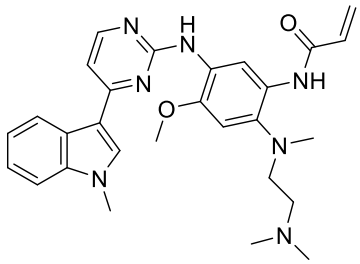
Product data sheet

MedKoo Cat#: 206042 Name: Osimertinib free base CAS#: 1421373-65-0 (free base) Chemical Formula: $C_{28}H_{33}N_7O_2$ Exact Mass: 499.26957 Molecular Weight: 499.61	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

Osimertinib, also known as AZD-9291 and Mereletinib, is a third-generation EGFR inhibitor, showed promise in preclinical studies and provides hope for patients with advanced lung cancers that have become resistant to existing EGFR inhibitors. AZD9291 is highly active in preclinical models and is well tolerated in animal models. It inhibits both activating and resistant EGFR mutations while sparing the normal form of EGFR that is present in normal skin and gut cells, thereby reducing the side effects encountered with currently available medicines. Osimertinib was approved in Nov. 2015 by FDA.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	15.0	30.0

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.00 mL	10.01 mL	20.02 mL
5 mM	0.40 mL	2.00 mL	4.00 mL
10 mM	0.20 mL	1.00 mL	2.00 mL
50 mM	0.04 mL	0.20 mL	0.40 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Chagoya G, Kwatra SG, Nanni CW, Roberts CM, Phillips SM, Nullmeyergh S, Gilmore SP, Spasojevic I, Corcoran DL, Young CC, Ballman KV, Ramakrishna R, Cross DA, Markert JM, Lim M, Gilbert MR, Lesser GJ, Kwatra MM. Efficacy of osimertinib against EGFRvIII+ glioblastoma. Oncotarget. 2020 Jun 2;11(22):2074-2082. doi: 10.18632/oncotarget.27599. PMID: 32547705; PMCID: PMC7275784.
2. Jiang XM, Xu YL, Huang MY, Zhang LL, Su MX, Chen X, Lu JJ. Osimertinib (AZD9291) decreases programmed death ligand-1 in EGFR-mutated non-small cell lung cancer cells. Acta Pharmacol Sin. 2017 Nov;38(11):1512-1520. doi: 10.1038/aps.2017.123. Epub 2017 Sep 7. PMID: 28880013; PMCID: PMC5672073.

In vivo study

1. MacLeod AK, Lin D, Huang JT, McLaughlin LA, Henderson CJ, Wolf CR. Identification of Novel Pathways of Osimertinib Disposition and Potential Implications for the Outcome of Lung Cancer Therapy. Clin Cancer Res. 2018 May 1;24(9):2138-2147. doi: 10.1158/1078-0432.CCR-17-3555. Epub 2018 Feb 6. PMID: 29437786.
2. Floc'h N, Martin MJ, Riess JW, Orme JP, Staniszewska AD, Ménard L, Cuomo ME, O'Neill DJ, Ward RA, Finlay MRV, McKerrecher D, Cheng M, Vang DP, Burich RA, Keck JG, Gandara DR, Mack PC, Cross DAE. Antitumor Activity of Osimertinib,

an Irreversible Mutant-Selective EGFR Tyrosine Kinase Inhibitor, in NSCLC Harboring EGFR Exon 20 Insertions. Mol Cancer Ther. 2018 May;17(5):885-896. doi: 10.1158/1535-7163.MCT-17-0758. Epub 2018 Feb 26. PMID: 29483211; PMCID: PMC5932243.

7. Bioactivity

Biological target:

Osimertinib (AZD-9291) is an irreversible and mutant selective EGFR inhibitor with IC_{50}s of 12 and 1 nM against $EGFR^{L858R}$ and $EGFR^{L858R/T790M}$, respectively.

In vitro activity

EGFR T790M mutant NCI-H1975 cells were treated with different concentrations of osimertinib. After treatment for 24 h, osimertinib clearly inhibited EGFR phosphorylation and significantly reduced the protein levels of PD-L1 (Figure 1A). NCI-H1975 cells were then incubated with 125 nmol/L osimertinib for different durations (3, 6, 12 and 24 h). As shown in Figure 1B, osimertinib down-regulated PD-L1 expression at 6 h. Furthermore, immunofluorescence was used to localize PD-L1 in NCI-H1975 cells. Compared with the osimertinib-untreated group, cell membranes exhibited weak PD-L1 signals at 6 and 24 h (Figure 1C). Consistently, the reduction of PD-L1 on the membranes was confirmed further by flow cytometry after treatment with osimertinib for 6 and 24 h (Figure 1D). To exclude the massive suppression of PD-L1 mRNA and protein expression caused by cell death, this study performed MTT assays to examine the cell viability after treatment with osimertinib. This study found that osimertinib could not trigger cell death in NCI-H1975 cells at 6 h (Figure 1E), which was further verified in HCC827 cells (data not shown). In addition, the apoptosis inhibitor Z-VAD-FMK and the necroptosis inhibitor NSA failed to reverse the osimertinib-triggered decrease of PD-L1 in NCI-H1975 cells (Figure 1F). Collectively, these findings demonstrate that osimertinib reduces PD-L1 expression in NCI-H1975 cells independent of cell death.

Reference: Acta Pharmacol Sin. 2017 Nov; 38(11): 1512–1520. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5672073/

In vivo activity

To explore the influence of CYP1A enzymes on osimertinib disposition in vivo, this study carried out pharmacokinetic analysis in novel Cyp1a1/1a2 knockout and CYP1A1/1A2 humanized mouse lines. The basal expression of CYP1A1 in the h1A1/1A2 line is low, however it can be induced in a number of tissues including liver, lung, and small intestine by exposure of the mice to TCDD, an activator of the Ah receptor (Ahr). In h1A1/1A2 mice pretreated with TCDD, there was a 3.4-fold decrease in AUC0−t and a 3.3-fold decrease in Cmax of osimertinib (Fig. 5A and Supplementary Table S7). There was no change in exposure in the 1a1/1a2KO line. Correspondingly, TCDD-pretreatment greatly increased circulating levels of the OH-1 metabolite in humanized mice, but had no effect in knockouts (Fig. 5B). In this experiment, TCDD-mediated activation of Ahr occurred in several tissues—liver, small intestine, and lung—hence the effects on osimertinib and metabolite disposition were likely to be driven by a combination of hepatic, intestinal, and pulmonary CYP1A1/1A2.

Reference: Clin Cancer Res. 2018 May 1;24(9):2138-2147. https://clincancerres.aacrjournals.org/content/24/9/2138.long