MINIMUM FONT SIZE: 7 pt

SAME SIZE ARTWORK
LEAFLET SIZE : 150 mm x 360 mm
FOLDING SIZE: 150 mm x 35 mm

75 mm

35 mm

For the use only of a registered Medicinal Practitioner or a hospital or a Laboratory

glenmark
Aprezo™

Apremilast 10 mg/20 mg/30 mg

Apremilast Tablets 10 mg
Each film coated tablet contains
Apremilast .....10 mg

Apremilast Tablets 20 mg
Each film coated tablet contains
Apremilast .....20 mg

Apremilast Tablets 30 mg
Each film coated tablet contains
Apremilast .....30 mg

PHARMACEUTICAL FORM
Film-coated tablet

CLINICAL PARTICULARS

Therapeutic indications
Apremilast is indicated for:
- Apremilast, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.
- The treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Posology and Method of Administration

Posology:
Treatment with apremilast should be initiated by specialists experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis.

The recommended dose of apremilast is 30 mg twice daily taken orally approximately 12 hours apart. An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration.

Table 1: 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.

No dosage adjustment is necessary for elderly patients.

No dose adjustment is needed in patients with mild renal impairment. There are limited data on moderate renal impairment. Apremilast should be dose reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockroft-Gault equation). For initial dosage titration in this group, it is recommended that apremilast be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped.

Dose adjustment is not required in patients with hepatic impairment. The safety of apremilast was not evaluated in PsA or PSOR patients with hepatic impairment.

In the event of intolerable adverse events, interruption or discontinuation of apremilast should be considered.

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

Contraindications

Apremilast is contraindicated:
- In patients with known hypersensitivity to the active substance or to any of the excipients .
- During pregnancy and in nursing women.

Special Warnings and Precautions for Use

Paediatric use

The safety and effectiveness of apremilast has not been established in patients under the age of 18 years.

Use in the elderly
No overall differences were observed in the safety or efficacy profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age.

No dosage adjustment is necessary for elderly patients.

Weight Decrease
In some patients treatment with apremilast has been associated with weight decrease. 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.

Diarrhea, 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. Patients who reduced dosage or discontinued apremilast generally improved quickly. Consider apremilast dose reduction or suspension if patients develop severe diarrhea, nausea or vomiting.

Depression
Treatment with apremilast is associated with an increase in occurrences of depression (see Adverse Effects section). Before using apremilast in patients with a history of depression and/or suicidal thoughts or behaviour, 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.

Renal Function
Assessment of renal function is recommended prior to initiation of apremilast.

Carcinogenicity
No evidence of treatment-related tumours following oral treatment with apremilast.

Genotoxicity
Apremilast is not genotoxic.

Use in patients with Lactose Intolerance
Apremilast tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interaction with other medicinal products and other forms of interaction
Apremilast has not been studied in combination with cyclosporin or biologic therapies.

Effect of apremilast on other medicinal products
There was no pharmacokinetic drug-drug interaction between apremilast and methotrexate. Apremilast can be co-administered with methotrexate.

There was no pharmacokinetic drug-drug interaction between apremilast and oral contraceptives containing ethinyl estradiol and norgestimate. apremilast can be taken with oral contraceptives without clinically relevant drug-drug interaction.

Apremilast is not an inhibitor or inducer of cytochrome P450 enzymes. Hence, apremilast coadministered with substrates of CYP enzymes is unlikely to affect the clearance and exposure of drugs that are metabolized by CYP enzymes.

Apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC>50μM).

Apremilast has little to no inhibitory effect (IC_{50}>10μM) on 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) and is not a substrate for these transporters.

Hence, clinically relevant drug-drug interactions are unlikely when apremilast is co-administered with drugs that are substrates or inhibitors of these transporters.

Effect of other medicinal products on apremilast
Co-administration of apremilast with multiple doses of rifampicin resulted in a decrease in apremilast area under-the concentration time curve (AUC) and maximum serum concentration (C_{max}) by approximately 72% and 43%, respectively. Apremilast exposure is decreased when administered concomitantly with strong inducers of CYP3A4 (e.g. rifampicin, phenobarbitone, carbamazepine, phenytoin and St. John's Wort) and may result in reduced clinical response.

Ketoconazole co-administration increased mean apremilast $AUC_{0-\infty}$ and C_{max} by approximately 36% and by 5%, respectively, which is not clinically meaningful. Apremilast can be co-administered with a potent CYP3A4 inhibitor like ketoconazole.

Fertility, Pregnancy and lactation

Use in Pregnancy
Apremilast is contraindicated in pregnant women, and should not be used in women attempting to become pregnant.

Use during lactation
Apremilast was detected in milk of lactating mice.

It is not known whether apremilast or its metabolites are excreted in human milk. Therefore, the use of apremilast is contraindicated in mothers who are breast-feeding.

Effects on fertility
No fertility data is available in humans.

Effects on ability to drive and use machines
Apremilast has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions with apremilast in PsA and PSOR are gastrointestinal (GI) disorders including diarrhoea (15.7%) and nausea (13.9%). The other most commonly reported adverse reactions include upper respiratory tract infections (8.4%), headache (7.9%), and tension headache (7.2%) and are mostly mild to moderate in severity.

The most commonly reported adverse drug reactions with apremilast in BD are diarrhoea (41.3%), nausea (19.2%), headache (14.4%), upper respiratory tract infection (11.5%), upper abdominal pain (8.7%), vomiting (8.7%) and back pain (7.7%) and are mostly mild to moderate in severity.

The gastrointestinal adverse reactions generally occurred within the first 2 weeks of treatment and usually resolved within 4 weeks.

Hypersensitivity reactions are uncommonly observed.

Tabulated list of adverse reactions
The adverse reactions observed in patients treated with apremilast are listed below by system organ class (SOC) and frequency for all adverse reactions. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The adverse drug reactions were determined based on data from the apremilast clinical development programme and post-marketing experience.

Table Summary of adverse reactions in psoriatic arthritis (PsA), psoriasis (PSOR) and Behçet's disease (BD)

System Organ Class	Frequency	Adverse reaction
Very common	Very common	Upper respiratory tract infection[a]
		Bronchitis
		Nasopharyngitis*
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Decreased appetite*
		Insomnia
		Depression
	Uncommon	Suicidal ideation and behaviour
	Very common	Headache*,[a]
		Migraine*
		Tension headache*
Respiratory, thoracic, and mediastinal disorders	Common	Cough

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		Diarrhoea*
		Nausea*
		Vomiting*
		Dyspepsia
		Frequent bowel movements
		Upper abdominal pain*
		Gastroesophageal reflux disease
	Uncommon	Gastrointestinal haemorrhage
		Rash
		Urticaria
	Not known	Angioedema
Musculoskeletal and connective tissue disorders	Common	Back pain*
General disorders and administration site conditions	Common	Fatigue
Investigations	Uncommon	Weight decrease

*At least one of these adverse reactions was reported as serious
a Frequency reported as common in PSA and PSOR

Description of selected adverse reactions

Psychiatric disorders
Uncommon cases of suicidal ideation and behaviour, as well as completed suicide were reported. Patients and caregivers should be instructed to notify the prescriber of any suicidal ideation.

Body weight loss
In some patients treatment with apremialst has been associated with weight decrease. Patients treated with apremialst should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of apremialst should be considered.

Special populations

Elderly patients
From post-marketing experience, elderly patients ≥ 65 years of age may be at a higher risk of complications of severe diarrhoea, nausea and vomiting.

Patients with hepatic impairment
The safety of apremilast was not evaluated in PsA, PSOR or BD patients with hepatic impairment.

Patients with renal impairment
The safety profile observed in patients with mild renal impairment was comparable to patients with normal renal function. The safety of apremilast was not evaluated in PsA, PSOR or BD patients with moderate or severe renal impairment.

Overdose
In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: Selective immunosuppressants; , ATC code: L04AA32

Mechanism of action
Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, 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 (PsA) and psoriasis (PSOR).

Clinical Pharmacodynamics
Apremilast significantly modulated, but did not fully inhibit, plasma protein levels of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, MMP-3, and TNF-α in patients with psoriatic arthritis. There was a decrease in plasma protein levels of IL-17 and IL-23, and an increase in IL-10. Apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro-inflammatory genes, including inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-17A, IL-22 and IL-8 in patients with psoriasis.

Cardiac Electrophysiology
Apremilast administered at doses of up to 50 mg twice daily did not prolong the QT interval in healthy patient.

Pharmacokinetic properties

Absorption
Apremilast is well absorbed with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours. Apremilast pharmacokinetics is linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 100 mg daily. Accumulation is minimal when apremilast is administered once daily and approximately 53% in healthy subjects and 68% in patients with psoriasis when administered twice daily. Co-administration with food does not alter the bioavailability; therefore, apremilast can be administered with or without food.

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

Metabolism
Apremilast is extensively metabolised by both CYP and non-CYP mediated pathways including oxidation, hydrolysis, and conjugation, suggesting inhibition of a single clearance pathway is not likely to cause a marked drug-drug interaction. Oxidative metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. Apremilast is the major circulating component following oral administration. Apremilast undergoes extensive metabolism with only 3% and 7% of the administered drug recovered in urine and faeces, respectively. The major circulating metabolite, M12, is the glucuronide conjugate of O-demethylated apremilast which is inactive.

Elimination
The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 9 hours. There is approximately 30% reduction in apremilast clearance observed in female subjects compared to male subjects. No dose adjustment is necessary for female patients. Following oral administration of radiolabeled apremilast, about 58% and 39% of the radioactivity is recovered in urine and faeces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and faeces, respectively.

Specific Populations

Renal impairment
No formal studies have been conducted in subjects with mild to moderately impaired renal function. In subjects with severe renal impairment administered a single dose of 30 mg apremilast, the AUC and Cmax of apremilast increased by approximately 89% and 42%, respectively. See Posology and Method of Administration section for dose adjustments for patients with severe renal impairment.

Hepatic impairment
The pharmacokinetics of apremilast and its major metabolite M12 is not affected by moderate or severe hepatic impairment. No dosage adjustment is necessary for patients with hepatic impairment. The pharmacokinetics of apremilast is not affected by moderate or severe hepatic impairment.

Elderly
No overall differences were observed in the safety or efficacy profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age.

No dosage adjustment is necessary for elderly patients.

PHARMACEUTICAL PARTICULARS

List of excipients
Inactive Ingredients: Lactose Monohydrate, Crospovidone, Magnesium Stearate, Corn Starch dried Opadry White, Purified water, Hypromellose, Titanium Dioxide, Macrogol

Incompatibilities
Not Applicable.

Shelf life
24 Months

Special precautions for storage
Store below 30ºC.

Product Description

Dosage Form	Strength	Description
Film-coated Tablets	10 mg	White coloured, round shaped, biconvex film coated tablet, with beveled edges, debossed with '96' on one side and 'G' on another side.
	20 mg	White coloured, round shaped, biconvex film coated tablet, with beveled edges, debossed with '56' on one side and 'G' on another side.
	30 mg	White coloured, round shaped, biconvex film coated tablet, with beveled edges, debossed with '510' on one side and 'G' on another side.

PRESENTATION

TWO WEEK STARTER PACK OF 27 TABLETS
13-tablets blister titration pack containing:
(4) 10-mg,
(4) 20-mg, and
(5) 30-mg tablets with
an additional (14) 30-mg tablets

28 DAYS STARTER PACK OF 55 TABLETS
13-tablets blister titration pack containing:
(4) 10-mg,
(4) 20-mg, and
(5) 30-mg tablets with
An additional (42) 30-mg tablets

28 COUNT CARTON
Two 30-mg blisters containing
(14) 30- mg tablets

56 COUNT CARTON
Four 30-mg blisters containing
(14) 30- mg tablets

PRODUCT REGISTRATION NUMBER(S)
10mg : MAL22086024AZ
20mg: MAL22086025AZ
30mg: MAL22086026AZ

DATE OF REVISION
10/10/2024

Product Registration Holder:
Glenmark Pharmaceuticals (Malaysia)
Sdn Bhd (660397-W)
D-31-02, Menara Suezcap 1,
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Manufactured by:
glenmark
Pharmaceuticals Ltd.
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TM - Trade Mark

MY
PE68463

PHARMACODE: 8463

ICONGRAPHICS CODE: E40507

GLENMARK PHARMACEUTICALS LTD.							This is an Important Document. Please handle it Carefully, Initials & Remarks only in Space Provided below.
PRODUCT	:	**GLENMARK APREZO TABLET**					
Product Code	:	**PE68463**		Version	:		
Item	:	**LEAFLET**		Location	:	**INDORE**	

Reason For Changing of A/W:

DEPARTMENT	CHECK LIST FOR APPROVAL	APPROVED BY:
Packaging Development	Item code, Version,Consistency of Design,over print area,Pack Size,Carton size,label size,foil width, repeat length,specification & Layout	Riddhi Patil Digitally signed by Riddhi Patil Date: 2024.12.03 16:48:53 +05'30'
Regulatory affair	Regulatory Text.	
Corporate QA	Entire Text Matter	
Site QA	Entire Text Matter	
Site Production	EMachine Suitability	

Points / notes for correction :

PANTONE SHADE

PANTONE BLACK PROCESS C

Supersedes Artwork Code