

# The Use of Apremilast in Psoriasis: An Indian Perspective on Real-World Scenarios

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**Abstract:** Apremilast, an oral phosphodiesterase-4 inhibitor, is approved for use in the management of psoriasis and psoriatic arthritis. Although its efficacy and safety have been well established in clinical studies, in real-world settings, different practice scenarios have been reported. This review paper serves to evaluate clinical real-world scenarios and aspects of treatment for which the information in the literature was considered to be lacking or controversial. Following a literature review, a panel of five dermatologists with expertise in psoriasis considered five scenarios; namely, the positioning of apremilast in psoriasis, its use in difficult-to-treat areas, special conditions and populations, safety, dose titration and dose in maintenance therapy. These were then assessed with psoriasis experts in India using a web-based questionnaire. A total of 28 questions were discussed regarding these scenarios. According to the responses, apremilast is effective in stable mild to moderate psoriasis as monotherapy and in severe psoriasis in combination. Also, a positive response was received with regard to its effectiveness in difficult locations such as the scalp, palms and soles. To reduce adverse effects, prolonged titration therapy over 4 weeks is required and lower doses can be prescribed to maintain remission. Apremilast therapy should be continued for a minimum of 8 weeks once initiated to achieve the desired results, and the total duration of therapy should be about 24 weeks for better efficacy. It is also effective in many other cases, such as obese patients, patients with hepatitis B or C and HIV, or patients on polypharmacy. It was also reported that apremilast requires less prescreening and monitoring than other conventional and biologic systemic therapies. Overall, apremilast is an attractive option for the individualized treatment of psoriasis owing to its favorable safety profile, its ease of oral administration without the need for screening or ongoing laboratory monitoring, and its positive impact on symptoms and lesions in difficult-to-treat areas.

**Keywords:** apremilast, psoriasis, titration, real world, safety

## Introduction

Apremilast, an oral phosphodiesterase-4 inhibitor, was approved by the US Food and Drug Administration in September 2014<sup>1</sup> and the Drug Controller General of India in October 2017 for the management of moderate to severe psoriasis and psoriatic arthritis. Apremilast has immunomodulatory activity which partially blocks the expression of proinflammatory cytokines and induces the expression of anti-inflammatory cytokines that have a pathogenic role in psoriasis. Although the efficacy and safety of apremilast have been extensively documented in clinical trials, as well as in real-world studies on the management of both psoriasis and psoriatic arthritis,<sup>2-7</sup> little is known about its real-world use, such as the correct positioning as monotherapy and combination therapy, titration practices, and

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variations in dosage. Apart from this, discontinuation of treatment owing to minor adverse events or indecision over its use in special populations is a commonly observed trend among dermatologists that can be attributed to a lack of adequate real-world experience from peers about the safety and optimization of apremilast.

Survey-based consensus recommendations from practicing dermatologists and panel experts using rigorous, validated methodologies may serve as useful guidelines for such situations and may provide valuable information on the use of apremilast in everyday clinical practice.<sup>8</sup> To augment the existing evidence on the use of apremilast, a group of experts with over 15 years' experience in psoriasis came together to evaluate clinical and real-world scenarios and aspects of treatment for which the information in the literature was considered to be lacking.

## Methodology and Study Design

To assess the real-world experience of apremilast use in psoriasis, an expert panel was formed composed of five dermatologists with a minimum of 15 years' experience in the management of psoriasis and experience of apremilast prescription for at least 2 years.

The entire survey process consisted of three steps: 1) literature review and questionnaire design 2) the survey of eligible clinical dermatologists; and 3) panel discussion for review of results and consensus generation.

## Literature Review

The goal of the literature review was to examine the existing usage pattern of apremilast. A systematic search of the literature databases, namely Scopus database, PubMed Database, and Google Scholar, was performed to obtain adequate data for questionnaire design.

Later, a web-based questionnaire was created and circulated among panel members. The questionnaire was created de novo and validated by all the panelists. The questionnaire comprised a total of 28 questions pertaining to the use of apremilast as monotherapy, combination, or switchover therapy, its role in special populations, the practices followed for dose titration, and its adverse effect (AE) profile.

The survey was beta tested and approved by the panelists before dissemination among participants. A total of 75 practicing dermatologists from India with a minimum of 10 years' experience in the management of psoriasis and 2 years of apremilast use were selected. Survey questionnaires were disseminated via a web link in

September 2020, followed by a reminder to participate in October 2020. Participants were given 15 days to reply and were guaranteed complete anonymity.

The panel discussed the response to each question and the opinion of each panelist was recorded. The results of the panelists' responses were considered qualitatively, and the final opinions were mentioned only after the consensus was generated.

## Results and Discussion

A total of 28 questions were asked regarding different domains such as positioning of apremilast in psoriasis, its use in difficult-to-treat areas, special conditions and populations, safety, dose titration, and dose in maintenance therapy. All participants answered all of the questions. All of the results are tabulated in Table 1.

### Positioning of Apremilast in Psoriasis

#### Effectiveness of Apremilast as Monotherapy and Combination Therapy

In the landmark clinical trials on apremilast in plaque psoriasis, monotherapy was found to be safe and efficacious for the long term. Even real-world studies in India<sup>9-11</sup> supported the long-term use of apremilast monotherapy as an efficacious and safe treatment option for the management of moderate-to-severe plaque psoriasis. But in our survey results, only 8% of the clinicians reported its use as monotherapy. About 77% of the clinicians preferred to use apremilast in combination form.

A Canadian study,<sup>6</sup> which compared monotherapy and a combination therapy of apremilast (with methotrexate, etanercept, and ustekinumab) in the real world, reported comparable therapeutic response maintained with monotherapy and combination therapy at week 52 (monotherapy, 66.7%; combination therapy, 63.0%;  $P=0.787$ ). The incidence of AEs reported by both cohorts (monotherapy, 14.3%; combination therapy, 22.2%;  $P=0.484$ ) was also comparable.

Besides monotherapy, apremilast in combination therapy could be used to reduce disease activity in recalcitrant plaque psoriasis. It can be used in patients who are insufficiently controlled and/or those who had a diminished response over time to phototherapy or systemic/biologic agents, without increasing the risk of AEs.<sup>12</sup>

Drug survival of apremilast in patients who were also on other systemic agents (84% survived the drug and 16%

**Table I** Expert-Validated Questionnaire and Summary of Responses

Sr. No	Questions	Response
1	Do you use apremilast as monotherapy or combination therapy?	Although 77% of the dermatologists use apremilast as monotherapy and combination therapy, most commonly, apremilast is prescribed along with other drugs as combination therapy
2	In which severity grade of plaque psoriasis (as measured by PGA) do you prescribe apremilast therapy?	85% response was received for moderate psoriasis with BSA involvement <10%
3	In psoriasis, do you consider apremilast as a first-line drug or second-line drug?	40% prescribe apremilast as a first-line drug, whereas 60% prescribe it as a second-line drug in the management of psoriasis, hence no consensus achieved
4	In which type of psoriasis other than plaque-type do you prescribe apremilast?	About 97% responded that they use apremilast in scalp, palmoplantar, and nail psoriasis, of which 35% prescribe it as the first-line and 65% as the second-line drug
5	After starting apremilast, how long on an average does it take for your patients to show clinical improvement (eg, PASI 50/equivalent fall in BSA or PGA) in patients with psoriasis?	89% responded that it takes about 4–6 weeks for apremilast to show clinical improvement
6	Once patients achieve disease clearance with apremilast, is it recommended to stop the apremilast therapy?	71% respondents feel that apremilast should not be stopped abruptly after achieving disease clearance
7	What is your preferred dose of apremilast in the maintenance phase?	No consensus achieved; 39% mentioned that the maintenance dose of apremilast varies from patient to patient, 27% preferred apremilast 30 mg twice a day, whereas 21% preferred 30 mg once a day
8	What is the percentage of your patients who achieve complete remission with apremilast?	87% of the respondents commented that they achieve complete remission in less than 50% of their patients
9	What is your general opinion regarding the predictability of clinical response to apremilast?	In 92% of the responses, predictability of apremilast is low to moderate, ie, in some of the patients it works well, whereas in some of the patients it does not show a satisfactory response
10	Do you prescribe apremilast with other systemic agents?	90% of the dermatologists combine apremilast with other systemic agents. Among all systemic agents, apremilast is commonly combined with methotrexate
11	Can apremilast be used as switchover therapy in patients who have achieved disease clearance with other systemic drugs?	93% responded positively for apremilast as switchover therapy, and in such cases, the previous systemic drug should be withdrawn gradually over time
12	Apremilast with biologics?	In India, only 29% of the dermatologists use biologics in the management of psoriasis. Of these, 65% combine biologics with apremilast to maintain the remission and reduce the cost of therapy, thus improving the patient outcome
13	Can apremilast be considered as a preferred drug compared to other immunosuppressive drugs in the current scenario of global COVID pandemic?	85% positive responses were received
14	Can apremilast be prescribed in patients with high risk of developing TB infection?	77% commented that apremilast can be used in patients with high risk of developing TB infection
15	Can apremilast be prescribed in HIV patients for the management of psoriasis?	A positive response was received from 79% of the respondents

(Continued)

Table I (Continued).

Sr. No	Questions	Response
16	Can apremilast be prescribed in patients with hepatitis B or hepatitis C?	67% voted that apremilast can be used in such patients
17	Since apremilast is associated with significant weight loss up to 10%, should it be stopped if >10% weight loss is experienced in patients with psoriasis?	Apremilast should be stopped in these cases, according to 72% of the dermatologists
18	Can apremilast be considered as a preferred drug in female patients in the reproductive age group trying to conceive?	No consensus achieved; 50% responded positively whereas 18% opted for the “do not know” option
19	Can apremilast be prescribed in patients with psychiatric disorders like depression?	60% responded as not to be used, whereas 40% responded that it can be used
20	Can apremilast be considered as a safe drug in the management of patients with psoriasis with other comorbid conditions like cardiac diseases, diabetes, or hypertension?	As per 91% of responses, apremilast is one of the safest drugs in comorbid conditions like cardiac disease and diabetes
21	Drug–drug interactions can be very crucial and can have a significant effect on patient outcomes, especially in patients who are on polypharmacy. Can it be considered as safe drug in such patients?	80% responded positively
22	Can apremilast be prescribed in paediatric patients with psoriasis?	45% voted negatively, whereas for 55%, it can be used and the dosage varies from patient to patient
23	Do you routinely do laboratory monitoring in psoriasis patients on apremilast?	No consensus achieved; 55% no, 45% yes
24	Can apremilast be considered as cost-effective therapy over a long period of time compared to other conventional medications?	83% considered apremilast as a cost-effective option over other conventional drugs
25	In how many patients are side effects seen with apremilast in your clinical practice?	About 40% of patients receiving apremilast experience side effects, most of them in the initial period, with 30 mg twice daily. Diarrhea, vomiting, and headache are at the top of the list
26	What is the most common titration method that you use in your clinical practice?	Although 62% of the dermatologists use a starter pack as recommended, there are many different titration methods available in real-world practice
27	According to you, can apremilast 20 mg twice daily be useful in those patients who are not tolerating 30 mg twice daily regimen?	79% were in agreement with this
28	Can apremilast be used in off-label indications?	Atopic dermatitis 79%, lichen planus 74%, alopecia areata 65%, and vitiligo 47%

**Abbreviations:** PGA, physician global assessment; BSA, body surface area; PASI, Psoriasis Area and Severity Index.

discontinued)<sup>7</sup> was much better compared to the poor drug survival reported in apremilast monotherapy (49%<sup>13</sup> and 65%<sup>14</sup>). Hence, combining other systemic agents with apremilast may increase the treatment adherence of patients and thus may reduce the relapse rate.

Our survey also revealed that a majority of the dermatologists preferred to use apremilast as a part of combination therapy in moderate to severe psoriasis. These

findings were reinforced by the expert panel. However, according to experts, apremilast monotherapy could also be used with good efficacy in patients with stable mild to moderate psoriasis with a body surface area (BSA) involvement <10%. This is supported by Del Alcazar et al, who concluded that apremilast may be an alternative for treating moderate psoriasis, with a Psoriasis Area and Severity Index (PASI) score of around 10.<sup>15</sup>

## Effectiveness of Apremilast in Combination with Systemic Drugs

According to the survey results, a combination of apremilast is documented with other anti-psoriatic agents, such as methotrexate, acitretin, cyclosporine, and other biologic therapy. This was corroborated by the published literature.<sup>16</sup>

Methotrexate was found to be most commonly prescribed drug, along with apremilast, followed by cyclosporine. This combination has been previously proven as a good and effective combination for the treatment of psoriasis. It has also been proven that methotrexate and apremilast can be coadministered without any effect on the pharmacokinetic exposure of either agent.<sup>17</sup> The panel suggested that the combination of cyclosporine and apremilast could be a viable option in severe psoriasis by virtue of rapid relief with cyclosporine, followed by apremilast continued for a longer duration to maintain remission.

## Effectiveness of Apremilast as Maintenance or Switchover

The panel remarked that apremilast could be added as a maintenance or switchover drug in patients receiving methotrexate or cyclosporine with acceptable control of psoriasis. This strategy is found to be effective in reducing the side-effect profile of other conventional systemic drugs.

However, withdrawal of conventional drugs may be associated with rebound or flares, hence it was cautioned that conventional drugs should be withdrawn slowly over 4–6 weeks.

## Effectiveness of Apremilast with Biologics

According to the LIBERATE trial, the use of apremilast can be considered in biologic-experienced or biologic-naïve patients. However, it is preferred more in biologic-naïve patients, because its efficacy appears to be better in this subgroup of patients.<sup>4</sup> Clinical trials reported significantly higher response rates with the use of apremilast in biologic-naïve patients.<sup>2</sup>

According to published reports,<sup>18,19</sup> the cost of biologics is a deterrent in their use in needy patients. Its long-term use adds further to the economic burden on the patients. Considering these factors, panel experts pointed out that in India, there is sparse use of biologics among dermatologists and hence a combination with apremilast

would be a sustainable choice for keeping the cost low over long-term therapy.

Regarding the combination therapy of apremilast and biologics, there was a general opinion that it can provide more effective disease control than biologic monotherapy alone. Apremilast could serve as an effective therapeutic option for maintaining remission, induced by biologics. This is corroborated by the findings of two case reports on the effectiveness of combination therapy of apremilast with adalimumab<sup>20</sup> and secukinumab,<sup>21,22</sup> as well as the personal clinical experience of some of the experts.

This strategy also helps to reduce the dosages of biologic drugs, ultimately reducing the cost of the therapy. In addition, this strategy may help to improve patients' perception of their quality of life, the economic burden of non-functional patients requiring several rescue therapies, and frequent visits to healthcare centers. In economically constrained situations, as in a country such as India, cost also plays a major role, particularly in therapies requiring long-term administration. Also, in India, not many patients are covered under medical insurance, so reasonably priced options such as apremilast can be a very viable option in such conditions.

## Effectiveness of Apremilast in Special Locations (Difficult-to-Treat Areas)

Currently, apremilast is approved for the treatment of moderate-to-severe psoriasis, but it has shown effectiveness in difficult-to-treat forms of psoriasis, such as scalp, face, palmoplantar, and nail psoriasis, and hence can be considered in these cases.<sup>15,23</sup>

The ESTEEM 1 AND ESTEEM 2 phase III double-blinded efficacy and safety trials evaluated the efficacy of apremilast in nail and scalp psoriasis.<sup>24</sup> Various other studies have also shown the efficacy of apremilast for the treatment of palmoplantar psoriasis<sup>25</sup> and nail psoriasis.<sup>26</sup>

The clinicians in our survey reported the use of apremilast for palmoplantar, scalp, and nail psoriasis, other than plaque psoriasis, as a second-line drug. The panel mentioned its use in nail and palmoplantar types more frequently than in others.

## Minimum Time Required for Showing Efficacy and Extent of Remission in Plaque Psoriasis

A study conducted on six patients with palmoplantar psoriasis showed that all the patients had improvement in



disease within the first 4 weeks of treatment.<sup>25</sup> The ACTIVE trial demonstrated the early onset of action (at week 2) of efficacy of apremilast in biologic-naïve patients with psoriatic arthritis.<sup>27</sup> The UK National Institute for Health and Care Excellence (NICE) recommends stopping apremilast if an adequate response is not attained by 16 weeks. An adequate response is defined as attainment of PASI 75 or PASI 50 with a five-point reduction in the Dermatology Life Quality Index (DLQI).<sup>28</sup>

When asked about the minimum time period to show efficacy, a consensus was generated that apremilast showed efficacy within 4–6 weeks of initiation of treatment, as evidenced by PASI 50 or an equivalent fall in BSA or physician global assessment (PGA) in patients.

Overall, 86.7% of the clinicians in our survey reported that up to 50% of their psoriasis patients have complete clearance of disease within 16 weeks of apremilast therapy. However, the results of this survey also showed that the response of apremilast in the remaining patients was low to moderate. This has been proved by Verbenko et al, who pointed out the role of genetic polymorphisms as important factors for individual variations in drug response in psoriasis.<sup>29</sup> Moreover, this rate of remission among Indian psoriasis patients as reported by the dermatologists is commensurate with worldwide trials.<sup>30</sup>

Apart from this, the experts also considered that treatment effectiveness should be measured by a combination of indicators, such as absolute PASI scores, and other factors, such as patient satisfaction, tolerability, and safety of the drug. They also commented that a leeway of 24 weeks should be considered before deciding about further continuation of the drug. This recommendation is in contrast to the treatment goals established in the clinical trials of apremilast.

The recommendations for these sections are summarized in Table 2.

## Use of Apremilast for Plaque Psoriasis in Special Populations Pediatric Age Group

Psoriasis is less common in the pediatric age group than in the adult population, with a prevalence rate of 1%. Despite the availability of guidelines in the pediatric age group, there are no recommendations regarding the use of apremilast because of insufficient data.<sup>31</sup>

The safety and efficacy of apremilast in the pediatric age group have not been evaluated in landmark clinical

**Table 2** Place of Apremilast in Psoriasis Management

<ul style="list-style-type: none"> <li>• Apremilast can be used as monotherapy in patients with stable mild to moderate psoriasis and as combination therapy in moderate to severe psoriasis</li> </ul>
<ul style="list-style-type: none"> <li>• Efficacy of apremilast is comparable to systemic and biologic agents (particularly stable disease plaque psoriasis) and it is relatively safe</li> </ul>
<ul style="list-style-type: none"> <li>• Apremilast can be added to ongoing systemic therapy to enhance the response; it is recommended that systemic therapy should be continued for a minimum of 6 weeks to maintain remission</li> </ul>
<ul style="list-style-type: none"> <li>• A combination of apremilast and biologics offers better disease control than biologic monotherapy. Apremilast could serve as the agent of preference for maintaining remission induced by biologics</li> </ul>
<ul style="list-style-type: none"> <li>• Although apremilast is approved in moderate to severe plaque psoriasis, it has been found to be effective in other types of psoriasis, such as palmoplantar, nail, and scalp psoriasis</li> </ul>
<ul style="list-style-type: none"> <li>• Apremilast usually takes 4–6 weeks to show initial efficacy, hence therapy should be continued for a minimum of 8 weeks once initiated. Also, it is recommended to continue therapy for about 24 weeks for better efficacy</li> </ul>
<ul style="list-style-type: none"> <li>• Most importantly, the response to apremilast is very unpredictable in psoriasis, ie, it works in some patients very well whereas other patients may not respond at all</li> </ul>

trials. However, a phase II study<sup>32</sup> and a few case reports<sup>33,34</sup> are available regarding its use in the pediatric population. Paller et al, in a phase II study,<sup>32</sup> reported that apremilast 20 mg twice daily in 21 children in the age group 6–11 years with psoriasis had a similar pharmacokinetic profile to that of adults on apremilast 30 mg twice daily. The authors also reported that the safety profile was generally similar to that in adults and improvements from baseline in mean PASI score were in the range of 68–79%.<sup>32</sup> In case reports by Smith and by Saporito and Cohen, despite the use of the adult dose (30 mg twice daily), no gastrointestinal or other side effects were reported.<sup>33,34</sup>

Based on the available evidence and results of the survey, the experts opined that apremilast can be considered in pediatric patients with plaque psoriasis who are not responding to topical therapy. Regarding the dosing of apremilast in the pediatric age group, the experts commented that the dosage should be individualized.

## Comorbid Conditions

Although skin involvement is often the most prominent and may be the only recognized clinical manifestation of

psoriasis, it is now considered a chronic multisystem inflammatory disorder.<sup>35</sup> Various epidemiological studies and meta-analyses have established that psoriasis is associated with an increased prevalence of cardiovascular and metabolic risk factors, such as diabetes, arterial hypertension, and hyperlipidemia, and an increased risk of myocardial infarction.<sup>36,37</sup> In a study by Mazzilli et al published in 2020, the authors confirmed the efficacy and safety of apremilast in favoring the improvement of skin and joint disease as well as the modulation of metabolic biomarkers in diabetic and non-diabetic psoriatic patients, and concluded that apremilast could be used successfully in psoriatic patients affected by cardiometabolic comorbidities, ensuring an improvement in both diseases.<sup>38</sup>

Another factor which further complicates the management of psoriasis that many patients are on polypharmacy because of their comorbidities. Duvetorp et al,<sup>39</sup> in a population-based register study, reported that polypharmacy was very common in patients with psoriasis, with only 1.3% of all patients being without any prescription. Thus, the management of patients with psoriasis becomes complicated because of the increased risk of drug–drug interactions. Also, many anti-psoriatic drugs are either contraindicated or not suitable in patients with such comorbid conditions because of the increased incidence of adverse events, worsening of existing diseases, and organ-specific and cumulative toxicities.<sup>40</sup>

The experts strongly recommended the use of apremilast in such scenarios because of several advantages, listed below.

1. Apremilast is not associated with any significant drug–drug interactions.<sup>41</sup>
2. No organ-specific or cumulative toxicity is seen, as reported by Crowley et al in their study, where apremilast exposure for >156 weeks was not associated with any increase in the incidence of major cardiac events, malignancies, or depression.<sup>42</sup>
3. Apremilast has beneficial effects on the metabolic profile. Gualtierotti and De Lucia, in their case study, reported that apremilast was associated with an improvement in the lipid profile of the patient.<sup>43</sup> Similarly, De La Rosa et al concluded that apremilast may reduce insulin resistance, inflammation, hypertension, lipids, and endothelial dysfunction.<sup>44</sup> Liu et al reported that apremilast reduces the formation of atherosclerotic plaque;

thus, it may be useful for the treatment and prevention of atherosclerosis.<sup>45</sup>

## Depression, Anxiety, and Suicidal Tendencies

Depression, anxiety, and suicidal tendencies are common comorbidities among psoriasis patients which may be a result of psychosocial difficulties as well as common inflammatory pathways.<sup>35,46,47</sup> However, little is known about whether systemic treatment for psoriasis is associated with an increased risk of anxiety and depression, and whether these risks differ between the various treatments.<sup>48</sup>

The results of short-term clinical trials and post-marketing cases suggested that apremilast was associated with an elevated risk of depression, anxiety, and suicidal thoughts, to a certain extent.<sup>48</sup> According to post-marketing data, out of 105,000 patients who received apremilast, only 65 patients reported either depression and/or suicidal thoughts or behavior, of whom 32 patients improved after discontinuation of therapy.<sup>49</sup> Based on these reports, precaution is recommended when prescribing apremilast in patients with a history of depression and/or suicidal thoughts or behavior, as per prescribing information.<sup>41</sup>

However, Crowley et al, in their long-term safety and tolerability study, reported that apremilast did not increase the incidence of depression.<sup>42</sup> Similarly, Vasilakis-Scaramozza et al reported that patients treated with apremilast had a similar risk of depression and anxiety compared to patients on conventional disease-modifying anti-rheumatic drugs (DMARDs) or biologic monotherapies.<sup>48</sup>

Based on all these facts and the results of the survey, the experts commented that the following precautions should be taken before prescribing apremilast to such patients.

1. A careful risk–benefit analysis of apremilast use must be conducted among psoriasis patients with a history of psychiatric symptoms or those who are taking medicines that are likely to cause psychiatric symptoms.
2. Treatment should be discontinued in patients who experience new psychiatric symptoms or worsening of existing ones, or if suicidal ideation or suicidal behavior is identified.
3. Patients and caregivers must be instructed to notify the prescriber of any changes in behavior or mood or of any signs of suicidal ideation.

## Females of Reproductive Age

Apremilast is contraindicated during pregnancy; therefore, pregnancy must be ruled out when initiating the treatment with apremilast.<sup>50</sup>

Because of a short washout period, it is recommended to stop apremilast 2 days before conception.<sup>51</sup> This period is significantly shorter than for other drugs, where precautions are recommended for a period of a few days to several weeks (eg, methotrexate 12 weeks; acitretin up to 2–3 years; secukinumab 19 weeks; tumor necrosis factor inhibitors [TNFi] 14–50 days).<sup>51</sup>

Considering the available literature and the results of the survey, the experts opined that apremilast seems to be a better option than other conventional or biological anti-psoriatic therapies in females of reproductive age.

## Obesity and Weight Loss

Weight loss is one of the important AEs associated with apremilast. In controlled clinical trials of psoriasis, a total of 14.3% of patients receiving apremilast observed weight loss of between 5% and 10%, while 5.7% observed weight loss >10%.<sup>49</sup> Crowley et al reported 21.9% of patients with >5% loss of their baseline body weight after the use of apremilast for >156 weeks.<sup>42</sup> However, none of the patients in these studies had overt clinical consequences resulting from weight loss.<sup>42,49</sup>

According to various population-based studies, obesity and psoriasis are interrelated with each other.<sup>35,52</sup> In addition, obese patients show a slow response to anti-psoriatic therapy, so weight loss has been suggested as a potential therapeutic option for these patients.<sup>53,54</sup> Various studies have also documented an association between weight loss and improvement in psoriasis.<sup>55,56</sup>

It has been found that weight loss associated with apremilast is more common in patients with higher baseline body mass index.<sup>42</sup> The experts opined that apremilast may be of particular interest in patients with psoriasis along with obesity and metabolic syndrome, who may benefit from the side effect of weight loss. However, the experts also recommended close monitoring of these patients and discontinuation of apremilast if weight loss exceeds 10%.

## Patients with HIV

The management of psoriasis in the HIV-positive population is challenging. The current first-line recommendations for treatment include topical therapies and phototherapy,

followed by oral retinoid as second-line agents.<sup>57</sup> However, the clinical course of psoriasis in HIV-positive patients is often progressive and refractory;<sup>58</sup> therefore, these therapies are inadequate to control both skin and joint manifestations. Currently, most of the available systemic therapies for psoriatic disease are immunosuppressive, which poses a distinct clinical challenge owing to the pre-existing immunocompromised status of HIV-positive patients, thus increasing the chances of opportunistic infections such as tuberculosis (TB).<sup>59</sup>

Unlike conventional immunosuppressants, apremilast, because of its unique immunomodulatory action, restores the balance of proinflammatory and anti-inflammatory cytokines.<sup>60</sup> In addition, apremilast, not being contraindicated in serious infections and providing other benefits, represents a promising therapeutic option in the management of psoriasis in HIV patients.

The safety and efficacy of apremilast in HIV patients have been evaluated in various case studies. Shah et al, in their case report, concluded that apremilast was associated with a significant reduction in the PASI score in patients with HIV, without any incidence of opportunistic infection or alteration in any of the laboratory parameters.<sup>61</sup> Reddy et al successfully treated a patient with both HIV and HCV infection using apremilast without any additional side effects.<sup>62</sup> Similar results were reported by Sacchelli et al in patients with plaque and nail psoriasis not responding to acitretin.<sup>63</sup> Manfreda et al reported significant improvements in PASI and Disease Activity in Psoriatic Arthritis (DAPSA) scores in a patient with both HIV and HBV after 24 weeks of apremilast use. No adverse events were observed or reported by the patient.<sup>64</sup>

The experts agreed with the published data and recommended that apremilast could be considered as first-line therapy in HIV patients; however, they recommended that the decision should be taken in collaboration with the infectious disease specialist.

## Patients with Hepatitis B or C

Similarly to patients with HIV, management of psoriatic patients with chronic infections such as hepatitis B and hepatitis C is challenging because of the increased chances of reactivation of the disease and liver toxicities associated with anti-psoriatic therapies.<sup>65</sup>

Only three patients with chronic viral hepatitis (two with HCV and one with HBV) treated with apremilast have been described in the published literature.<sup>62,66,67</sup> From these reports, it was concluded that apremilast was



associated with neither reactivation of disease, nor elevation of liver enzymes, nor viral load in active disease. Excessive alcoholism is associated with fatty liver and is also a trigger factor for psoriasis.<sup>68</sup> It has been found that apremilast produces stable reductions in voluntary ethanol consumption and is rapidly distributed to plasma and tissues (including the brain), suggesting its usefulness for medication development and repurposing efforts to treat alcohol misuse.<sup>69</sup>

Apremilast is not contraindicated in patients with active infections and does not have hepatotoxic effects; hence, it can be used in severe hepatic impairment without dose reduction.<sup>65</sup>

Apremilast exerts an anti-fibrotic action in animal models by inhibiting pro-fibrotic factors such as transforming growth factor- $\beta$  and interleukin-13,<sup>70</sup> which could potentially have a positive impact on liver fibrosis. In light of these data, apremilast is not only innocuous but also potentially beneficial in patients with commonly prevalent non-alcoholic fatty liver disease.

The panel experts consented on apremilast use in patients with HBV or HCV infection; however, they also commented that a hepatologist should be consulted only in case of clinically significant liver enzyme elevation (3–5 times more than the upper normal limit).

## Patients at Risk of Developing Tuberculosis

A high prevalence of latent TB infection has been reported in autoimmune disorders such as psoriasis.<sup>71</sup> In addition, conventional and biologic therapies such as TNFi are associated with an increased risk of developing opportunistic infections such as TB.<sup>72</sup> Hence, the management of such patients becomes challenging.

A pooled analysis of landmark clinical trials in psoriasis did not report reactivation of TB with apremilast.<sup>41</sup> In the post-marketing report of 117,728 psoriasis patients who were exposed to apremilast, only three patients reported TB and none of the patients discontinued therapy with apremilast.<sup>49</sup> Therefore, TB screening and monitoring are not recommended routinely in patients receiving apremilast.<sup>41</sup>

Based on these facts, apremilast can be considered as a therapeutic option in patients with TB or those who are at risk of developing TB. However, rifampicin, being a strong inducer of CYP3A4, may result in a loss of efficacy of apremilast.<sup>30</sup> Thus, the concurrent use of rifampicin with apremilast is not recommended.

## Apremilast and Vaccination

Live vaccination is not recommended in patients receiving conventional (methotrexate, cyclosporine) or biological (TNFi, secukinumab) anti-psoriatic therapies.<sup>73–76</sup> Therefore, vaccination in patients with psoriasis can involve informed decision making.

There is no published information or prescribing information mentioning the use of apremilast in the context of vaccination.<sup>49</sup> However, live vaccinations were permitted in patients enrolled in the randomized controlled clinical trials.<sup>49</sup>

Based on these facts, the experts suggested that any decisions regarding vaccination during apremilast therapy should be made after considering the risk–benefit ratio.

Recommendations for these sections are summarized in Table 3.

## Safety Profile of Apremilast Laboratory Monitoring While Using Apremilast

In clinical trials on the efficacy and safety of apremilast, laboratory parameters did not show any significant derangements. Also, there was no evidence of cumulative or organ-specific toxicity.<sup>50</sup> According to the prescribing information for apremilast, no laboratory monitoring is required.<sup>41</sup> However, in a consensus study on the use of apremilast in psoriasis, published in 2020,<sup>8</sup> and a real-world study by Mayba and Gooderham,<sup>7</sup> it was recommended that laboratory monitoring should be carried out only in selected cases.

Based on the evidence, clinical experience, and survey results, the experts recommended that:

- Laboratory monitoring in the form of complete blood count should be conducted at least once or twice a year in patients receiving apremilast. In patients on combination therapy, laboratory monitoring guidelines of the other agent should be adhered to.
- Additional laboratory monitoring should be conducted according to the patient's underlying disease(s).
- From the above findings and less rigorous pre-screening, apremilast therapy is more convenient than other conventional therapies.

## Common Side Effects of Apremilast

AEs with the use of apremilast are not uncommon. The incidence of AEs reported in landmark clinical trials such as ESTEEM and PALACE studies was as high as 73–74%

**Table 3** Recommendations on the Use of Apremilast for Psoriasis in Special Populations

Special Conditions	Expert Panel Recommendations Regarding Apremilast Use
Children	Apremilast dosage in the pediatric age group should be individualized
Patients with comorbidity/polypharmacy	Conventional agents should be carefully evaluated in each patient considering the possible organ impairment, comorbidities, concomitant medications, and contraindications. Additional care is recommended in the population aged >65 years
Patients with depression	Careful risk–benefit analysis of apremilast use is recommended by means of the complete history of psychiatric symptoms, drug history, vigilant monitoring by caregivers, and cessation of therapy if a new psychiatric symptom is seen
Reproductive age group	The panel recommended judicious use in reproductive-age females and cessation of therapy prior to conception
Obesity and weight loss	Consensus was in favor of withdrawing the drug in case of >10% weight loss than baseline. But at the same time, apremilast may be of particular interest in patients with psoriasis with obesity and obesity-related comorbidities
HIV patients	Owing to its unique immunomodulatory action, apremilast can be considered as a first-line therapy in HIV patients, but the decision should be taken in collaboration with the infectious disease specialist
Patients with hepatitis B or C	Apremilast can be considered in patients with HBV or HCV infection and a hepatologist should be consulted only in case of clinically significant liver enzyme elevation (3–5 times more than the upper normal limit)
Patients at risk of developing tuberculosis	Apremilast can be considered in the treatment of psoriasis in patients with active or latent TB provided they are not on active rifampicin therapy
Vaccination	The decision regarding vaccination during apremilast therapy should be taken after considering the risk–benefit ratio

over a 52-week observation period.<sup>2,3</sup> However, the incidence of AEs with the use of apremilast in the initial 16–24 weeks of use was in the range of 30–40% in real-world studies,<sup>9,10</sup> compared to 66–70% reported in landmark clinical trials.<sup>2,3</sup> The most common AEs reported in these studies were diarrhea, nausea, headache, nasopharyngitis, upper respiratory tract infections, weight loss, and depression, similar to the observations by dermatologists in the present survey.

In a pooled safety analysis of randomized controlled trials over 156 weeks by Crowley et al, discontinuation of apremilast therapy owing to adverse events was seen in only 11.2% of the patients.<sup>42</sup> A few real-world studies from India reported discontinuation rates in the range of 5–7%. The most common reasons cited for discontinuation were headache and diarrhea.<sup>9–11</sup> However, Langley and Beecker, in their review, pointed out that the medical criteria for diarrhea in these studies were ill defined in view of the frequency or characteristics of the stools.<sup>77</sup>

Based on the above findings and clinical experience with the use of apremilast, the experts opined that most of these AEs are mild in severity and resolve with time and appropriate pharmacotherapy, as also noted in the published literature.<sup>78</sup>

### Dose Titration of Apremilast

AEs, especially gastrointestinal intolerance, with apremilast therapy, are encountered in the initial 2 weeks.<sup>78</sup> It is a standard recommendation to titrate the dose over 5 days in pursuit of reducing the incidence of these AEs.<sup>41</sup> However, in real-world clinical practice, the occurrence of AEs is still high despite the standard dose titration. Therefore, various dose titration regimens over a longer duration (varying from 2 to 4 weeks) are tried in order to combat the occurrence of AEs. In an as-yet unpublished (in Press) real-world Indian retrospective study, it was concluded that slower titration of apremilast in the initial phase over 4 weeks led to a lower AE profile and hence reduced discontinuation of therapy and thus increased adherence.<sup>79</sup> In addition, in a Spanish consensus study on the use of apremilast in psoriasis, it was recommended that a prolonged induction phase will serve as an effective strategy to mitigate gastrointestinal AEs.<sup>8</sup>

Dose modification is also required in certain patients, such as those with severe renal impairment (CrCl of <30 mL/min, as estimated by the Cockcroft–Gault

equation). When titrating the initial dosage in such individuals, it is recommended that the evening dose be eliminated (ie, 10 mg in the morning on days 1, 2, and 3, followed by 20 mg on days 4 and 5, and 30 mg on day 6).<sup>80</sup>

Based on these findings and clinical experience, the experts recommended that the dose of apremilast should be titrated gradually and tailored according to the patient's tolerance, especially in patients who do not tolerate the standard dose titration.

## Maintenance Therapy with Apremilast

In various studies, apremilast has been evaluated as monotherapy or in combination therapy for long-term maintenance in patients with plaque psoriasis.<sup>4,6,7</sup> After considering these facts, the experts commented that apremilast should be preferred as long-term maintenance therapy in patients with plaque psoriasis because of its better safety profile, lack of organ toxicity, and reduced need for laboratory monitoring.

Even though the approved dose of apremilast is 30 mg twice daily, a few studies have evaluated the efficacy and safety of apremilast 20 mg twice daily in patients with plaque psoriasis and psoriatic arthritis. In the PALACE trials, apremilast 20 mg twice daily was equally effective compared to apremilast 30 mg twice daily.<sup>81–83</sup> Ohtsuki et al reported similar results in patients with plaque psoriasis with apremilast 20 mg twice daily.<sup>84</sup>

Based on these facts, the results of the survey, and their personal experience, the experts commented that a lower dosage of apremilast, such as 20 mg twice daily or 30 mg once daily as long-term maintenance therapy, can be considered in patients who have achieved clearance of their lesions. This strategy may help in reducing the side-effect profile and the cost of the therapy, resulting in better patient compliance and thus improving treatment outcomes.

Recommendations for this section are summarized in Table 4.

## Conclusion

The clinicians who participated in this study view apremilast as an attractive option for the individualized treatment of psoriasis. In particular, they appreciate its favorable safety profile, ease of oral administration, without the need for screening or ongoing laboratory monitoring, and its positive impact on symptoms and lesions in difficult-to-

**Table 4** Recommendations on Dose Titration and Maintenance, and Laboratory Monitoring

<ul style="list-style-type: none"> <li>Regarding laboratory monitoring, the panel considered that a complete blood count once or twice a year was sufficient for patients on apremilast monotherapy, and that other tests or procedures in patients on combination therapy should be performed keeping in mind monitoring recommendations of the other drug(s)</li> </ul>
<ul style="list-style-type: none"> <li>The most relevant adverse events are gastrointestinal problems, headache, and weight loss. Prompt management of adverse effects can help to minimize their impact and enable patients to continue with treatment</li> </ul>
<ul style="list-style-type: none"> <li>Apremilast should be titrated gradually and tailored according to the patient's tolerance, especially in patients who do not tolerate standard dose titration</li> </ul>
<ul style="list-style-type: none"> <li>Apremilast as 20 mg twice daily or 30 mg once daily can be considered as a long-term maintenance therapy in patients who have achieved clearance of their lesions</li> </ul>

treat areas. However, its lower effectiveness in psoriasis compared with other new-generation drugs and certain tolerability aspects in the initial period should be considered as disadvantages. But as the availability of newer formulations, such as 10 mg and 20 mg, in the Indian pharmaceutical market widens, so too will the scope of its use in dose titrations in various settings and as maintenance therapy. In the end, considering the chronicity of the disease and the comparative efficacy, safety, and use of this drug in comorbid conditions, apremilast has become one of the favorable options in the armamentarium of psoriasis management.

## Acknowledgment

We express our sincere gratitude to the team of the global medical affairs department of Glenmark Pharmaceuticals Limited for help in data collation, analysis, and preparation of the manuscript of this expert consensus.

## Funding

This consensus was carried out with a grant from Glenmark Pharmaceuticals Limited, as an unrestricted educational grant.

## Disclosure

The authors declare that they have no conflicts of interest. The design or procedure of the consensus and the content of the paper are in no way influenced by the grant provider.

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