success parameters were introduced by the FDA to provide for even greater efficacy endpoints. As a result of that meeting, terms such as PASI 50, PASI 75, PASI 90, clear, and almost clear have become the hallmarks of treatment success in clinical trials for plaque psoriasis and in the marketing of individual biologic agents. While the language between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individual biologics vary slightly, the FDA-approved indications generally state that the agent is for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy, indicating this therapeutic group is intended for widespread clinical disease. Attention to more treatment-resistant areas of psoriasis (eg, scalp, inverse, nails, palms and soles, localized pustular variants) went unanswered.

Because subgroup analyses of difficult to treat psoriasis subtypes were not a subject of attention at that time, there were probably too few patients with such presentations enrolled in the pivotal trials for the plaque psoriasis indication. However, following their plaque psoriasis approval, biologic agents have seen an increased focus on these subgroups in recent years.

Attention to more treatment-resistant areas of psoriasis (eg, scalp, inverse, nails, palms and soles, localized pustular variants) went unanswered…However, following their plaque psoriasis approval, biologic agents have seen an increased focus on these subgroups in recent years.

Evidence of Biologics for Difficult to Treat Psoriasis

There is an overall paucity of data regarding difficult to treat areas of psoriasis. In short, the following paragraphs will highlight literature published to date on the three various classes of biologic agents for the treatment of psoriasis of the nails, scalp, and palmoplantar regions. However, it is important to note that post-hoc analyses are less persuasive to the FDA as evidence of efficacy and safety, and a priori study designs are required for meaningful analyses.

TNF. In 2017, adalimumab achieved treatment success with separate studies for fingernail psoriasis and gained FDA approval for this indication.[7] Elewski et al[8] reported the trial results that led to the fingernail psoriasis approval. This study was a 52-week, placebo-controlled trial in moderate to severe plaque psoriasis, in which participants had moderate to severe fingernail disease. Patients who were on placebo were switched to adalimumab at week 26 (or sooner starting at week 16 if their disease was worsening) in an open-label extension and continued for the remainder of the study. Treatment success required an improvement in the modified Nail Psoriasis Severity Index (mNAPSI) score as well as the Physician Global Assessment. For mNAPSI 75, 47% in the treatment group vs 3% in the placebo group achieved an improvement, and this was statistically significant.

In a study of plaque psoriasis of the palms, soles, and nails by Poulin et al,[9] participants were treated with adalimumab for a 16-week period. NAPSI 50 was the primary endpoint for treatment success. Greater numbers of those treated with the biologic medication achieved NAPSI 50 at week 16 vs placebo (56.5% vs 12.5%, respectively). Additionally, scaling, fissuring, induration, scaling, and pain scores had greater improvement in the active treatment group vs the placebo. Leonardi et al[10] reported on the long-term safety of adalimumab in clinical trials for 13 clinical trials on the treatment of moderate to severe plaque psoriasis. There were low numbers of serious adverse events and serious infectious adverse events. There was no evidence of cumulative toxicity with adalimumab.

Etanercept is the oldest TNF inhibitor on the market, and its efficacy in difficult to treat areas is well-documented, including as a comparator in newer clinical trials. Bagel et al[11] looked at the efficacy and safety of etanercept for scalp psoriasis. Their randomized, placebo-controlled study examined the percentage change in Psoriasis Scalp Severity Index (PSSI) after 12 weeks of treatment with placebo or etanercept. At study completion, the mean PSSI improvement for patients treated with etanercept was 86.8% vs only 20.4% for those receiving placebo, and 86% of patients achieved PSSI 75.

It has also been established as an effective treatment for nail psoriasis. In 2013, Ortonne et al[12] showed decreases in NAPSI of 4.3 and 4.4 for etanercept 50 mg twice weekly for 12 weeks followed by once weekly for 12 weeks and for 50 mg twice weekly for 24 weeks, respectively. The nail-specific results showed significant correlation with improvements in overall PASI. A 54-week study showed sustained NAPSI improvements as well.[13]

Golimumab, which is only indicated for PsA, is another TNF inhibitor that has several trials showing improvement in skin and nail psoriasis in patients with PsA.[14,15] In addition, there is some evidence from 2014 that certolizumab pegol, another TNF inhibitor approved for PsA, can show rapid improvements in nail psoriasis in patients who have PsA.[16] Given their wider use for treating PsA, to the best of the author's knowledge, there is no specific analyses of the effectiveness of either golimumab or certolizumab pegol for scalp or palmoplantar psoriasis.

IL-17. An excellent review of fingernail psoriasis treatment with biologics was presented by Wind and Weinberg.[17] They described a 60-week clinical trial in which the IL-17 antibody ixekizumab was superior for treatment of nail psoriasis over both the etanercept and placebo treatment arms and resulted in complete nail clearance in more than 50% of patients at study end. Langley et al[18] reported on a clinical study involving scalp and nail psoriasis with ixekizumab at increasing doses vs placebo. At week 16, the placebo group was switched to ixekizumab, and all participants were treated with active drug to the 48-week evaluation. The PSSI and NAPSI were primary endpoints. Both scalp psoriasis and fingernail psoriasis had complete clearing in 78% and 51%, respectively.

Similarly, van de Kerkhof et al[19] demonstrated significant improvements in fingernail psoriasis with ixekizumab. In a subgroup analysis of the UNCOVER-3 trial, they found that patients who received 80 mg of ixekizumab at 4-week maintenance dosing showed additional improvement through 60 weeks, with more than 50% of patients achieving complete resolution. Leonardi et al[14] extended out the analysis through

3 years, finding sustained high responses of skin and nail clearance with ixekizumab. For scalp and palmoplantar psoriasis, the UNCOVER subgroup analysis through week 60 of treatment also revealed sustained clearance for these difficult to treat areas.[21,22]

As another IL-17 inhibitor approved for the treatment of psoriasis, brodalumab was studied as monotherapy for scalp and nail psoriasis in the phase 3 AMAGINE studies. At week 12, more patients receiving brodalumab had lower mean PSSI scores vs placebo; after 52 weeks of treatment, the brodalumab arm had a lower mean NAPSI vs ustekinumab.[23]

In a phase 2 regiment-finding study, secukinumab was evaluated for the treatment of psoriasis of the hands, feet, and/or nails.[24] Patients received either secukinumab 150 mg in a single dose (week 0), a monthly dose (weeks 0, 4, 8), an early dose (weeks 0, 1, 2, 4), or placebo. At week 12 of treatment, more patients with hand and/or foot psoriasis achieved an Investigator Global Assessment (IGA) response with the early doses of secukinumab vs placebo, and the composite fingernail score was improved with the early and monthly regiments. In 2017, Bagel et al[25] found secukinumab was efficacious and well-tolerated for the treatment of scalp psoriasis in a phase 3b study. A more recent study published in British Journal of Dermatology found that secukinumab demonstrated significant and clinically meaningful improvements for patients with nail psoriasis up to 32 weeks.[26]

IL-23. Foley et al[27] reported on a post-hoc data analysis of clinical trials for guselkumab in the treatment of moderate to severe plaque psoriasis vs a placebo group and an active treatment arm (adalimumab) for a 24-week study. At week 16, the placebo group was switched to guselkumab while adalimumab subjects continued therapy. The scalp, palms, and soles were graded for clear or near clear in the IGA and nails were graded by NAPSI. At week 24, guselkumab was superior to placebo for treatment success in all areas studied and had improved results against adalimumab for scalp, palm, and sole psoriasis. There was no difference in the success rates between the two biologic medications for fingernail disease. A Japanese phase 3 trial has found that guselkumab demonstrated a significant decrease in mNAPSI score in a subgroup analysis among patients with nail psoriasis.[28]

The only anti-IL-12/IL-23 biologic, ustekinumab has conflicting evidence for certain difficult to treat areas. In the PHOENIX 1 trial, Rich et al[29] assessed the improvement in fingernail psoriasis by comparing the efficacy of 45 mg vs 90 mg dose of ustekinumab vs placebo over a 52-week study. After week 24, there was no statically significant difference between the percentage improvement in NAPSI for the ustekinumab doses (46.5% for 45mg vs 48.7% for 90mg). Maintenance treatment showed improvements until up to 1 year of treatment with ustekinumab. However, another phase 2/3 study out of Japan reported no significant NAPSI improvement with ustekinumab vs placebo after week 12.[30] Ustekinumab has also been frequently used as a comparator product for newer biologics, showing various degrees of efficacy.

Current Severity Definitions vs Difficult to Treat Areas

Psoriasis is a complex skin disease, and severity cannot be judged by involved surface area only. Great examples of the limitations of the current definition of severity based on BSA or PASI are the difficult to treat areas of the groin, buttocks, axillae, scalp, palms, soles, and nails. While psoriatic involvement may be entirely limited to these anatomical locations (thus considered mild severity by BSA alone), they still may be considered by providers as moderate to severe disease.

Over the past 15 years since the very first FDA approval, biologic agents for plaque psoriasis in less difficult to treat areas (eg, trunk, extremities) have converted many doubtful physicians into believers for the treatment of widespread plaque disease based on BSA. The addition of biologics to our armamentarium has resulted in higher treatment success rates. While adalimumab was successful for clinical trials to show safety and efficacy for fingernail psoriatic disease, few other biologics have received additional clinical indications in difficult to treat disease. We need further evidence from clinical trials that study these difficult to treat localized areas of psoriasis. The literature is just beginning to demonstrate biologic safety and efficacy in these localized areas of psoriasis.

Individual holders of each FDA biologic medication (ie, sponsors) would need to make such requests to the FDA to claim additional clinical indications for psoriasis and will hopefully obtain approved label changes and advertising rights in the future. As always, the risk-benefit ratio will determine its use for any patient by the medical provider based on disease severity, morbidity, quality of life factors, and any disability from psoriasis. Sometimes the cost of biologics is prohibitive for individual patients and biosimilars may be helpful for the future to allow wider use.

Biologic Safety Information

As with most medications, there are adverse events that are well tolerated and occur in small numbers that led to approval of these medications. On occasion, there are serious adverse events as well as death.

Dermatologists should always keep in mind that these biologics are not appropriate for all patients with psoriasis, including those with psoriasis in difficult to treat areas previously discussed. Patients who may not be candidates for biologic therapies include those who have reduced immunity to infections, those with a current or history of malignancies, and other specific concurrent or past conditions. The FDA-approved product label for these biologics frequently has warnings/precautions about infections, tuberculosis, hypersensitivity, and inflammatory bowel disease. Adverse events include injection site reactions, headache, anaphylaxis, diarrhea, flu-like illness, rash, nasopharyngitis, and upper respiratory tract infections, and mucocutaneous *Candida*. Extra consideration should be given to the elderly population because mature patients are usually more susceptible to demonstrating adverse events. The medical provider must assess the risk-benefit ratio and judge whether a biologic is safe to use for a particular


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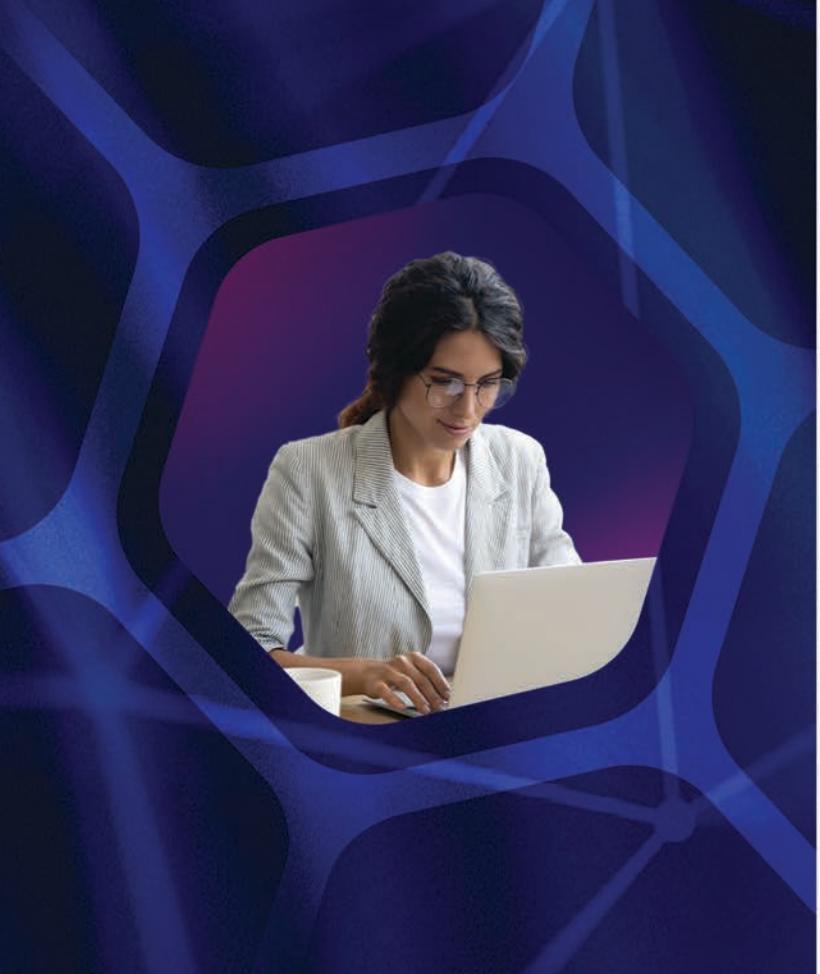

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patient. Further study of long-term safety would be helpful for each biologic medication approved for psoriasis.

Conclusion

Biologics for psoriasis offer a compelling treatment consideration for both plaque and difficult to treat psoriasis in limited areas because they directly target the inflammatory markers for this disease. They result in reduced inflammation and greater numbers of patients having a clear and almost clear treatment status. This heightened efficacy over traditional systemic agents must be weighed against the unknown long-term side effects of biologics as well as their tendency to result sometimes in infections and possible malignancy in the elderly population.

Biologic agents for psoriasis are becoming a first-line therapy to treat this disease for both plaque and resistant types of disease. The FDA may wish to expand the indications for biologics to the treatment of psoriasis and localized psoriasis than moderate to severe disease.

Dr Rand is formerly a clinical associate professor of medicine at Georgetown University Medical School in Washington, DC. Dr Rand also served as an acting supervisory medical officer in the Dermatology Group at FDA's Center for Drug Evaluation and Research. He currently resides in Hummelstown, PA.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe DUOBRII safely and effectively. See full Prescribing Information for DUOBRII.

DUOBRII® (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% for topical use

INDICATIONS AND USAGE

DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS

Pregnancy

DUOBRII Lotion is contraindicated in pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Risk

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Tazarotene is teratogenic, and it is not known what level of exposure is required for teratogenicity in humans *[see Contraindications and Clinical Pharmacology in full Prescribing Information]*. Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits *[see Use in Specific Populations]*.

Advise pregnant females of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to DUOBRII Lotion therapy. Initiate DUOBRII Lotion therapy during a menstrual period. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion therapy *[see Use in Specific Populations]*.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Unwanted Systemic Glucocorticoid Effects

DUOBRII Lotion contains halobetasol propionate, a corticosteroid, and has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment of the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with DUOBRII Lotion was evaluated in a study of 20 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area. The subjects were treated once daily for 8 weeks and assessed for HPA axis suppression at Weeks 4 and 8. HPA axis suppression occurred in 3 out of 20 (15%) subjects at Week 4 and none (0%) of these 20 subjects had HPA axis suppression at Week 8 *[see Clinical Pharmacology in full Prescribing Information]*.

Because of the potential for systemic absorption, use of topical corticosteroids, including DUOBRII Lotion, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug or reduce the frequency of application. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to topical corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids because of their larger surface-to-body mass ratio *[see Use in Specific Populations]*.

Local Adverse Reactions

Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. Some local adverse reactions may be irreversible. If these adverse reactions occur, discontinue the medication at least until the integrity of the skin is restored; do not resume treatment if allergic contact dermatitis is identified.

Avoid use of DUOBRII Lotion on eczematous skin, as it may cause severe irritation.

Photosensitivity and Risk for Sunburn

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of DUOBRII Lotion. Patients must be instructed to use sunscreens and protective clothing when using DUOBRII Lotion. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using DUOBRII Lotion.

DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Ophthalmic Adverse Reactions

Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported postmarketing with the use of topical corticosteroid products. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

Concomitant Skin Infections

Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of DUOBRII Lotion until the infection has been adequately treated.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 410 adults with plaque psoriasis were treated with DUOBRII Lotion or vehicle lotion and had post-baseline safety data. Subjects applied DUOBRII Lotion or vehicle lotion once daily for up to eight weeks. The adverse reactions occurring in ≥1% of the subjects treated with DUOBRII through Week 8 were contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), excoriation (2%), rash (1%), skin abrasion (1%), and skin exfoliation (1%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk to the fetus outweighs the potential benefit to the mother from DUOBRII Lotion during pregnancy; therefore, DUOBRII Lotion should be discontinued as soon as pregnancy is recognized *[see Contraindications, Warnings and Precautions, and Clinical Pharmacology in full Prescribing Information]*.

Observational studies suggest an increased risk of low birthweight in infants with the maternal use of potent or very potent topical corticosteroids *(see Data)*.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose 11 times the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 116 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 9 and 228 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 9 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during the period of organogenesis to pregnant rats and rabbits *(see Data)*. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of DUOBRII Lotion.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (11 times the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5%, 0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (116 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 9 and 228 times, respectively, the MRHD (based on AUC comparisons).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (16 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at that dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to 5 times the MRHD (based on AUC comparison).

Lactation

Risk Summary

There are no data on the presence of tazarotene, halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with DUOBRII Lotion.

After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUOBRII Lotion and any potential adverse effects on the breastfed child from DUOBRII Lotion.

Clinical Considerations

Advise breastfeeding women not to apply DUOBRII Lotion directly to the nipple and areola to avoid direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing

DUOBRII Lotion is contraindicated in women who are pregnant. Females of reproductive potential should be warned of the potential risk and use adequate birth-control measures during treatment with DUOBRII Lotion. The possibility that a female of reproductive potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy should be obtained within 2 weeks prior to DUOBRII Lotion therapy, which should begin during menstruation.

Contraception

Based on animal studies, DUOBRII Lotion may cause fetal harm when administered to a pregnant female *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion.

Pediatric Use

Safety and effectiveness of DUOBRII Lotion in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children *[see Warnings and Precautions]*.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema *[see Warnings and Precautions]*.

Geriatric Use

Of the 270 subjects exposed to DUOBRII Lotion in clinical trials, 39 subjects were 65 years or older. Clinical trials of DUOBRII Lotion did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 1.4 times the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposure at the highest dose was 35 times the MRHD (based on AUC comparison).

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day, approximately 0.53 times the MRHD based on BSA comparisons, indicated no impairment of fertility or general reproductive performance.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was 5 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene, which produced a systemic exposure 17 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, which produced a systemic exposure 30 times the MRHD (based on AUC comparison).

Distributed by:
Bausch Health US, LLC
Bridgewater, NJ 08807 USA

Manufactured by:
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Based on 9645602 **Revised:** 01/2020 **Issued:** 03/2021

For adults with plaque psoriasis

workingtogether

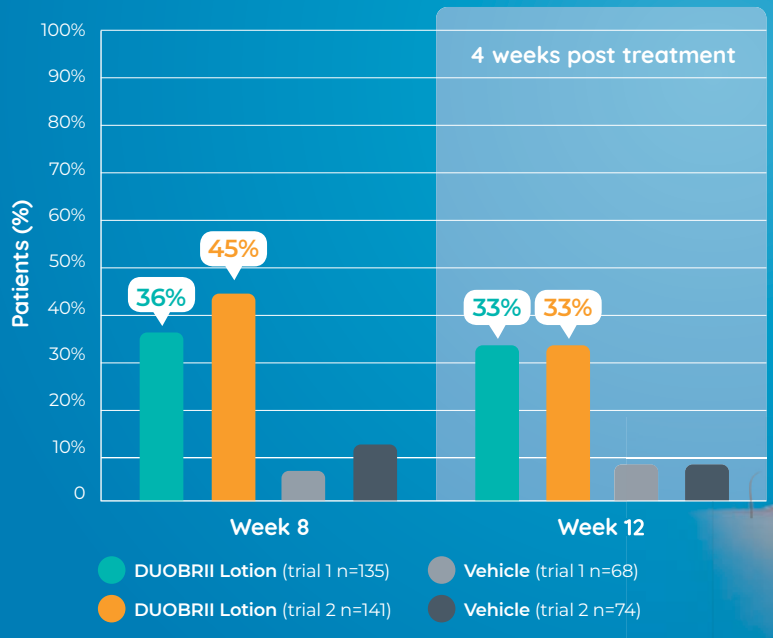
DUOBRII® (halobetasol propionate and tazarotene) Lotion 0.01% / 0.045%

DUOBRII Lotion is the only steroid/retinoid topical therapy. The AAD confirms that the combination of a steroid and a retinoid, such as **halobetasol** and **tazarotene**, may delay the relapse of plaque psoriasis and extend treatment duration.[1-3]

DUOBRII Lotion demonstrated extended remission 4 weeks post treatment[1]

2 phase 3 trials

Patients who achieved treatment success* with QD dosing (8 week primary endpoint)[1,4]



The only potent-to-superpotent steroid that has no time limits on dosing; use only until control is achieved.[1,5-9]

DUOBRII Lotion was studied in two 8-week clinical trials and a 1-year safety study. Discontinue treatment if atrophy, striae, telangiectasias, or folliculitis occurs.[1,10]

Indication

DUOBRII® (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, is indicated for the topical treatment of plaque psoriasis in adults.

Important Safety Information

Contraindication

DUOBRII Lotion is contraindicated in pregnancy.

Warnings and Precautions

- Women of child-bearing potential should be warned of the potential risk of fetal harm from DUOBRII and use adequate birth-control. A negative result for pregnancy should be obtained within 2 weeks prior to treatment. If the patient becomes pregnant during treatment, discontinue DUOBRII Lotion and advise patient of the potential hazard to the fetus.
- DUOBRII Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during or after treatment and may require that patients be evaluated periodically during treatment.
- Predisposing factors for HPA axis suppression include: use of more potent corticosteroids, use on large areas, use under occlusive dressings, use on altered skin barrier, concomitant use of other steroids, liver failure and young age.
- Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria.
- Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. If these effects occur, discontinue until the integrity of the skin has been restored. Do not resume treatment if contact dermatitis is identified. DUOBRII Lotion should not be used on eczematous skin, as it may cause severe irritation.
- Avoid exposure to sunlight, sunlamps and weather extremes. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers because of the increased potential for photosensitivity.
- Topical corticosteroids may increase the risk of cataracts and glaucoma; advise patients to report any visual symptoms and refer to an ophthalmologist if needed.

Adverse Events

- The most common adverse events in clinical trials were contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), and excoriation (2%).

To report SUSPECTED ADVERSE REACTIONS, contact Ortho Dermatologics at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on the following page.

AAD = American Academy of Dermatology
QD = once daily

*Treatment success was defined as at least a 2-grade improvement from baseline in Investigator's Global Assessment (IGA) score, and a score of "clear" or "almost clear" (primary endpoint at week 8).[1]

Study design: DUOBRII Lotion was assessed in 2 prospective, multicenter, randomized, double-blind, phase 3 clinical trials in 418 adult patients with psoriasis. Patients were treated with DUOBRII Lotion or vehicle, applied once daily and evaluated at 2, 4, 6, 8 weeks (primary endpoint), and post treatment at 12 weeks.[1]

References: 1. DUOBRII Lotion [prescribing information]. Bridgewater, NJ: Bausch Health US, LLC. **2.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed April 12, 2021. **3.** Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60(4):643-659. **4.** Gold LS, Lebwohl MG, Sugarman JL, et al. Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: results of two phase 3 randomized controlled trials. *J Am Acad Dermatol*. 2018;79(2):287-293. **5.** Clobetasol propionate cream [prescribing information]. Lincolnton, NC: Cosette Pharmaceuticals, Inc. **6.** Diprolene lotion [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp. **7.** Enstilar foam [prescribing information]. Madison, NJ: LEO Pharma Inc. **8.** Halobetasol propionate cream [prescribing information]. South Plainfield, NJ: G&W Laboratories, Inc. **9.** Mometasone furoate cream [prescribing information]. South Plainfield, NJ: G&W Laboratories, Inc. **10.** Data on file.

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