Linifanib (ABT-869) Datasheet

Technical Data

<table>
<thead>
<tr>
<th>Molecular Weight (MW)</th>
<th>Solubility (25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>375.41</td>
<td>DMSO 7.5 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Water &lt;1 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Ethanol &lt;1 mg/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Formula</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{21}H_{18}FN_{2}O</td>
<td>2 days -20°C Powder</td>
</tr>
<tr>
<td></td>
<td>2 weeks 4°C in DMDS</td>
</tr>
<tr>
<td></td>
<td>6 months -80°C in DMDS</td>
</tr>
</tbody>
</table>

CAS No. 796967-16-3, 1145655-58-8 (HCl), 796967-17-4 (TFA)

Synonyms AL-39324

Biological Activity

**Description**
Linifanib (ABT-869) is a novel, potent ATP-competitive RTK inhibitor for KDR, CSF-1R, Flt-1 and Flt-3 with IC50 of 4 nM, 3 nM, 3 nM and 3 nM, respectively.

**Targets**
- KDR
- CSF-1R
- Flt-1
- Flt-3

**IC50**
- 4 nM
- 3 nM
- 3 nM
- 4 nM

In vitro
Linifanib shows inhibitory to Kit, PDGFRβ and Flt4 with IC50 of 14 nM, 66 nM and 190 nM in kinases assay. Linifanib also inhibits ligand-induced KDR, PDGFRβ, Kit, and CSF-1R phosphorylation with IC50 of 2 nM, 2 nM, 31 nM and 10 nM at cellular level and this cellular potency could be affected by serum protein. Linifanib suppresses VEGF-stimulated HUAEC proliferation with IC50 of 0.2 nM. While Linifanib has weak activity against tumor cells which are not induced by VEGF or PDGF, except for MV4-11 leukemia cells (with constitutively active form of Flt3) with IC50 of 4 nM. Linifanib could cause a decrease in S and G2-M phases with a corresponding increase in the sub-G0-G1 apoptotic population in MV4-11 cells. Linifanib binds to the ATP-binding site of CSF-1R with K_i of 3 nM. Linifanib (10 nM) exhibits a reduced phosphorylation of Akt at Ser473 and decreased phosphorylation of GSK3β at Ser9 in BaF3 FLT3 ITD cell lines.

In vivo
Linifanib (0.3 mg/kg) results in complete inhibition of KDR phosphorylation in lung tissue. Linifanib also inhibits the edema response with ED50 of 0.5 mg/kg. Linifanib (7.5 and 15 mg/kg, bid) significantly inhibits both bFGF- and VEGF-induced angiogenesis in the cornea. Linifanib inhibits tumor growth in flank xenograft models including HT1080, H526, MX-1 and DLD-1 with ED75 from 4.5-12 mg/kg. Linifanib also shows efficacy in A431 and MDA-231 xenografts. Linifanib shows a Cmax and AUC_{24 hours} with 0.4 μg/mL and 2.7 μg·h/mL in HT1080 fibrosarcoma model.

**Clinical Trials**
Linifanib is in a Phase III evaluation for hepatocellular carcinoma.

**Features**

**Protocol (Only for Reference)**

**Kinase Assay**[1]

**Kinase assays**
Potencies (IC50 values) are determined by assays of active kinase domains cloned and expressed in baculovirus using the FastBac baculovirus expression system or obtained commercially. For tyrosine kinase assays, a biotinylated peptide substrate containing a single tyrosine is used with 1 mM ATP, [α-33P]ATP, and a biotinylated peptide substrate with peptide capture and incorporation of 33P determined using a SA-Flashplate. Linifanib is assayed at multiple concentrations prepared by serial dilution of a DMDS stock solution of Linifanib. The concentration resulting in 50% inhibition of activity is calculated using nonlinear regression analysis of the concentration response data.

**Cell Assay**[1]

**Cell Lines**
HUAEC, HT-29, A431, MDA-435, MDA-231, H526, DLD-1, 9L and MV4-11 cells

**Concentrations**
0-100 μM

**Incubation Time**
72 hours

**Methods**
Cells are seeded into 96-well plates at 2.5 × 10^3 per well and incubated with serum-free medium for 24 hours. Linifanib and VEGF (final, 10 ng/mL) are added and incubated for 72 hours in serum-free medium. For carcinoma cell lines, 3 × 10^3 cells/well are plated overnight in full growth medium. Linifanib is added to the cells in full growth medium and incubated for 72 hours. For leukemia cells, generally 5 × 10^5 per well are plated in full growth medium. Linifanib is added, and incubated for 72 hours. The effects on proliferation are determined by addition of Alamar Blue (final solution, 10%), incubation for 4 hours at 37°C in a CO2 incubator and analysis in a fluorescence plate reader (544 nm, excitation: 590 nm, emission).

**Animal Study**[1]

**Animal Models**

**References**
[1]
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<table>
<thead>
<tr>
<th>animal models</th>
<th>xenografts are established in mice.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>2% ethanol, 5% Tween 80, 20% PEG400, 73% saline</td>
</tr>
<tr>
<td>Doses</td>
<td>~ 10 mg/kg</td>
</tr>
<tr>
<td>Administration</td>
<td>Oral administration</td>
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</tbody>
</table>

References

Customer Reviews
Data from [Liver Int, 2011, 32(3), 400-409]
Linifanib (ABT-869) purchased from Selleck
(B and C) KMCH-1 cells were plated alone (monoculture) or together with PDGF-BB-secreting LX-2 cells (co-culture) in a transwell insert co-culture system (KMCH-1 cells in the bottom wells and LX-2 cells in the inserts; 1:1 ratio) for 2 days. Cells were treated as indicated with vehicle, rhTRAIL (10 ng/ml for 6 h on day 2); rhTRAIL plus imatinib [rhTRAIL:10 ng/ml for 6 h on day 2; Imatinib: 5 μmol/L for 24 h (day 2)]; or rhTRAIL plus linifanib [rhTRAIL: 10 ng/ml for 6 h on day 2; Linifanib:0.5 μmol/L for 24 h (day 2)]. After rhTRAIL treatment for 6 h, KMCH-1 cells were analysed for apoptotic nuclear morphology by DAPI-staining (B) and for DNA fragmentation by transferase-mediated dUTP nick end labelling assay (C) with quantitation of apoptotic nuclei by fluorescence microscopy.

![A and B graphs](https://example.com/graphs.png)

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Not for human, veterinary diagnostic or therapeutic use.

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www.selleckchem.com/datasheet/ABT-869-DataSheet.html