Apremilast

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Apremilast, brand name **Otezla** among others, is an analog of thalidomide, and a medication for the treatment of certain types of psoriasis and psoriatic arthritis. It may also be useful for other immune system related inflammatory diseases. The drug acts as a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) and inhibits spontaneous production of TNF-alpha from human rheumatoid synovial cells.[3] It is taken by mouth.

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Medical use [edit]

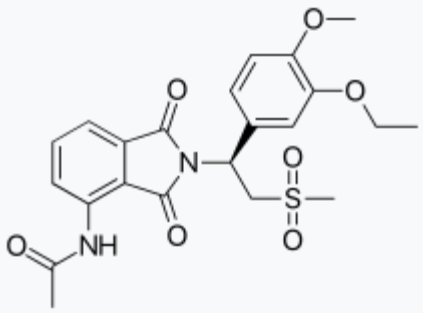
Apremilast was approved by the United States Food and Drug Administration in 2014 for treatment of adults with active psoriatic arthritis and moderate to severe plaque psoriasis.[4][5] Apremilast is taken by mouth.[6]

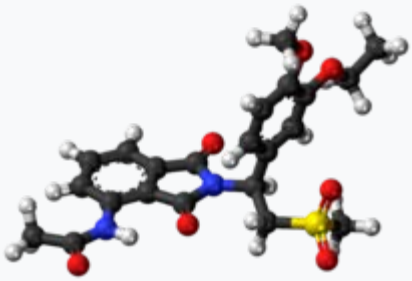
Contraindications [edit]

In Europe, the drug is contraindicated during pregnancy because mice and monkeys receiving very high doses of apremilast have been observed to suffer miscarriages and other pregnancy problems.[2] In the U.S., it may be used for pregnant women "if the potential benefit justifies the potential risk to the fetus".[7]

Adverse effects [edit]

Apremilast





Clinical data	
Pronunciation	/əˈprɛmɪlæst/ *ə-PREM-i-last*
Trade names	Otezla, Aplex, others
Synonyms	CC-10004
AHFS / Drugs.com	Otezla
MedlinePlus	a614022
License data	EU EMA: by INN US FDA: Apremilast
Pregnancy category	AU: B3 US: C (Risk not ruled out)
Routes of administration	by mouth (tablets)
ATC code	L04AA32 (WHO)
Legal status	
Legal status	AU: S4 (Prescription only) US: Rx-only
Pharmacokinetic data	
Bioavailability	73%;[1] T_{max} = ~2.5 hours
Protein binding	c. 68%[1]

Severe Diarrhea, Nausea, Vomiting [edit]

Diarrhea occurs in about 25% of patients taking apremilast. Severe gastrointestinal symptoms, when they occur, typically start within the first few weeks of treatment. [8][9]

Depression and Suicidal Thoughts [edit]

Worsening depression, suicidal thoughts, and other mood changes may occur with apremilast.[10]

Weight loss [edit]

Weight loss: Weight loss has been associated with apremilast. Reports from clinical studies indicated a 5 to 10% decrease in body weight in 10% of patients taking apremilast (compared to 3.3% of patients taking placebo).[10]

Other Adverse effects [edit]

Common, usually mild to moderate adverse effects associated with apremilast include headache, back pain, nausea, diarrhea, fatigue, nasopharyngitis and upper respiratory tract infections.[11]

Interactions [edit]

Concurrent use of strong cytochrome P450 enzyme inducers has been shown to decrease exposure of apremilast and can result in reduced or loss of efficacy of apremilast. It is not recommended to use simultaneously with strong P450 enzyme inducers, including rifampicin, phenobarbital, carbamazepine, phenytoin,[10] and St. John's Wort.[12]

Metabolism	Liver (CYP3A4, with minor contributions from CYP2A6, CYP1A2)[1]
Metabolites	*O*-desmethylapremilast glucuronide (and others)[2]
Elimination half-life	6–9 hours[1]
Excretion	Urine (58%), faeces (39%)[1]
Identifiers	
IUPAC name	[show]
CAS Number	608141-41-9
PubChem CID	11561674
DrugBank	DB05676
ChemSpider	9736448
UNII	UP7QBP99PN
KEGG	D08860
ChEBI	CHEBI:78540
ChEMBL	ChEMBL514800
ECHA InfoCard	100.234.786
Chemical and physical data	
Formula	$C_{22}H_{24}N_2O_7S$
Molar mass	460.500 g/mol
3D model (JSmol)	Interactive image
SMILES	[show]
InChI	[show]

Pharmacology [edit]

Mechanism of action [edit]

Apremilast is a small molecule inhibitor of PDE4,[13] an enzyme that breaks down cyclic adenosine monophosphate (cAMP). In inflammatory cells, PDE4 is the dominant enzyme responsible for this reaction. The resulting increase in cAMP levels down-regulates expression of a number of pro-inflammatory factors like tumor necrosis factor alpha (TNFα), interleukin 17, interleukin 23, and many others, and up-regulates the anti-inflammatory interleukin 10. The importance of these individual factors for the clinical effect of apremilast is not clear.[2]

Pharmacokinetics [edit]

Apremilast is absorbed from the gut well (73%) and independently of food intake, and reaches peak blood plasma concentrations after 2.5 hours. Plasma protein binding is 68%. It is metabolised in the liver, mainly via the enzyme CYP3A4, but to a minor extent via CYP1A2 and CYP2A6. The main metabolite is *O*-

desmethylapremilast glucuronide.[1][2]

The half-life is 6–9 hours. The substance is eliminated through the kidney (58%) and feces (39%), mainly in form of its metabolites. Only 3% of the original substance are found in the urine, and 7% in the feces.[1][2]

Chemistry [edit]

Apremilast is a phthalimide derivative. It is a white to pale yellow, non-hygroscopic powder that is practically insoluble in water and buffer solutions in a wide pH range, but is soluble in lipophilic solvents such as acetone, acetonitrile, butanone, dichloromethane, and tetrahydrofuran.[14]

In vitro, apremilast reduces PDE4 activity leading to an increase in cyclic-adenosine monophosphate (cAMP) concentrations in immune and non-immune cell types, partially inhibiting the production of many pro-inflammatory cytokines such as TNF-α, IFN-γ IL-2, IL-12 and IL-23 and elevating the production of the anti-inflammatory cytokine IL-10.[15][16] The inhibition potency of apremilast in TNF-α production is similar to lenalidomide.[17]

Celgene reported seven kinds of crystal form A, B, C, D, E, F, and G and thought the crystal form B was the most thermodynamically stable anhydrous form. However, Utopharm reported another more thermodynamically stable anhydrous crystal form II than the crystal form B.[18]

Accessibility [edit]

Otezla is available in the U.S., but is dispensed only through a network of specialty pharmacies.[4] The estimated wholesale price is $22,500 for a year of treatment.[6] In Austria, the drug is available in all pharmacies, and a year of treatment costs health insurances about €11,000.[19]

See also [edit]

- Discovery and development of thalidomide and its analogs

References [edit]

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v · t · e · **Phosphodiesterase inhibitors**	[show]

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