**Product**  Lapatinib

<table>
<thead>
<tr>
<th><strong>Nomenclature</strong></th>
<th>N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine</th>
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<tr>
<td><strong>OtherNames</strong></td>
<td>Lapatinib Ditosylate (USAN)</td>
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<td><strong>DevelopmentCode</strong></td>
<td>GW-572016 ; GW572016 ; GW-2016 ; GW2016 ; GW-572016F ; GW572016F ; GSK-572016 ; GSK572016 ; 572016</td>
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<tr>
<td><strong>Brand</strong></td>
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<td><strong>RN</strong></td>
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Preparation of IV (6-iodo-4(3H)-quinazolinone):

Preparation of VI (4-chloro-6-iodoquinazoline):
Substituted Heteroaromatic Compounds And Their Use In Medicine:

Preparation of IX (5-formyl-2-furanboronic acid):
Method for metal-organic production of organic intermediate products by means of aryl lithium-bases

Bicyclic Heteroaromatic Compounds As Protein Tyrosine Kinase Inhibitors:

Anilinoquinazolines As Protein Tyrosine Kinase Inhibitors:
Lapatinib Study Supports Cancer Stem Cell Hypothesis, Encourages Industry Research.
Schmidt C.
J Natl Cancer Inst. 2008 May 13;


Xia W. et al., Lapatinib antitumor activity is not dependent upon phosphatase and tensin homologue deleted on chromosome 10 in ErbB2-overexpressing breast cancers, Cancer Res. 2007 Feb 1;67(3):1170-5.


Bai F. et al., Determination of lapatinib (GW572016) in human plasma by liquid chromatography electrospray tandem mass spectrometry (LC-ESI-MS/MS), J


Wood ER. et al., A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells, Cancer Res. 2004 Sep 15;64(18):6652-9.

L.A. McHugh et al. GW572016, a dual tyrosine kinase inhibitor, blocks activation of ErbB1 and ErbB2 in a bladder cancer cell line. AACR Annual Meeting [March 27-31, Orlando (Florida)], 2004, Abst 4398.


Kim TE. et al., Lapatinib ditosylate GlaxoSmithKline, IDrugs. 2003 Sep;6(9):886-93.


Originator GlaxoSmithKline (GSK)
Lapatinib is a dual kinase inhibitor indicated for the treatment of breast cancer and several other solid tumors.

June 2010: The UK National Institute for Health and Clinical Excellence (NICE), did not recommend publicly-funded use of Tyverb. This is the final rejection.

February 2010: The EMEA European Medicines Agency’s Committee for Medicinal Products for Human Use issued a positive opinion for the authorisation of a new therapeutic indication for Tyverb® (lapatinib) in the European Union. Lapatinib, in combination with an aromatase inhibitor (AI), is indicated for the treatment of post-menopausal women with hormone receptor (HR)-positive, HER2 (ErbB2) over-expressing metastatic breast cancer and for whom chemotherapy is currently not intended. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor.

January 2010: The US FDA approved Tykerb combination of lapatinib and letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor.

May 2008: results from recent clinical trials demonstrated that lapatinib decreased tumorigenic breast cancer stem cells in the primary breast cancers among women receiving lapatinib treatment. The prevention of the renewal of tumorigenic stem cells is of major importance because tumorigenic stem cells are resistant to conventional chemotherapy.

March 2007: The US FDA has approved Tykerb (TM) (Lapatinib) to be used in combination with Capectabine (Xeloda TM), for patients with advanced, metastatic breast cancer that is HER2 positive (tumors that exhibit HER2 protein). The combination treatment is indicated for women who have received prior therapy with other cancer drugs, including an anthracycline, a taxane, and Trastuzumab (Herceptin TM).

Marketing applications for Lapatinib (Tykerb/Tyverb) have been filed in the European Union, Switzerland, Canada, Brazil, Australia, and South Korea.

December 2006: Lapatinib is ongoing 56 clinical trials, from phase I to III, alone or
in combination to treat several types of solid tumors. These trials are sponsored by GlaxoSmithKline and major academic institutions, and carried out in the USA as well as in the whole world.

2003: Phase III

The compound is developed as the ditosylate salt (CAS-RN: 388082-78-8)

Tykerb (lapatinib ditosylate) is an epidermal growth factor receptor (EGFR) and ErbB-2 (Her2/neu) dual tyrosine kinase inhibitor, under development by GlaxoSmithKline as a treatment for solid tumours such as breast and lung cancer. This novel investigational agent has attracted considerable interest, as it appears to arrest the development of breast cancer in some patients with metastatic, treatment-refractory disease.

Protein tyrosine kinases are enzymes that provide a central switch mechanism in cellular signal transduction pathways. As such they are involved in many cellular processes such as cell proliferation, metabolism, survival and apoptosis. Several protein tyrosine kinases are known to be activated in cancer cells and to drive tumour growth and progression.

Tyverb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

- in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (see section 5.1).
- in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor.

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \rightarrow \quad \text{CONH}_2 \\
\text{NH}_2 & \quad \text{CHO} \\
\text{135-165^\circ C} & \quad 43\% \\
\text{NH}_2 & \quad \text{CONH} \\
\text{CHO} & \quad \text{CONH} \\
\end{align*}
\]

\[
\begin{align*}
\text{POCl}_3 & \quad \text{NEt}_3 \quad \text{PhMe} \\
\text{reflux} & \quad 1 \text{ hr.} \\
\text{Cl} & \quad \text{F} \\
\text{H}_2\text{N} & \quad \text{NaOH} \\
\text{70^\circ C} & \quad 90-95\% \\
\end{align*}
\]
Intermediates List

I 2-aminobenzoic acid
II 2-amino-5-bromobenzoic acid
III formamide
IV 6-iodo-4(3H)-quinazolinone
V phosphoryl chloride
VI 4-chloro-6-iodoquinazoline
VII 3-chloro-4-[(3-fluorophenyl)methoxy]benzenamine
VIII 6-iodo-N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-4-quinazolinamine
IX 5-formyl-2-furanboronic acid
X 5-[4-[[3-chloro-4-[[3-fluorophenyl]methoxy]phenyl]amino]-6-quinazolinyl]-2-furancarboxaldehyde
XI 2-(methylsulfonyl)ethanamine
XII 3-methylbenzenamine
XIII 3-methylbenzenediazonium fluoride
XIV 1-fluoro-3-methylbenzene
XV 1-(chloromethyl)-3-fluorobenzene
XVI 2-chloro-4-nitrophenol
XVII 2-chloro-1-[[3-fluorophenyl]methoxy]-4-nitrobenzene
XVIII 2-chlorophenol
XIX 2-(diethoxymethyl)furan
XX lithium
XXI boric acid trimethyl ester

Sales

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DMF(Type II) and COS
Certificates

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