Lapatinib, used in the form of Lapatinib Ditosylate, is a potent EGFR and ErbB2 inhibitor with IC50 of 10.8 and 9.2 nM, respectively.

In vitro kinase assays:

The IC50 values for inhibition of enzyme activity are generated by measuring inhibition of phosphorylation of a peptide substrate. The intracellular kinase domains of EGFR and ErbB2 are purified from a baculovirus expression system. EGFR and ErbB2 reactions are performed in 96-well polystyrene round-bottomed plates in a final volume of 45 μL. Reaction mixtures contain 50 mM 4-morpholinepropanesulfonic acid (pH 7.5), 2 mM MnCl2, 10 μM ATP, 1 μCi of [γ-32P] ATP/reaction, 50 μM Peptide A [BioIn-(amino hexononic acid)-EEEEYPHELVAKK-CONH2], 1 mM dithiothreitol, and 1 μL of DMSO containing serial dilutions of Lapatinib beginning at 10 μM. The reaction is initiated by adding the indicated purified type-1 receptor intracellular domain. The amount of enzyme added is 1 pmol/reaction (20 nM). Reactions are terminated after 10 minutes at 23°C by adding 45 μL of 0.5% phosphoric acid in water. The terminated reaction mix (75 μL) is transferred to phosphocellulose filter plates. The terminated reaction mix is subsequently rinsed with water, and the plates are filtered and washed three times with 200 μL of 0.5% phosphoric acid. Scintillation cocktail (50 μL) is added to each well, and the assay is quantified by counting in a Packard Topcount. IC50 values are generated from 10-point dose-response curves.

Cell Assay:

Cells are exposed to various concentrations of Lapatinib for 72 hours. Relative cell number is estimated using methylene blue staining. The absorbance at 620 nm is read in a Spectra microplate reader. Cell death and cell cycle analysis are assessed by propidium iodide staining and antibody detection of incorporated BrdUrd and methylbenzenesulfonate.

Lapatinib displays higher inhibitory activity against EGFR- or ErbB2-overexpressing cells with IC50 of 3-12 μM, and exhibits ~100-fold selectivity over normal fibroblast cells. Lapatinib potently inhibits the growth of HN5 cells (IC50 = 41 nM) and A-431 cells, as well as ErbB2-overexpressing BT474 and N87 cells, and significantly induces G1 arrest of HN5 cells and apoptosis of BT474 cells, which are associated with inhibition of AKT phosphorylation.

In vivo study of Lapatinib in treating patients with recurrent prostate cancer has been completed.
<table>
<thead>
<tr>
<th>Uses</th>
<th>Nontoxic</th>
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<td>Administration</td>
<td>Orally twice daily</td>
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References

PLEASE KEEP THE PRODUCT UNDER -20°C FOR LONG-TERM STORAGE.

NOT FOR HUMAN, VETERINARY DIAGNOSTIC OR THERAPEUTIC USE

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