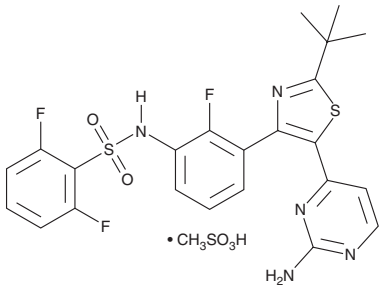
PRODUCT INFORMATION

Dabrafenib (mesylate)

Item No. 35251



CAS Registry No.:	1195768-06-9
Formal Name:	N-[3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluoro-benzenesulfonamide, methanesulfonate
Synonym:	GSK2118436B
MF:	$C_{23}H_{20}F_3N_5O_2S_2 \bullet CH_3SO_3H$
FW:	615.7
Purity:	≥98%
Supplied as:	A solid
Storage:	-20°C
Stability:	≥4 years

Information represents the product specifications. Batch specific analytical results are provided on each certificate of analysis.

Laboratory Procedures

Dabrafenib (mesylate) is supplied as a solid. A stock solution may be made by dissolving the dabrafenib (mesylate) in the solvent of choice, which should be purged with an inert gas. Dabrafenib (mesylate) is soluble in the organic solvent DMSO at a concentration of approximately 1 mg/ml.

Description

Dabrafenib is an ATP-competitive inhibitor of Raf kinases (IC_{50}s = 0.64, 0.68, and 5 nM for wild-type B-RAF kinase, mutant B-RAF^{V600E}, and wild-type C-RAF kinase, respectively).[1] It also inhibits the tyrosine kinase-like kinases ALK5 and LIMK1 (IC_{50}s = 11 and 15 nM, respectively) and the calcium/calmodulin-dependent protein kinases SIK2 and PDK2 (IC_{50}s = 27 and 57 nM, respectively), as well as NEK11, CK1, and BRK (IC_{50}s = 20, 41, and 79 nM, respectively) in a panel of 270 kinases at 300 nM. Dabrafenib inhibits the growth of 16 cancer cell lines expressing mutant B-RAF^{V600E} (GI_{50}s = <200 nM), five cell lines expressing other B-RAF mutants (GI_{50}s = <30 nM), and 19 cell lines expressing wild-type Ras and RAF (GI_{50}s = <7,000 nM). However, it does not inhibit the growth of four cancer cell lines expressing mutant B-RAF^{V600E}, 133 cell lines expressing wild-type Ras and Raf, or 18 cell lines expressing mutant Ras (GI_{50}s = >10 µM) in a panel of 195 cancer cell lines. Dabrafenib (8 nM) inhibits MAPK signaling, inhibiting phosphorylation of MEK and ERK, and activates caspase-3/7 in B-RAF^{V600E}-expressing A375P melanoma cells but not in wild-type B-RAF-expressing human foreskin fibroblasts (EC_{200}s =71 and >10,000 nM, respectively). It reduces tumor growth in an A375P mouse xenograft model when administered at doses ranging from 3 to 100 mg/kg. Formulations containing dabrafenib have been used in the treatment of B-RAF^{V600E}-expressing cancers.

Reference

1. King, A.J., Arnone, M.R., Bleam, M.R., *et al.* Dabrafenib; Preclinical characterization, increased efficacy when combined with trametinib, while BRAF/MEK tool combination reduced skin lesions. *PLoS One* **8(7)**, e67583 (2013).

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