Apremilast Tablets 10, 20, 30 mg

Biocon

ALIZAP® एलिज़ैप

COMPOSITION:

Apremilast Tablets 10 mg
Each film coated tablet contains:
Apremilast 10 mg
Excipients q.s.
Colours: Red Oxide of Iron Lake and Titanium dioxide IP

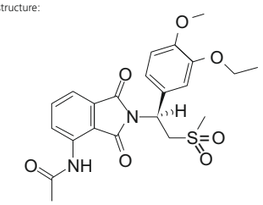
Apremilast Tablets 20 mg
Each film coated tablet contains:
Apremilast 20 mg
Excipients q.s.
Colours: Yellow Oxide of Iron Lake and Titanium dioxide IP

Apremilast Tablets 30 mg
Each film coated tablet contains:
Apremilast 30 mg
Excipients q.s.
Colours: Sunset Yellow Lake and Titanium dioxide IP

Description:
Apremilast is an oral phosphodiesterase 4 (PDE 4) inhibitor. Its empirical formula is $C_{22}H_{24}N_2O_7S$ and the molecular weight is 460.5

Chemical name:
Apremilast is known chemically as N-[2-((1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2, 3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide.

Structural formula:
Apremilast has the following structure:



Clinical Pharmacology:
Pharmacotherapeutic group: immunosuppressant's, selective immunosuppressant's.

ATC code: L04AA32

Mechanism of action:
Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels. Which in turn down-regulates the inflammatory response by modulating the expression of TNF alpha, IL -23, IL 17 and other inflammatory cytokines, Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10.These pro and anti-inflammatory mediators have been implicated in psoriatic arthritis and psoriasis.

Pharmacodynamic effects:
In clinical trials in patients with psoriasis, Apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration and expression of pro-inflammatory genes, including those for inducible nitric oxide synthase (iNOS) IL 12/IL 23 p40, IL 17A, IL 22 and IL 8.
Apremilast administered at doses of up to 50 mg BID did not prolong the QT interval in healthy subjects.

Clinical studies:
The safety and efficacy of Apremilast were evaluated in two multicenter, randomized, double-blind, placebo controlled studies (ESTEEM 1and ESTEEM 2) which enrolled a total of 1257 patients with moderate to severe plaque psoriasis who had a body surface area (BSA) involvement of ≥ 10%, Psoriasis Area and Severity Index (PASI) score ≥ 12, static Physician Global Assessment (sPGA) of ≥ 3 (moderate or severe), and who were candidates for phototherapy or systemic therapy.

These studies had a similar design through Week 32. In both studies patients were randomized 2:1 to Apremilast 30 mg BID or placebo for 16 weeks (placebo-controlled phase) and from Weeks 16-32, all patients received Apremilast 30 mg BID (maintenance phase). During the Randomized Treatment Withdrawal Phase (Weeks 32-52),patients originally randomized to Apremilast who achieved at least a 75% reduction in their PASI score (PASI 75) (ESTEEM 1) or a 50% reduction in their PASI score (PASI 50) (ESTEEM 2)were re-randomized at Week 32 to either placebo or Apremilast 30 mg BID. Patients who were re randomized to placebo and who lost PASI 75 response (ESTEEM 1) or lost 50% of the PASI improvement at Week 32 compared to baseline (ESTEEM 2) were retreated with Apremilast 30 mg BID. Patients who did not achieve the designated PASI response by week 32, or who were initially randomized to placebo remained on Apremilast until Week 52. The use of low potency topical corticosteroids on the face, axillae, and groin, coal tar shampoo and/or salicylic acid scalp preparations was permitted throughout the studies . In addition, at Week 32, subjects who did not achieve a PASI 75 response in ESTEEM 1,or a PASI 50 response in ESTEEM 2, were permitted to use topical psoriasis therapies and/or phototherapy in addition to Apremilast 30 mg BID treatment.

In both studies the primary endpoint was the proportion of patients who achieved PASI 75 at Week 16. The major secondary endpoint was the proportion of patients who achieved a sPGA score of clear (0) or almost clear (1) at Week 16.

The mean baseline PASI score was 19.07 (median 16.80), and the proportion of patients with sPGA score of 3 (moderate) and 4 (severe) at baseline was 70.0% and 29.8%, respectively with a mean baseline BSA involvement of 25.19% (median 21.0%). Approximately 30% of all patients had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis (including treatment failures), with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one third of patients had not received prior phototherapy, conventional systemic or biologic therapy. A total of 18% of patients had a history of psoriatic arthritis.

The proportion of patients achieving PASI 50, PASI 75 and PASI 90 responses, and sPGA score of clear (0) or almost clear (1), are presented in Table 1 below. Treatment with Apremilast resulted in significant improvement in moderate to severe plaque psoriasis as demonstrated by the proportion of patients with PASI 75 response at week 16 compared to placebo. Clinical improvement measured by sPGA, PASI 50 and PASI 90 responses were also demonstrated at Week 16. In addition, Apremilast demonstrated a treatment benefit across multiple manifestations of psoriasis including pruritus, nail disease, scalp involvement and quality of life measures.

Table 1: Clinical response at week 16 in studies ESTEEM 1 and ESTEEM 2 (FAS*, LOCF[3])

	ESTEEM 1		ESTEEM 2	
	Placebo	**30 mg BID APR***	**Placebo**	**30 mg BID APR***
N	282	562	137	274
PASIc 75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGAd of clear or Almost clear, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)
PASI 50, n (%)	48 (17.0)	330 (58.7)	27 (19.7)	152 (55.5)
PASI 90, n (%)	1 (0.4)	55 (9.8)	2 (1.5)	24 (8.8)
Percent change BSAe (%) Mean ± SD	- 6.9 ± 38.95	- 47.8 ± 38.48	- 6.1 ± 47.57	- 48.4 ± 40.78
Change in pruritus VASf (mm), Mean ± SD	- 7.3 ±27.08	- 31.5 ± 32.43	- 12.2 ± 30.94	- 33.5 ±35.46
Change in DLQIg, Mean ± SD	- 2.1 ± 5.69	- 6.6 ± 6.66 2.39	- 2.8 ± 7.22	- 6.7 ± 6.95
Change in SF - 36 MCS h, Mean ± SD	- 1.02 ± 9.161	2.39 ± 9.504	0.00 ± 10.498	2.58 ± 10.129

*p< 0.0001 for apremilast vs placebo, except for ESTEEM 2 PASI 90 end Change in SF-36 MCS where p=0.0042 and p=0.0078, respectively.
FAS= Full Analysis Set
[3]LOCF = Last Observation Carried forward
[c]PASI =Psoriasis Area and Severity Index
[d]PGA = Static Physician Global Assessment
[e]BSA = Body Surface Area
[f]VAS = Visual Analog Scale: O =best, 100 = worst
[g]DLQI = Dermatology Life Quality Index: 0 = best, 30 = worst
[h]SF-36 MCS = Medical Outcome Study Short Form 36-Item Health Survey, Mental Component Summary

The Clinical benefit of Apremilast was demonstrated across multiple subgroups defined by baseline demographics and baseline clinical disease characteristics (Including psoriasis disease duration and patients with a history of psoriatic arthritis). The clinical benefit of Apremilast was also demonstrated regardless of prior psoriasis medication usage and response to prior psoriasis treatments. Similar response rates were observed across all weight ranges.

Response to Apremilast was rapid, with significantly greater improvements in the signs and symptoms of psoriasis, including PASI, skin discomfort/pain and pruritus, compared to placebo by Week 2. In general, PASI responses were achieved by Week 16 and were maintained through Week 32.

In both studies, the mean percent improvement in PASI from baseline remained stable during the Randomized Treatment Withdrawal Phase for patients re-randomized to apremilast at Week 32 (Table 2).

Table 2: Persistence of effect among subjects randomized to APR 30 BID at week 0 and re-randomized to APR 30 BID at week 32 to week 52.

	Time point	ESTEEM 1	ESTEEM 2
		Patients who achieved PASI 75 at week 32	Patients who achieved PASI 50 at week 32
Percent change in PASI from baseline, mean (%) ± SD[c]	Week 16	-77.7 ± 20.30	- 69.7 ± 24.23
	Week 32	- 88 ± 8.30	- 76.7 ± 13.42
	Week 52	- 80.5 ±12.60	- 74.4 ± 18.91
Change in DLQI from baseline, mean ± SD[c]	Week 16	- 8.3 ± 6.26	- 7.8 ± 6.41
	Week 32	- 8.9 ± 6.68	- 7.7 ± 5.92
	Week 52	- 7.8 ± 5.75	- 7.5 ± 6.27
Proportion of subjects with scalp psoriasis PGA (ScPGA) 0 or 1, n/N(%)[b]	Week 16	40/48 (83.3)	21/37 (56.8)
	Week 32	39/48 (81.3)	27/37 (73.0)
	Week 52	35/48 (72.9)	20/37 (54.1)

[a]includes subjects re randomized to APR 30 BID at Week 32 with a baseline value and a post-baseline value at the evaluated study week.
[b]N is based on subjects with moderate or greater scalp psoriasis at baseline who were re-randomized to APR 30 BID at Week 32. Subjects with missing data were counted as non-responders.

In Study ESTEEM 1, approximately 61% of patients re-randomized to Apremilast at Week 32 had a PASI 75 response at Week 52. Of the patients with at least a PASI 75 response who were re-randomized to placebo at Week 32 during a Randomized Treatment Withdrawal Phase, 11.7% were PASI 75 responders at Week 52. The median time to loss of PASI 75 response among the patients re-randomized to placebo was 5.1 weeks.

In Study ESTEEM 2, approximately 80.3% of patients re-randomized to Apremilast at Week 32 had a PASI 50 response at Week 52. Of the patients with at least a PASI 50 response who were re-randomized to placebo at Week 32, 24.2% were PASI 50 responders at Week 52.The median time to loss of 50% of their Week 32 PASI improvement was 12.4 weeks.

After randomized withdrawal from therapy at Week 32, approximately 70% of patients in Study ESTEEM 1, and 65.6% of patients in Study ESTEEM 2, regained PASI 75 (ESTEEM 1) or PASI 50 (ESTEEM 2) responses after re-initiation of Apremilast treatment. Due to the study design the duration of re-treatment was variable, and ranged from 2.6 to 22 .1 weeks.

In Study ESTEEM 1, patients randomized to apremilast at the start of the study who did not achieve a PASI 75 response at Week 32 were permitted to use concomitant topical therapies and/or UVB phototherapy between Weeks 32 to 52. Of these patients, 12% achieved a PASI 75 response at Week 52 with Apremilast plus topical and/or phototherapy treatment.

In Studies ESTEEM 1 and ESTEEM 2, significant improvements (reductions) in nail psoriasis, as measured by the mean percent change In Nail Psoriasis Severity Index (NAPSI) from baseline, were observed in patients receiving Apremilast compared to placebo-treated patients at Week 16 (p< 0.0001 and p=0.0052, respectively). Further improvements in nail psoriasis were observed at Week 32 in patients continuously treated with Apremilast.

In Studies ESTEEM 1 and ESTEEM 2, significant improvements in scalp psoriasis of at least moderate severity (≥3), measured by the proportion of patients achieving Scalp Psoriasis Physician's Global Assessment (ScPGA) of clear (0) or minimal (1) at Week 16, were observed in patients receiving Apremilast compared to placebo-treated patients (p< 0.0001 for both studies). The improvements were generally maintained in subjects who were re-randomized to Apremilast at Week 32 through Week 52 (Table 2).

In Studies ESTEEM 1 and ESTEEM 2, significant improvements in quality of life as measured by the Dermatology Life Quality Index (DLQI) and the SF-36v2MCS were demonstrated in patients receiving Apremilast compared with placebo-treated patients (Table 1). Improvements in DLQI were maintained through Week 52 in subjects who were randomized to Apremilast at Week 32 (Table 2). In addition, in Study ESTEEM 1, significant improvement in the Work Limitation Questionnaire (WLQ-25) Index was achieved in patients receiving Apremilast compared to placebo.

Pharmacokinetics:

Absorption
Apremilast when taken orally is absorbed with an absolute bioavailability of ~73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of ~2.5 hours. Co-administration with food does not alter the extent of absorption of Apremilast.

Distribution
Human plasma protein binding of Apremilast is approximately 68% . Mean apparent volume of distribution (Vd) is 87 L.

Metabolism
Following oral administration in humans, apremilast is a major circulating component (45%) followed by inactive metabolite M12 (39%), a glucuronide conjugate of O-demethylated apremilast. It is extensively metabolized in humans with up to 23 metabolites identified in plasma, urine and feces. Apremilast is metabolized by both cytochrome (CYP) oxidative metabolism with subsequent glucuronidation and non-CYP mediated hydrolysis. *In vitro*, CYP metabolism of Apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6.

Elimination
The plasma clearance of Apremilast is about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 6-9 hours. Following oral administration of radio-labeled apremilast, about 58% and 39% of the radioactivity is recovered in urine and feces, respectively, with about 3% and 7% of the radioactive dose recovered as Apremilast in urine and feces, respectively.

INDICATIONS and USAGE:
Apremilast Tablets are Indicated for treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

For the use of Registered Dermatologist and Medical Practitioner or Hospital or Laboratory

Apremilast Tablets 10, 20, 30 mg

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DOSAGE AND ADMINISTRATION:
Treatment with Apremilast should be initiated by specialists experienced in the diagnosis and treatment of psoriasis.
Posology
The recommended initial dosage titration of Apremilast from Day 1 to Day 5 is shown in Table 3. Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy.

Apremilast can be administered without regard to meals. Do not crush, split, or chew the tablets.

Table 3: Dosage Titration Schedule.

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

If patients miss a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose, the missed dose should not be taken and the next dose should be taken at the regular time

During pivotal trials the greatest improvement was observed within the first 24 weeks of treatment. If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis.

Specific Populations:

Hepatic Impairment: The pharmacokinetics of Apremilast is not affected by moderate or severe hepatic impairment.

Renal Impairment: The pharmacokinetics of Apremilast is not affected by mild or moderate renal impairment. In 8 subjects with severe renal impairment administered a single dose of 30 mg Apremilast, the AUC and C_{max} of Apremilast increased by approximately 88% and 42%, respectively.

Age: A single oral dose of 30 mg Apremilast was studied in young adults and elderly healthy subjects. The Apremilast exposure in elderly subjects (65 to 85 years of age) was about 13% higher in AUC and about 6% higher in C_{max} than in young subjects (18 to 55 years of age).

Gender: In pharmacokinetic studies in healthy volunteers, the extent of exposure in females was about 31% higher and C_{max} was about 8% higher than that in male subjects.

Race and Ethnicity: The pharmacokinetics of Apremilast in Chinese and Japanese healthy male subjects is comparable to that in Caucasian healthy male subjects. In addition, Apremilast exposure is similar among Hispanic Caucasians, non-Hispanic Caucasians, and African Americans.

WARNING AND PRECAUTIONS

Diarrhoea, Nausea, and Vomiting
There have been post marketing reports of severe diarrhoea, nausea, and vomiting associated with the use of Apremilast. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhoea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhoea or vomiting. Patients who reduced dosage or discontinued Apremilast generally improved quickly. Consider Apremilast dose reduction or suspension if patients develop severe diarrhoea, nausea, or vomiting.

Depression
Treatment with Apremilast is associated with an increase in adverse reactions of depression. Before using Apremilast in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with Apremilast in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider.
Prescribers should carefully evaluate the risks and benefits of continuing treatment with Apremilast if such events occur.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of subjects treated with Apremilast reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/1308) of subjects treated with Apremilast discontinued treatment due to depression compared with none in placebo-treated subjects (0/506). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to Apremilast, compared to none in placebo-treated subjects (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving Apremilast, compared to 0.2% (1/506) in placebo treated subjects. In the clinical trials, one subject treated with Apremilast attempted suicide while one who received placebo committed suicide.

Psoriatic arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of subjects treated with Apremilast reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with Apremilast discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/495). Depression was reported as serious in 0.2% (3/1441) of subjects exposed to Apremilast, compared to none in placebo treated subjects (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of subjects while receiving Apremilast, compared to none in placebo treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in Apremilast-treated subjects.

Weight Decrease
During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (49/497) of subjects treated with Apremilast 30 mg twice daily compared to 3.3% (16/495) treated with placebo.

During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of subjects treated with Apremilast compared to 5% (19/382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16/784) of subjects treated with Apremilast 30 mg twice daily compared to 1% (3/382) subjects treated with placebo. Patients treated with Apremilast should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of Apremilast should be considered.

NON CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies were conducted in mice and rats with Apremilast to evaluate its carcinogenic potential. No evidence of Apremilast induced tumors was observed in mice at oral doses up to 8.8 times the Maximum Recommended Human Dose (MRHD) on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1 times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively).

Apremilast tested negative in the Ames assay, *in vitro* chromosome aberration assay of human peripheral blood lymphocytes, and the *in vivo* mouse micronucleus assay.

In a fertility study of male mice, Apremilast at oral doses up to approximately 3 times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, Apremilast was administered at oral doses of 10, 20, 40, or 80 mg/kg/day. At doses ≥1.8-times the MRHD (≥20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early post implantation losses. There was no effect of Apremilast approximately 1.0-times the MRHD (10 mg/kg/day).

ADVERSE EFFECTS
Clinical trial 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.

Psoriasis Clinical Trials
The safety of Apremilast was assessed in 1426 subjects in 3 randomized, double-blind, placebo-controlled trials in adult subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Subjects were randomized to receive Apremilast 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days.
Subjects ranged in age from 18 to 83 years, with an overall median age of 46 years.
Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking Apremilast were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for subjects treated with Apremilast 30 mg twice daily and 4.1% for placebo-treated subjects.

Table 4: Adverse Reactions Reported in ≥1% of Subjects on Apremilast and With Greater Frequency than in Subjects on Placebo; up to Day 112 (Week 16).

Preferred Term	**Placebo (N=506) n (%)**	**Apremilast 30 mg BID (N=920) n (%)**
Diarrhea	32 (6)	160 (17)
Nausea	35 (7)	155 (17)
Upper respiratory tract infection	31 (6)	84 (9)
Tension headache	21 (4)	75 (8)
Headache	19 (4)	55 (6)
Abdominal pain*	11 (2)	39 (4)
Vomiting	8 (2)	35 (4)
Fatigue	9 (2)	29 (3)
Dyspepsia	6 (1)	29 (3)
Decreased appetite	5 (1)	26 (3)
Insomnia	4 (1)	21 (2)
Back pain	4 (1)	20 (2)
Migraine	5 (1)	19 (2)
Frequent bowel movements	1 (0)	17 (2)
Depression	2 (0)	12 (1)
Bronchities	2 (0)	12 (1)
Tooth abscess	0 (0)	10 (1)
Folliculitis	0 (0)	9 (1)
Sinus headache	0 (0)	9 (1)

*Two subjects treated with Apremilast experienced serious adverse reaction of abdominal pain.
Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) subjects following discontinuation of treatment with Apremilast.

Drug Interactions
In vitro data: Apremilast is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 and not an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4. Apremilast is a substrate, but not an inhibitor of P-glycoprotein (P-gp) and is not a substrate or an inhibitor of organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP).
Drug interaction studies were performed with Apremilast and CYP3A4 substrates (oral contraceptive containing ethinyl estradiol and norgestimate), CYP3A and P-gp inhibitor (ketoconazole), CYP450 inducer (rifampin) and frequently co-administered drug in this patient population (methotrexate).
No significant pharmacokinetic interactions were observed when 30-mg oral Apremilast was administered with either oral contraceptive, ketoconazole, or methotrexate. Co-administration of the CYP450 inducer rifampin (600 mg once daily for 15 days) with a single oral dose of 30 mg apremilast resulted in reduction of Apremilast AUC and Cmax by 72% and 43%, respectively.

USE IN SPECIFIC POPULATIONS

Women of childbearing potential
Pregnancy should be excluded before treatment can be initiated. Women of childbearing potential should use an effective method of contraception to prevent pregnancy during treatment.

Pregnancy
There are limited data about the use of Apremilast in pregnant women

Apremilast is contraindicated during pregnancy. Effects of Apremilast on pregnancy included embryofetal loss in mice and monkeys, and reduced fetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. No such effects were observed when exposure in animals was at 1.3-fold the clinical exposure

Breast-feeding
Apremilast was detected in milk of lactating mice. It is not known whether Apremilast, or its metabolites, are excreted in human milk. A risk to the breastfed infant cannot be excluded, therefore Apremilast should not be used during breast feeding.

Fertility
No fertility data is available in humans. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels 3-fold clinical exposure and in females at exposure levels 1-fold clinical exposure.

EFFECTS ON ABILITY TO DRIVE & OPERATE MACHINES
Apremilast has no influence on the ability to drive and use machines

OVERDOSAGE
Apremilast was studied in healthy subjects at a maximum total daily dose of 100 mg (given as 50 mg BID) for 4.5 days without evidence of dose limiting toxicities. In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment is instituted. In the event of overdose, symptomatic and supportive care is advised.

STORAGE CONDITIONS:
Store below 30°C, Protect from light & moisture.
Keep out of reach of children.

Presentation: Starter Pack: Each blister contains 13 Tablets,
4 Tablets of Apremilast Tablets 10 mg, 4 Tablets of Apremilast Tablets 20 mg, 5 Tablets of Apremilast Tablets 30 mg
Each Blister pack contain 10x10 Tablets

Shelf Life: Refer blister/carton/outer carton.

References:

1. Papp K, Reich K, Leonardi L C, Kircik L et al., Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial. JAAD, 2015; 73:37-49.
2. Paul C et al., Efficacy and safety of apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis over 52 weeks: results of a phase III, randomized, controlled trial. British journal of dermatology. 2015 Dec; 173 (6): 1355-6.

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