

**August 2018 revised (3rd version)
*February 2017 revised

Storage: Store at room temperature.

Expiration date: 3 years (to be used within the period indicated on the package)

Standard Commodity Classification No. of Japan 873999
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Powerful drug
Prescription drug*

PDE4 Inhibitor

OTEZLA[®] Tablet 10 mg

OTEZLA[®] Tablet 20 mg

OTEZLA[®] Tablet 30 mg

OTEZLA[®] Tablets
Apremilast Tablets
*Caution – Use only pursuant to the prescription of a physician, etc.

	10 mg tablet	20 mg tablet	30 mg tablet
Approval No.	22800AMX00729000	22800AMX00730000	22800AMX00731000
*Date of listing in the NHI reimbursement price	February, 2017		
*Date of initial marketing in Japan	March, 2017		
International birth date	March, 2014		

CONTRAINDICATIONS (OTEZLA is contraindicated in the following patients)

1. Patients with a history of hypersensitivity to ingredients of OTEZLA.
2. Pregnant woman or in women who may possibly be pregnant [Refer to Administration During Pregnancy, Delivery or Lactation]

DESCRIPTION

Brand name	OTEZLA Tablet 10 mg	OTEZLA Tablet 20 mg	OTEZLA Tablet 30 mg	
Active ingredient/content (in each tablet)	Contains 10 mg of apremilast	Contains 20 mg of apremilast	Contains 30 mg of apremilast	
Excipients	Microcrystalline cellulose, lactose hydrate, croscarmellose sodium, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), titanium oxide, macrogol 4000, talc, iron sesquioxide	Microcrystalline cellulose, lactose hydrate, croscarmellose sodium, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), titanium oxide, macrogol 4000, talc, iron sesquioxide, yellow iron sesquioxide	Microcrystalline cellulose, lactose hydrate, croscarmellose sodium, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), titanium oxide, macrogol 4000, talc, iron sesquioxide, yellow iron sesquioxide, black iron oxide	
Color/dosage form	Pink, film-coated tablets	Brown, film-coated tablets	Beige, film-coated tablets	
Appearance	Front Surface			
	Back Surface			
	Side Surface			
Size	Major Axis (mm)	8.18	10.32	11.81
	Minor Axis (mm)	4.42	5.55	6.35
	Thickness (mm)	3.45	4.34	4.97
	Weight (mg)	104.0	208.0	312.0

INDICATION

OTEZLA is indicated for the following diseases:

- Psoriasis vulgaris that is with an inadequate response to topical therapies
- Psoriasis arthropathica

<Precautions for INDICATION>

Apply for the patients with Psoriasis vulgaris or Psoriasis arthropathica as per below.

- (1) Patients with an inadequate response to steroids topical therapies, and with skin lesion more than or equal to 10% of BSA.
- (2) Patients with refractory to skin lesion or articular symptom.

DOSAGE AND ADMINISTRATION

Generally, in adults administer apremilast orally according to the following. On Day 6 and thereafter, administer orally as 30 mg of apremilast twice daily in the morning and evening with or without food.

Day1	Day2		Day3		Day4		Day5		Day6 and thereafter	
Morni ng	Morni ng	Eveni ng	Morni ng	Eveni ng						
10mg	10mg	10mg	10mg	20mg	20mg	20mg	20mg	30mg	30mg	30mg

<Precautions for DOSAGE AND ADMINISTRATION>

- (1) If not apply titration for initiation, the high incidence of nausea, diarrhoea, vomiting, etc is suggested. Follow the "DOSAGE AND ADMINISTRATION".
- (2) OTEZLA dosage should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance (CL_{cr}) of less than 30 mL/min estimated by the Cockcroft–Gault equation), due to the possibility of increasing blood concentration. Carefully administer to the patients with renal impairment, considering dose reduction such as reducing dosage as 30 mg QD. For the first dose, it is recommended to administer OTEZLA only in the morning. [refer to "CAREFUL ADMINISTRATION" and "PHARMACOKINETICS"]
- (3) Clinical response will be observed within 24 weeks treatment. Therefore, reconsider whether or not to continue if clinical response is not observed within 24 weeks treatment.

PRECAUTIONS FOR USE

1. Careful Administration (OTEZLA should be carefully administered to the following patients.)

- 1) Patients with severe renal impairment (creatinine clearance (CL_{cr}) of less than 30 mL/min by the Cockcroft–Gault equation). [possibility of increasing blood concentration and cause of adverse reactions. See "Precautions for DOSAGE AND ADMINISTRATION" and "PHARMACOKINETICS".]
- 2) Patients with infection, suspected infection, or medical history of recurrent infection [may worsen or emerge]
- 3) Elderly patients [See "Administration in the Elderly" section.]

2. Important Precautions

Apremilast is to be administered by the physicians who have adequate knowledge and experience with treatment for Psoriasis vulgaris and Psoriasis arthropathica.

3. Drug Interactions

Precautions for co-administration (Caution should be given in co-administration)

Drug name, etc.	Clinical signs, Symptoms, and Treatment	Mechanism and Risk Factors
Inducers of CYP3A4 (rifampicin, phenobarbital, carbamazepine, phenytoin, etc.)	It has been reported that co-administration of apremilast with rifampicin resulted in a decrease in apremilast. Therefore, if co-administering these drugs, attention should be paid to reduction of the clinical response.	Because apremilast is metabolized by CYP3A4, if apremilast is co-administered with CYP3A4 inducers, it is considered that the plasma concentration of apremilast is reduced.

4. Adverse Reactions

In a Japanese study, adverse reactions were observed in 71 cases (29.5%) of 241 cases in the safety evaluation during the Apremilast Exposure period. The adverse drug reactions most commonly reported included diarrhea (11, 4.6%), abdominal discomfort (9, 3.7%), nasopharyngitis (8, 3.3%), faeces soft (6, 2.5%), psoriasis (5, 2.1%), nausea (4, 1.7%).

In foreign studies, adverse reactions were observed in 1046 cases (44.4%) of 2357 cases in the safety evaluation during the Apremilast exposure

Period (30mg BID). The drug reactions most commonly reported included nausea (310, 13.2%), diarrhoea (296, 12.6%), headache (130, 5.5%), tension headache (64, 2.7%), upper respiratory tract infections (64, 2.7%), vomiting (61, 2.6%), nasopharyngitis (56, 2.4%), dyspepsia (53, 2.2%) and abdominal pain upper (46, 2.0%) (At the time of approval).

1) Significant Adverse Reactions

- (1) Serious infection (0.7%) ^{Note1}: there is a possibility of serious infections (virus, bacterial, fungi). Careful monitoring, and if infection is suspected, proper action should be considered.
- (2) Serious hypersensitivity (<0.1%) ^{Note1}: Hypersensitivity including anaphylaxis may occur. The condition of patients should be closely monitored, and if anaphylaxis is suspected, immediately discontinue the drug, and take appropriate measures.

**** (3) Severe diarrhea (frequency unknown) ^{Note2}: Severe diarrhea may occur.**
The condition of patients should be closely monitored, and if severe diarrhea is suspected, discontinue the drug and take appropriate measures.

2) Other Adverse Reactions ^{Note 1}

If following adverse reactions are suspected, take appropriate measures including interruption.

	5% or more	1 to less than 5%	Less than 1%
Infections and infestations		Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Sinusitis	Urinary tract infection, Pharyngitis
Gastrointestinal	Nausea, Diarrhoea	Vomiting, Abdominal pain upper, Dyspepsia, Abdominal pain, Frequent bowel movements, Abdominal discomfort, Gastroesophageal reflux disease, Faeces soft	Abdominal distension
Psychiatric/Nervous	Headache	Tension headache, Dizziness, Migraine	Insomnia, Depression
Metabolism		Decreased appetite, Weight decreased	
Others		Fatigue, Psoriasis	Pruritus, Cough, Rash, Hypersensitivity, Back pain, Hypertension

Note 1) AE rate occurred in overseas clinical studies (APR 30 mg BID pool)

Note 2) Frequency of adverse reaction reported post-marketing is as "frequency unknown".

**5. Administration in the Elderly

Generally, elderly patients should be administered cautiously with well observation of condition with paying attention for adverse reactions such as infection, diarrhea, nausea and vomiting due to their decreased a physiology function. [See "Careful Administration" section.]

6. Administration During Pregnancy, Delivery or Lactation

There are no adequate and well controlled studies of apremilast in pregnant women.

- 1) Do not administer apremilast in pregnant woman or in women who may possibly be pregnant. Inform them to use appropriate contraception during administration. [Effects of apremilast on pregnancy included increased early embryo resorptions/post-implantation embryo-fetal loss, reduced fetal weight, and delayed ossification in mice at 2.3-fold the clinical exposure. Spontaneous abortion occurred in monkeys was observed at 2.1-fold the clinical exposure.]
- 2) It is preferable to not administer apremilast to nursing mothers. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. [Although it is not known whether apremilast is present in human milk, it is reported that apremilast was detected in milk of lactating mice.]

7. Pediatric Use

The safety in low birth weight infants, neonates, nursing infants, infants or children has not been established.

8. Precautions Concerning Use

When dispensing the drug

The patient should be instructed that PTP-packaged tablets must be taken out from the PTP sheet when taking the drug [It has been reported that an acute angle of a mistakenly swallowed PTP sheet injured the esophagus mucosa and caused a perforation which led to serious complications such as mediastinitis, etc.].

When taking the drug

The tablets should not be chewed or split.

9. Other precautions

In clinical study in Japan (N=254), depression or suicide/self-injury events were not reported.

In clinical studies in foreign countries (APR pool), during Placebo controlled period, drug related depression was reported by 0.2% (4/1668) patients who received 30mg BID and 0.1% (2/1411) who received placebo. During Apremilast exposure period, drug related depression was reported by 0.4% (10/2357). No drug related suicide/self-injury events were reported with Apremilast 30mg BID in the placebo controlled period and Apremilast exposure period.

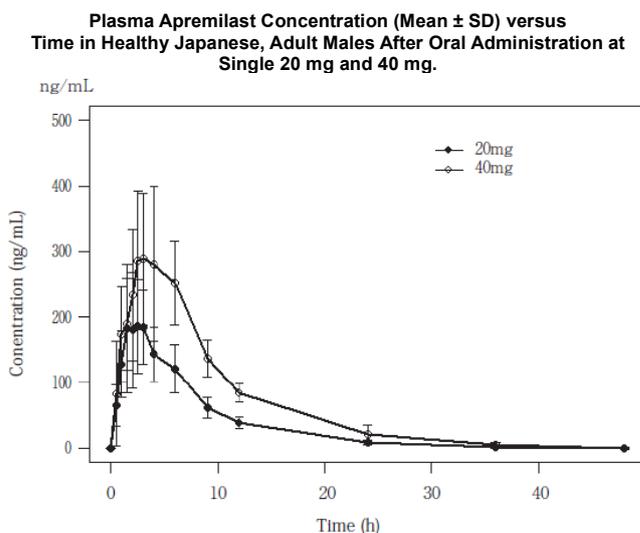
PHARMACOKINETICS

1. Absorption and Plasma Concentration

1) Plasma concentration (Results from Japanese subjects)

(1) Single dose

The pharmacokinetics (PK) of apremilast was characterized in Japanese healthy subjects. The steady-state pharmacokinetic parameters of apremilast in Japanese healthy subjects following single doses at 20 mg and 40 mg are shown below.



PK parameters When Administered as a Single 20- or 40-mg Oral Dose in Japanese healthy subjects

Pharmacokinetic Parameter (unit)	Geometric mean (Geometric CV%)	
	20mg n=12	40mg n=12
AUC _{0-t} (ng•hr/mL)	1515 (21.9)	2921 (17.2)
AUC _{0-inf} (ng•hr/mL)	1532 (21.2)	2943 (17.1)
C _{max} (ng/mL)	211 (31.3)	343 (25.9)
T _{max} ^a (hr)	2.50 (1.00, 6.00)	3.50 (2.00, 6.00)
t _{1/2} (hr)	5.44 (15.8)	5.32 (16.3)
CL/F (L/hr)	13.1 (21.2)	13.6 (17.1)
V _z /F (L)	102 (27.2)	104 (28.4)

^a Median (minimum, maximum) presented for t_{max}

(2) Multiple dose

The pharmacokinetics (PK) of apremilast was characterized in Japanese subjects plaque type psoriasis. The steady-state pharmacokinetic parameters of apremilast in Japanese subjects following multiple doses at 30 mg BID are shown below.

Pharmacokinetic Parameters (Geometric Mean [Geometric CV%]) of OTEZLA in Japanese Subjects with Moderate to Severe Plaque-type Psoriasis at Week 20

Pharmacokinetic Parameter (unit)	30 mg BID n=20
AUC _t (ng•h/mL)	2397 (39.5)
C _{max} (ng/mL)	374 (32.0)
T _{max} ^a (h)	2.00 (0.98, 4.00)
t _{1/2} (h)	4.06 (23.6)
CL _{ss} /F (L/h)	12.9 (34.1)
V _{ss} /F (L)	83.1 (32.2)

^a Median (minimum - maximum)

2) Plasma concentration (Results from overseas subjects)

In healthy overseas subjects, apremilast was rapidly absorbed following oral administration, with maximum plasma concentrations occurring approximately 2.5 hours postdose and an average absolute bioavailability of approximately 73%. AUC_{0-∞} and C_{max} of apremilast increased in a dose-proportional manner through 50 mg BID or 80 mg QD.

In overseas subjects with moderate-to-severe plaque-type psoriasis, the steady-state plasma concentration versus time profiles and pharmacokinetic parameters of apremilast following multiple doses at 10 mg BID, 20 mg BID, and 30 mg BID are shown above. Apremilast was rapidly absorbed with T_{max} occurring at approximately 2 hours post dose in overseas subjects. After achieving C_{max}, plasma concentrations of apremilast declined with an apparent elimination t_{1/2} of 4.93 to 6.56 hours. C_{max} and AUC_t of apremilast increased in an approximately dose-proportional manner.

3) Food Effect (Results from overseas subjects)

No food effect was observed in plasma concentration (C_{max} and AUC) in healthy subjects (N=46) after administered apremilast 30 mg.

2. Plasma protein binding ratio (Results from overseas subjects)

Human plasma protein binding of apremilast is approximately 68%.

3. Metabolism and Elimination (Results from overseas subjects)

<Metabolism>

Following oral administration in humans, the key circulating component in apremilast is (45%) followed by inactive metabolite (39%), a glucuronide conjugate of O-demethylated apremilast (overseas results). 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, CYP1A2 and CYP2A6.

<Elimination>

In healthy subjects 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 4% of the radioactive dose recovered as apremilast in urine and feces, respectively.

4. Pharmacokinetics in Patients with Renal Impairment (Results from overseas subjects)

In subjects with severe renal impairment administered with a single dose of 30 mg apremilast, the AUC and C_{max} of apremilast increased by approximately 88% and 42%, respectively.

PK parameter in patients with renal impairment

eGFR (mL/min/1.73 m ²)	C _{max} (ng/mL)	T _{max} (h)	T _{1/2} (h)	AUC _{inf} (ng•h/mL)
Mild (60≤eGFR<90)	265 (30)	3.0 [2.0, 4.0]	8.4 (19)	2,975 (21)
Reference to mild	250 (17)	3.0 [2.0, 4.1]	8.1 (24)	3,464 (19)
Moderate (30≤eGFR<60)	182 (47)	3.5 [0.5, 8.0]	10.5 (40)	3,466 (67)
Reference to moderate	208 (32)	2.0 [1.0, 6.0]	8.3 (24)	2,838 (24)
Severe (eGFR <30)	366 (35)	3.0 [1.0, 6.0]	11.8 (18)	5,425 (53)
Reference to severe	255 (40)	3.0 [2.0, 4.0]	9.4 (18)	2,879 (18)

Geometric mean and CV% of 7 or 8 subjects, t_{max}: median [min, max], Reference Group: group other factors except renal function

5. Pharmacokinetics in patients with hepatic impairment (Results from overseas subjects)

The pharmacokinetics of apremilast and its major metabolite, a glucuronide conjugate of O-demethylated apremilast is not affected by moderate a (Child-Pugh 7 to 9) or severe (Child-Pugh 10 to 13) hepatic impairment.

6. Drug Interaction(Results from overseas subjects)

Co-administration of apremilast with multiple doses of rifampin resulted in a decrease in apremilast AUC and C_{max} by approximately 72% and 43%, respectively. Co-administration of apremilast with ketoconazole resulted in increase in apremilast AUC and C_{max} by approximately 36% and 5%, respectively, which is not clinically meaningful. Co-administration of Apremilast with methotrexate in psoriasis patients resulted the extent of exposure for apremilast AUC_t and C_{max} were 0.7% and 5% lower when apremilast was administered co-administered with methotrexate.

7. Drug Interaction(Results from overseas subjects)

Apremilast was studied in healthy subjects by gender. The extent of exposure in females was about 31% higher and C_{max} was about 8% higher than that in male subjects.

Apremilast was studied in young and elderly healthy subjects. The exposure in elderly subjects (65-85 years of age) is about 13% higher in AUC and about 6% higher in C_{max} for apremilast than that in young subjects (18-55 years of age).

CLINICAL RESULTS

<Clinical study results in Japan>

The results from randomized, placebo-controlled, double-blind, parallel-group study of Japanese patients with moderate to severe plaque psoriasis who had a BSA involvement of ≥ 10% and PASI score ≥ 12 are shown below. Significant improvement in the proportion of patients achieving primary endpoint, PASI-75 and secondary endpoint, sPGA scores of clear (0) or minimal (1) at Week 16, occurred in subjects treated with apremilast 30 mg twice daily compared with placebo.

Japanese Phase 2b study: Clinical Responses at week 16 (mITT, LOCF)

	20mg	30mg	placebo	Difference to placebo (95%CI) p-value ^{a,b}	
				20mg	30mg
PASI 75 response	23.5 (20/85)	28.2 (24/85)	7.1 (6/84)	16.4 [5.8, 27.0] p=0.0032	21.1 [10.1, 32.1] p=0.0003
sPGA (0 or 1) response ^c	23.9 (17/71)	29.6 (21/71)	8.8 (6/68)	15.1 [3.1, 27.1]	20.8 [8.2, 33.3]

% (n/N)

a 2-sided chi-square test

b Statistically significant after multiplicity adjustment by Hochberg method

c for patients with sPGA score ≥ 3 at baseline

<Results from overseas clinical studies^{5), 6)>}

The results from 2 overseas, randomized, placebo-controlled, double-blind, parallel-group, Phase 3 studies (PSOR-008 and PSOR-009) subjects with moderate to severe plaque psoriasis who had a BSA involvement of ≥ 10%, sPGA score ≥ 3 and PASI score ≥ 12 are shown below.

Significant improvement in the proportion of patients achieving primary endpoint, PASI-75 and secondary endpoint, sPGA scores of clear (0) or minimal (1) at week 16, occurred in subjects treated with apremilast 30 mg twice daily compared with placebo.

Overseas Phase 3 studies: Clinical Responses at week 16 (FAS, LOCF)

	PSOR-008			PSOR-009		
	30 mg	placebo	Difference [95%CI] p-value ^a	30 mg	placebo	Difference [95%CI] p-value ^a
PASI 75 response	33.1 (186/562)	5.3 (15/282)	27.8 [23.1, 32.5] p<0.0001	28.8 (79/274)	5.8 (8/137)	23.0 [16.3, 29.6] p<0.0001
sPGA (0 or 1) response	21.7 (122/562)	3.9 (11/282)	17.8 [13.7, 21.9]	20.4 (56/274)	4.4 (6/137)	16.1 [10.2, 21.9]

% (n/N)

a 2-sided chi-square test

<Results from overseas clinical studies^{1), 2), 3)>}

The results from 3 randomized, double-blind, placebo-controlled, parallel-group studies (Studies PSA-002, PSA-003 and PSA-004) of similar design in patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment with DMARDs, and of similar design in patients with DMARDs naive (PSA-005) are shown below. OTEZLA may be used in combination with small molecule DMARDs, including methotrexate. A significantly greater proportion of patients achieved the primary endpoint, ACR 20 response compared with placebo, at week 16.

Overseas Phase 3: Clinical Responses at Week 16 (FAS, NRI)

	PSA-002 ^a		PSA-003 ^a		PSA-004 ^a		PSA-005 ^b	
	30mg	placebo	30mg	placebo	30mg	placebo	30mg	placebo
ACR20 response	38.1 (64/168)	19.0 (32/168)	32.1 (52/162)	18.9 (30/159)	40.7 (68/167)	18.3 (31/169)	30.7 (54/176)	15.9 (28/176)
Difference [95%CI] p-value ^c	19.0 [9.7, 28.3] p=0.0001	13.4 [4.0, 22.7] p=0.0060	22.3 [13.0, 31.6] p<0.0001	14.8 (6.1, 23.5) p=0.0010				

% (n/N)

a Cochran-Mantel-Haenszel test, stratified by DMARD use

b 2-sided chi-square test

c Statistically significant after multiplicity adjustment by Hochberg method

PHARMACOLOGY

1. Pharmacology^{4), 7), 8)}

In vitro pharmacology

1) Apremilast inhibits the enzymatic activity of phosphodiesterase 4 (PDE4) as measured by hydrolysis of cyclic adenosine monophosphate (cAMP), with a 50% inhibitory concentration (IC₅₀) value of 74 nM, and an affinity constant (K_i) of 68 nM, in a cAMP-competitive and

reversible manner. Inhibition of the PDE4A, PDE4B, PDE4C, and PDE4D subtypes is observed.

- 2) In purified human T cells, apremilast inhibits the production of inflammatory cytokines, such as interleukin-17 (IL-17) with an IC₅₀ of 90 nM.
- 3) In human peripheral blood mononuclear cells, apremilast inhibits the endotoxin-induced production of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) with an IC₅₀ of 110 nM, while increasing the production of anti-inflammatory cytokine interleukin-10 (IL-10).

In vivo pharmacology

- 1) In a mouse model of psoriasis, using beige-severe combined immunodeficient mice xenotransplanted with normal human skin and triggered with human psoriatic NK cells, apremilast (5 mg/kg/day) significantly reduced epidermal thickness and proliferation, decreased the general histopathological appearance of psoriasiform features and reduced expression of TNF-alpha, human leukocyte antigen-DR and intercellular adhesion molecule-1 in the lesioned skin.
- 2) In mouse models of arthritis, using mice induced by passive transfer of anti-type II collagen mAb and immunization with type II collagen, respectively, apremilast (5 mg/kg/day and 25 mg/kg/day) significantly reduced clinical score.

2. Mode 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 IL-17, TNF-α, IL-23 and other inflammatory cytokines.

PHYSICOCHEMICAL INFORMATION ON ACTIVE INGREDIENT

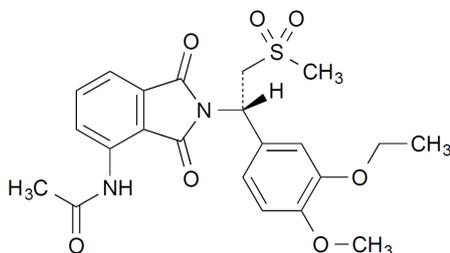
Nonproprietary name: Apremilast (JAN), apremilast (INN)

Chemical name: *N*-[2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1*H*-isoindol-4-yl]acetamide

Molecular formula: C₂₂H₂₄N₂O₇S

Molecular weight: 460.50

Structural formula:



Description: Apremilast is a white to pale yellow non-hygroscopic powder.

It is practically insoluble in water, slightly soluble in ethanol, and soluble in acetone. Apremilast is the *S*-enantiomer with a specific rotation of +28.1° in acetonitrile at a concentration of 20 mg/mL.

Melting point: Approximately 156.1°C

CONDITIONS FOR APPROVAL

Prepare Risk Management Plan and conduct appropriately.

PACKAGING

OZEZLA Tablet starter pack: 27 Tablets (10 mg x 4 tablets), 20 mg x 4 tablets, 30 mg x 19 tablets) x 1 packs

OZEZLA Tablet 30 mg: 56 Tablets (14 tablets (PTP) x 4 sheets)

REFERENCES and CONTACT for REQUESTING REFERENCES

<Key References>

- 1) Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Ann Rheum Dis 2016;75:1065-1073.
- 2) Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Ann Rheum Dis 2014;73:1020-1026.
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- 6) Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Br J Dermatol 2015;173:1387-99.
- 7) Schafer PH, Parton A, Capone L, Cedzik D, Brady H, Evans JF, et al. Cell Signal 2014 Sep;26(9):2016-29.
- 8) Schafer PH, Parton A, Gandhi AK, Capone L, Adams M, Wu L, et al. Br J Pharmacol 2010 Feb;159(4):842-55.

<Contact for requesting references and inquiries for product information>

Among the key references those given as "in house reports" can also be requested at the following address:

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