4000002830

Apezla

(Apremilast Tablets)

Product specifications: Innovator
Apezla Tablets 28 Days Starter Pack
Product contains Lactose
Each Pack contains
Apezla Tablets 10 mg: Each film coated tablet contains: Apremilast ..... 10 mg
Apezla Tablets 20 mg: Each film coated tablet contains: Apremilast ..... 20 mg
Apezla Tablets 30 mg: Each film coated tablet contains: Apremilast ..... 30 mg
Apezla Tablets 30 mg
Each film coated tablet contains: Apremilast ..... 30 mg
Product contains Lactose

DESCRIPTION

The active ingredient in Apezla tablets is apremilast. Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. 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. Its empirical formula is $C_{22}H_{24}N_2O_7S$ and the molecular weight is 460.5.

CLINICAL PARTICULARS

Therapeutic indications

Psoriatic arthritis

Apezla (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.

Psoriasis

Apezla (apremilast) is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

Behçet's disease

Apezla (apremilast) is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

Posology and method of administration

Posology

The recommended dose of Apezla (apremilast) is 30 mg taken orally twice daily, approximately 12 hours apart (morning and evening). An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy.

Table 1. Dose 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
10mg	10mg	10mg	10mg	20mg	20mg	20mg	20mg	30mg	30mg	30mg

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 for psoriatic arthritis and psoriasis and within the first 12 weeks of treatment for Behçet's disease. If a patient shows no evidence of therapeutic benefit after this time period, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis.

Special populations:

Elderly patients: No dose adjustment is required for this patient population.

Patients with renal impairment: No dose adjustment is needed in patients with mild and moderate renal impairment. The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute). For initial dose 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.

Patients with hepatic impairment: No dose adjustment is necessary for patients with hepatic impairment.

Paediatric population: The safety and efficacy of apremilast in children aged 0 to 17 years have not been established. No data are available.

Method of administration: Apezla (aprimelast) is for oral use. Apezla (aprimelast) can be administered with no food restrictions. Apezla (aprimelast) should be taken as whole, do not crush, split, or chew the tablets.

Contraindication

- Apremilast is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation.
- Pregnancy

Warnings 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 diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued apremilast generally improved quickly. Consider apremilast dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

Psychiatric disorders: Apremilast is associated with an increased risk of psychiatric disorders such as insomnia and depression. Instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression. The risks and benefits of starting or continuing treatment with apremilast should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended. If patients suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with apremilast.

Underweight patients: Patients who are underweight at the start of treatment should have their body weight monitored regularly. In the event of unexplained and clinically significant weight loss, these patients should be evaluated by a medical practitioner and discontinuation of treatment should be considered.

Lactose content:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Use in specific populations

Fertility, Pregnancy and lactation:

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 embryofoetal loss in mice and monkeys, and reduced foetal 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.

Drug Interactions:

- Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin and St. John's Wort) with apremilast is not recommended.
- In clinical studies, apremilast has been administered concomitantly with topical therapy (including corticosteroids, coal tar shampoo and salicylic acid scalp preparations) and UVB phototherapy.
- There was no clinically meaningful interaction between ketoconazole and apremilast. Apremilast can be co-administered with a potent CYP3A4 inhibitor such as ketoconazole.
- There was no pharmacokinetic interaction between apremilast and methotrexate in psoriatic arthritis patients. Apremilast can be co-administered with methotrexate.
- There was no pharmacokinetic interaction between apremilast and oral contraceptives containing ethinyl estradiol and norgestimate. Apremilast can be co-administered with oral contraceptives.

Carcinogenesis, Mutagenesis:

Carcinogenicity studies in mice and rats showed no evidence of carcinogenicity related to treatment with apremilast. Apremilast is not genotoxic. Apremilast did not induce mutations in an Ames assay or chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. Apremilast was not clastogenic in an in vivo mouse micronucleus assay at doses up to 2,000 mg/kg/day.

Other studies:

There is no evidence of immunotoxic, dermal irritation, or phototoxic potential.

Adverse Reactions:

Summary of the safety profile:

- The most commonly reported adverse reactions with apremilast in psoriatic arthritis and psoriasis 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 Behçet's disease 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.

Summary of adverse reactions in psoriatic arthritis (PsA), psoriasis (PSOR) and Behçet's disease (BD):
Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).
Very common: Upper respiratory tract infection, Headache, Diarrhoea, Nausea.
Common: Bronchitis, Nasopharyngitis, Decreased appetite, Insomnia, Depression, Migraine, Tension headache, Cough, Vomiting, Back pain, Fatigue,
Uncommon: Hypersensitivity, Suicidal ideation and behaviour, Dyspepsia, Frequent bowel movements, Upper abdominal pain, Gastroesophageal reflux disease, Gastrointestinal haemorrhage, Rash, Urticaria, Weight decrease.
Not known: Angioedema.
Adverse Reactions Reported in ≥ 1%:
Tooth abscess, Folliculitis, Sinus headache.
Adverse Reactions Reported in ≥ 5%:
Arthralgia.

Effects on ability to drive and use machines

Apremilast has no or negligible 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 twice daily) 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.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Immunosuppressants, 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 and psoriasis.

Pharmacodynamics

In clinical studies in patients with psoriatic arthritis, 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. After 40 weeks of treatment with apremilast, there was a decrease in plasma protein levels of IL-17 and IL-23, and an increase in IL-10. In clinical studies 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-23p40, IL-17A, IL-22 and IL-8. In clinical studies in patients with Behçet Disease treated with apremilast, there was a significant positive association between the change in plasma TNF-alpha and clinical efficacy as measured by the number of oral ulcers. Apremilast administered at doses of up to 50 mg twice daily did not prolong the QT interval in healthy subjects.

Pharmacokinetics

Absorption:
Apremilast is well absorbed with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (Cmax) occurring at a median time (tmax) of approximately 2.5 hours. Apremilast pharmacokinetics are 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%. The mean apparent volume of distribution (Vd) is 87 L, indicative of extravascular distribution.
Biotransformation:
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. Following oral administration in humans, apremilast is the 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.
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).
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.
Special population:
Patients with Hepatic Impairment: The pharmacokinetics of apremilast and its metabolite M12 is not affected by moderate or severe hepatic impairment.
Patients with 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 Cmax 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 Cmax than in young subjects (18 to 55 years of age). There is limited pharmacokinetic data in subjects over 75 years of age in clinical trials.
Gender: In pharmacokinetic trials in healthy volunteers, the extent of exposure in females was about 31% higher and Cmax was about 8% higher than that in male subjects.

HOW SUPPLIED

Apezla Tablets 28 Days Starter Pack : Pack of 55 Tablets
Each Pack contains
Apezla Tablets 10 mg: (4 Tablets)
Apezla Tablets 20 mg: (4 Tablets)
Apezla Tablets 30 mg: (47 Tablets)

Apezla Tablets 30mg : Pack of 56 Tablets

STORAGE

Do not store above 30°C.
The expiration date refers to the product correctly stored at the required condition.

INSTRUCTIONS

Keep away from heat, light and moisture.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:
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