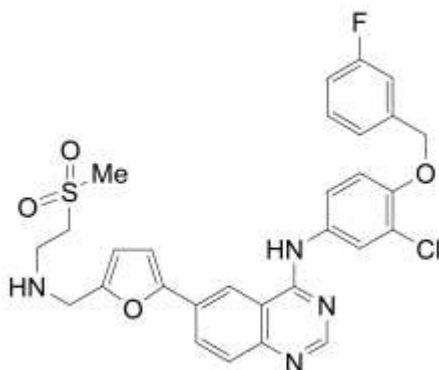


**Product**      **Lapatinib**



<i>Nomenclature</i>	N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine
<i>OtherNames</i>	Lapatinib Ditosylate (USAN)
<i>DevelopmentCode</i>	GW-572016 ; GW572016 ; GW-2016 ; GW2016 ; GW-572016F ; GW572016F ; GSK-572016 ; GSK572016 ; 572016
<i>Brand</i>	Tyverb (GSK: EU) Tykerb (GSK: USA)
<i>RN</i>	231277-92-2 ; 388082-78-8
<i>GeneralFormula</i>	C <sub>29</sub> H <sub>26</sub> ClFN <sub>4</sub> O <sub>4</sub> S
<i>MW</i>	581,1
<i>PriorityDate</i>	1998
<i>LaunchingDate</i>	2007
<i>LastUpdate</i>	2011/01
<i>Patent Info</i>	WO2006026313 (2006) Priority : US20040605404P, 27 Aug. 2004 (Smithkline Beecham Cork)

Preparation of IV (6-iodo-4(3H)-quinazolinone):

Junhui You, et al., Synthesis and anticoccidial activity of 4-(2-methoxyphenyl)-2-oxobutylquinazolinone derivatives , ARKIVOC 2008 (xvii) 1-11

Preparation of VI (4-chloro-6-iodoquinazoline):

Substituted Heteroaromatic Compounds And Their Use In Medicine:  
WO9609294 (1996) Priority : GB19940018852, 19 Sep. 1994 (Wellcome Found, GB)

Preparation of IX (5-formyl-2-furanboronic acid):

Method for metal-organic production of organic intermediate products by means of aryl lithium-bases

US20060131762 (2006) Priority : DE20021040262, 31 Aug. 2002 (Clariant Corporation)

Bicyclic Heteroaromatic Compounds As Protein Tyrosine Kinase Inhibitors:

WO9935146 (1999) Priority : GB19980000569, 12 Jan. 1998 (Glaxo Group Ltd., GB)

Anilinoquinazolines As Protein Tyrosine Kinase Inhibitors:

WO0104111 (2001) Priority : GB19990016213, 9 Jul. 1999 (Glaxo Group Ltd, GB)

Lapatinib Study Supports Cancer Stem Cell Hypothesis, Encourages Industry Research.

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Nahta R. et al., Lapatinib induces apoptosis in trastuzumab-resistant breast cancer cells: effects on insulin-like growth factor I signaling, Mol Cancer Ther. 2007 Feb;6(2):667-74.

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Nelson MH. et al., Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors, Ann Pharmacother. 2006 Feb;40(2):261-9.

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

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B.R. Keith et al. Anti-tumor activity of GW2016 in the ErbB-2 positive human breast cancer xenograft, BT474. *Proc Amer Assoc Cancer Res* 2001, 42: Abst 4308.

K.E. Lackey et al. The discovery of a new anti-cancer agent GW2016: A potent, dual EGFR/ErbB-2 tyrosine kinase inhibitor. *Proc Amer Assoc Cancer Res* 2001, 42: Abst 4582.

R.J. Mullin et al. Antitumor activity of GW2016 in the EGFR positive human head and neck cancer xenograft, HN5. *Proc Amer Assoc Cancer Res* 2001, 42: Abst 4579.

D.W. Rusnak et al. The effects of the novel EGFR/ErbB-2 tyrosine kinase inhibitor, Gw2016, on the growth of human normal and transformed cell lines. *Proc Amer Assoc Cancer Res* 2001, 42: Abst 4309.

W. Xia et al. GW2016, a dual inhibitor of ErbB-2 and EGFR tyrosine kinases: Effects on receptor tyrosine autophosphorylation downstream signalling intermediates, and in vivo anti-tumor activity. *Proc Amer Assoc Cancer Res* 2001, 42: Abst 3635.

*Originator*

GlaxoSmithKline (GSK)

<i>Developer</i>	GlaxoSmithKline (GSK)
<i>Market</i>	Launched
<i>Uses</i>	Antineoplastic High Potency Drug
<i>BioClass</i>	Cytotoxic ; Apoptotic ; Antiproliferative
<i>Reactions &amp; Technology</i>	Iodination Chlorination N-Arylation Palladium catalyzed coupling Reductive Amination Diazotation Sandmeyer Reaction O-Alkylation Nitro Reduction Nitration Lithiation Boric acid Synthesis
<i>Comments</i>	<p>High Potency Drug Technology</p> <p>Lapatinib is a dual kinase inhibitor indicated for the treatment of breast cancer and several othe solid tumors.</p> <p>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.</p> <p>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.</p> <p>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</p> <p>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.</p> <p>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).</p> <p>Marketing applications for Lapatinib (Tykerb/Tyverb) have been filed in the European Union, Switzerland, Canada, Brazil, Australia, and South Korea.</p> <p>December 2006: Lapatinib is ongoing 56 clinicals trials, from phase I to III, alone or</p>

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

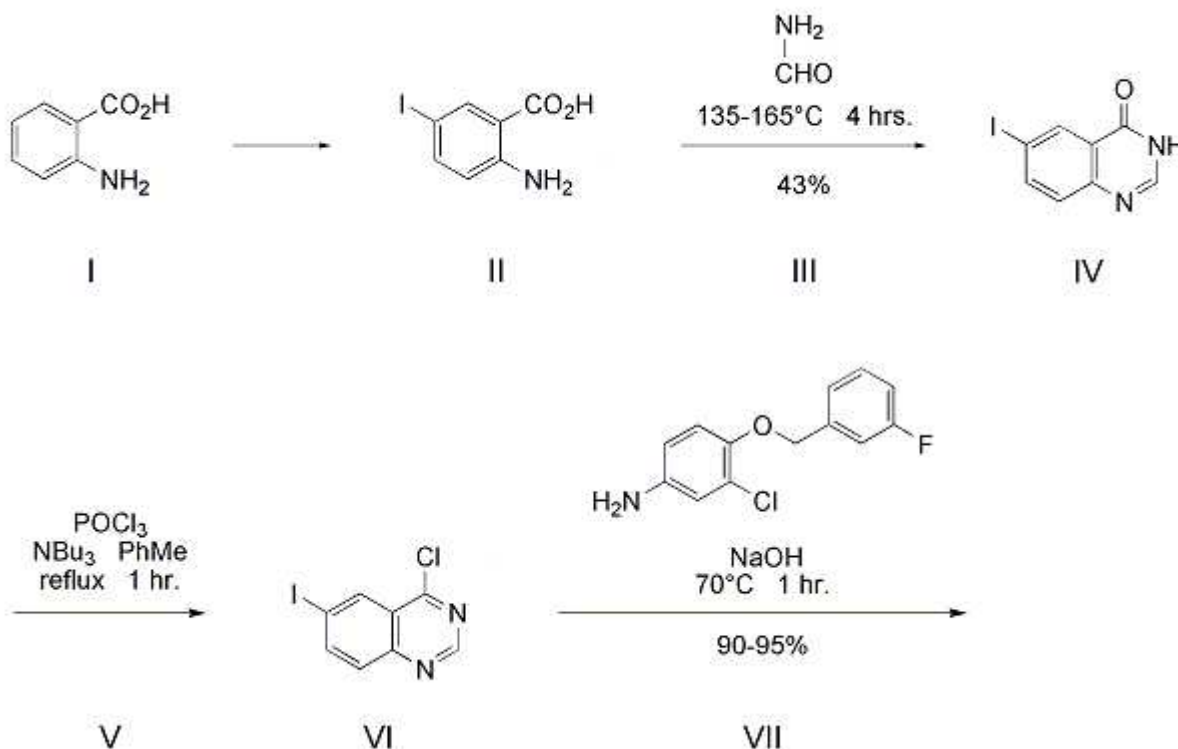
The compound is developed as the ditosylate salt (CAS-RN: 388082-78-8)

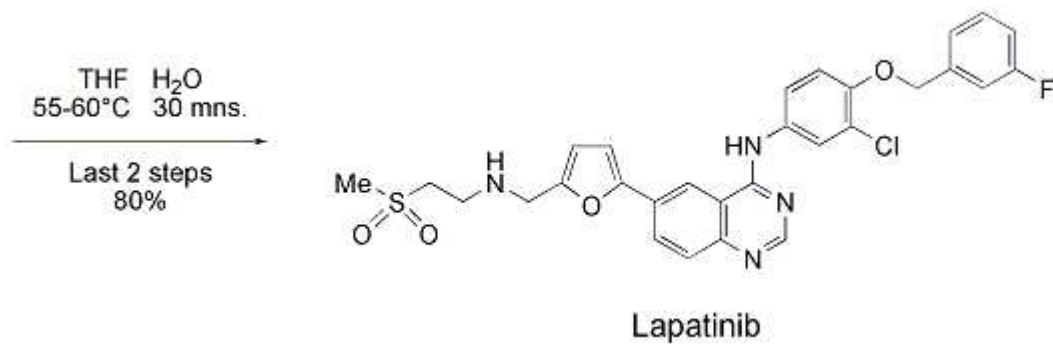
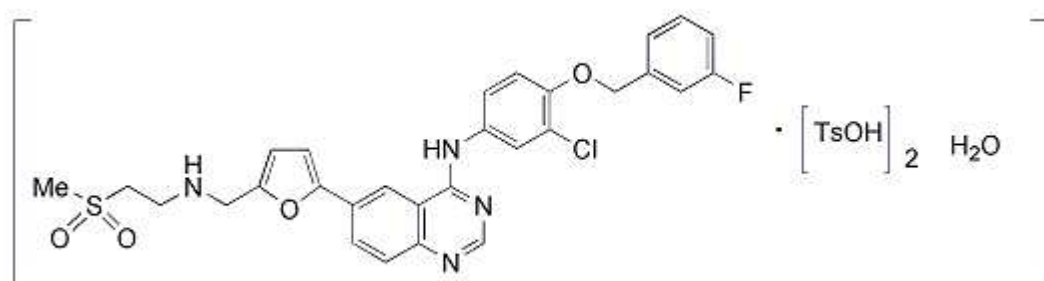
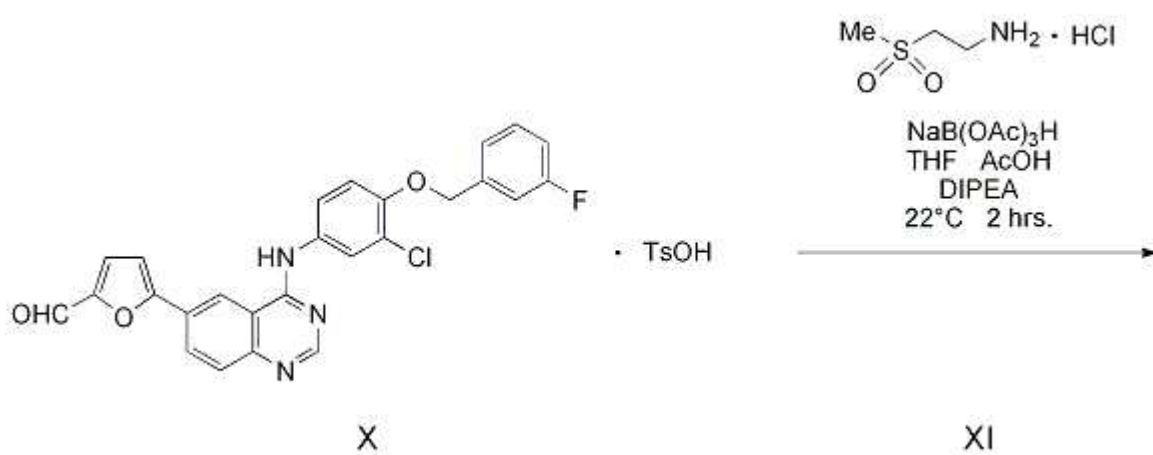
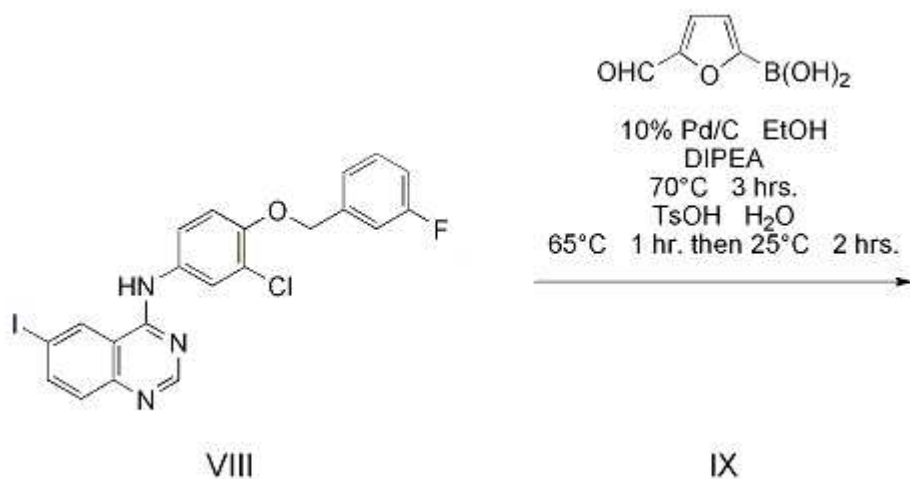
Tykerb (lapatinib ditosylate) is an epidermal growth factor receptor (EGFR) and ErbB-2 (Her2/neu) dual tyrosine kinase inhibitor, under development by GlaxoSmithKline as a treatment for solid tumours such as breast and lung cancer. This novel investigational agent has attracted considerable interest, 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.

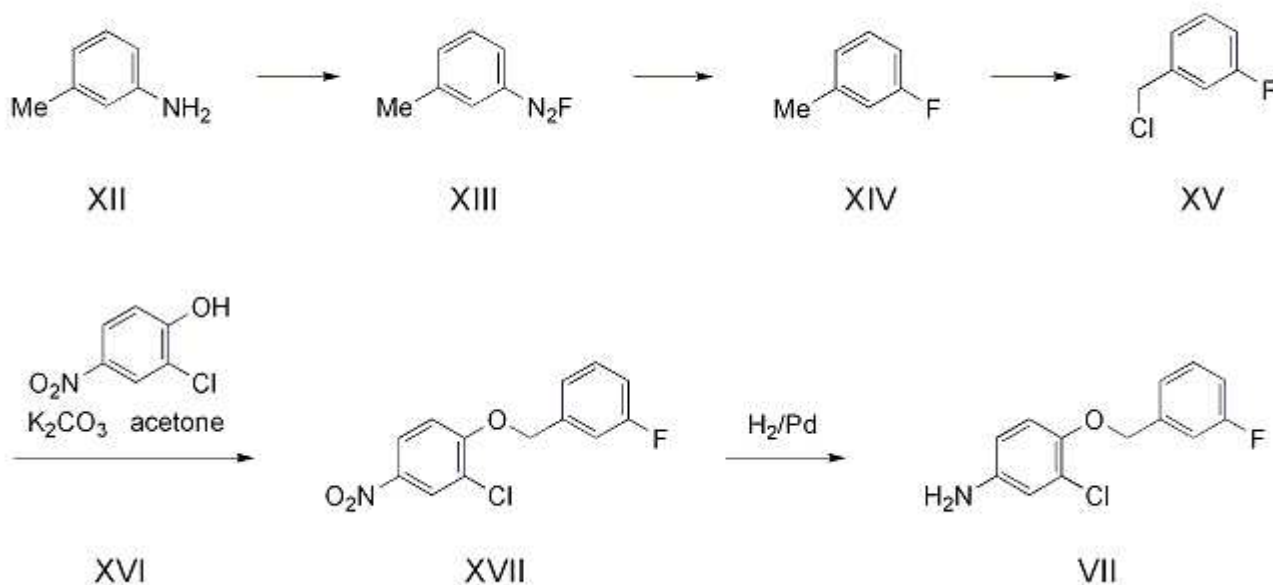
Tykerb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

- 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

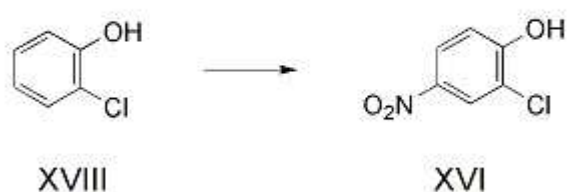




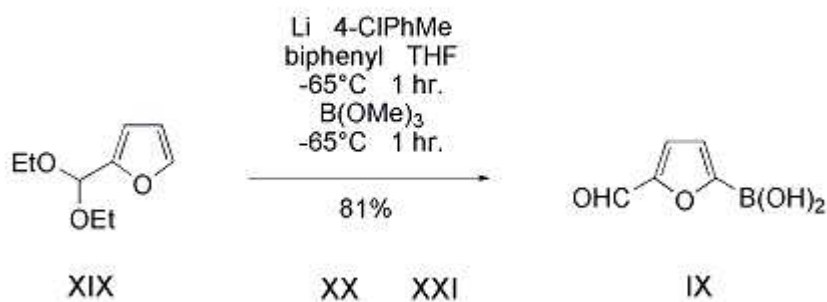
### Preparation of VII



### Preparation of XVI



### Preparation of IX



### 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-quinazoliny]-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**

<i>Brand</i>	<i>Year</i>	<i>Currency</i>	<i>Sales (millions)</i>	<i>Region</i>	<i>Volumes (kg)</i>
Tyverb/Tykerb - GSK	2010	EURO	330	World	3400
Tyverb/Tykerb - GSK	2010	USD	102	US	790
Tyverb/Tykerb - GSK	2010	EURO	137	Europe	1400
Tyverb/Tykerb - GSK	2010	EURO	92	Rest of the World	950
Tyverb/Tykerb - GSK	2009	USD	250	World	3800
Tyverb/Tykerb - GSK	2009	USD	110	US	1200
Tyverb/Tykerb - GSK	2009	EURO	110	Europe	1700
Tyverb/Tykerb - GSK	2009	EURO	58	Rest of the world	880
Tykerb - GSK	2008	EURO	149	World	
Tykerb - GSK	2008	EURO	68	US	
Tykerb - GSK	2008	EURO	61	Europe	
Tykerb - GSK	2008	EURO	19	Rest of the world	
Tykerb - GSK	2007	EURO	74	World	
Tykerb - GSK	2007	EURO	52	US	
Tykerb - GSK	2007	EURO	19	Europe	
Tykerb - GSK	2007	EURO	3	Rest of the world	

### **DMF(Type II) and COS Certificates**

<i>Entry</i>	<i>Dmf-Cos</i>	<i>Number</i>	<i>Holder</i>	<i>Status</i>	<i>Subs. Date</i>	<i>Certificate Title</i>
1	DMF	24788	FORMOSA LABORATORIES INC	Active	18/03/11	LAPATINIB DITOSYLATE AS MANUFACTURED IN TAOYUAN, TAIWAN

## ***Dosage***

<i>Country</i>	<i>Brand</i>	<i>Estimated Bulk Price (/kg API)</i>	<i>Formulation Average Price (/kg API)</i>
France	Tyverb	EURO 66000	EURO 6600

## ***SPC***

<i>Country</i>	<i>Patent Number</i>	<i>Original Expiry</i>	<i>Brand</i>	<i>Certificate Granted</i>	<i>Current Expiry</i>
Australia	AU749549B	08/01/19	TYKERB	yes	28/06/22
Austria	EP1047694	08/01/19		yes	10/06/23
Belgium	EP1047694	08/01/19		yes	11/06/23
Denmark	EP1047694	08/01/19		pending	08/01/19
Estonia	EE4616	08/01/19	Tyverb	yes	10/06/23
Finland	EP1047694	08/01/19		pending	08/01/19
France	EP1047694	08/01/19		pending	08/01/19
Germany	DE69918528T	08/01/19		pending	08/01/19
Iceland	IS2276	27/06/20		yes	10/06/23
Ireland	EP1047694	08/01/19		pending	08/01/19
Netherlands	EP1047694	08/01/19		yes	09/06/23
Norway			TYVERG	pending	
Sweden	EP1047694	08/01/19		pending	08/01/19
Switzerland	EP1047694	08/01/19		yes	22/05/22
UK	EP1047694	08/01/19		yes	08/01/19
USA	Product Exclusivity Data		TYKERB		13/03/12
USA	Product Exclusivity Data		TYKERB		29/01/13
USA	US6391874		TYKERB	yes	11/07/17
USA	US6713485		TYKERB	yes	29/09/20
USA	US6727256		TYKERB	yes	08/01/19
USA	US6828320		TYKERB	yes	11/07/17
USA	US7157466		TYKERB	yes	19/11/21

## ***SPC Details***

<i>Country</i>	Australia
<i>Patent Number</i>	AU749549B
<i>Original Expiry</i>	08/01/19
<i>Certificate Application</i>	yes
<i>Certificate Granted</i>	yes
<i>Current Expiry</i>	28/06/22

*Brand* TYKERB  
*Patent Title* Bicyclic heteroaromatic compounds as protein tyrosine kinase inhibitors  
*Inventor* GLAXO GROUP  
*Extension Granted* yes  
*Delivery Date* 27/09/07  
*Original Expiry Date* 08/01/19  
*Current Expiry Date* 28/06/22

*Country* Austria  
*Patent Number* EP1047694  
*Original Expiry Date* 08/01/19  
*Certificate Application* yes  
*Certificate Granted* yes  
*Current Expiry Date* 10/06/23  
*Patent Title* Bicyclic heteroaromatic compounds as protein  
*Inventor* GLAXO GROUP  
*International* EU/1/07/440/001-002  
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*Current Expiry Date* 10/06/23

*Country* Belgium  
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*Patent Title* Bicyclic heteroaromatic compounds as protein  
*Inventor* GLAXO GROUP LIMITED  
*International* EU/1/07/440/001  
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*Current Expiry Date* 11/06/23

*Country* Denmark

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*Patent Title* BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS  
*Inventor* Glaxo Group Limited  
*International* EU/1/07/440/001-002  
*Certificate Number* CA 2008 00040  
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*Inventor* Glaxo Group Limited  
*International* C(2008)2742  
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*Patent Title* BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS  
*Inventor* Glaxo Group

*International* EU/1/07/440/001-002  
*Certificate Number* C 2008 0022  
*Certificate Date* 18/09/08  
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*Original Expiry Date* 08/01/19  
*Current Expiry Date* 08/01/19

*Country* France  
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*Current Expiry* 08/01/19  
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*Inventor* GLAXO GROUP  
*International* EU/1/07/440/001  
*Certificate Number* 08C0038  
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*Extension Granted* pending  
*Original Expiry Date* 08/01/19  
*Current Expiry Date* 08/01/19

*Country* Germany  
*Patent Number* DE69918528T  
*Original Expiry* 08/01/19  
*Certificate Application* yes  
*Certificate Granted* pending  
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*Patent Title* BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS  
*Inventor* Glaxo Group  
*International* EU/1/07/440/001-002  
*Certificate Number* 12 2008 000 048.3  
*Extension Granted* pending  
*Original Expiry Date* 08/01/19  
*Current Expiry Date* 08/01/19

*Country* Iceland  
*Patent Number* IS2276  
*Original Expiry* 27/06/20

*Certificate Application* yes  
*Certificate Granted* yes  
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*Patent Title* BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS  
*Inventor* Glaxo Group Limited  
*International* EU/1/07/440/001-002/IS  
*Certificate Number* 0001/08  
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*Extension Granted* yes  
*Delivery Date* 15/02/09  
*Original Expiry Date* 27/06/20  
*Current Expiry Date* 10/06/23

*Country* Ireland  
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*Original Expiry* 08/01/19  
*Certificate Application* yes  
*Certificate Granted* pending  
*Current Expiry* 08/01/19  
*Patent Title* Bicyclic heteroaromatic compounds as protein  
*Inventor* GLAXO GROUP LIMITED  
*International* EU/1/07/440/001-002  
*Certificate Number* 2008/026  
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*Country* Netherlands  
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*Patent Title* BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS  
*Inventor* Glaxo Wellcome House  
*International* EU/1/07/440/001-002  
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*Delivery Date* 04/12/08  
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*Current Expiry Date* 09/06/23

*Country* Norway  
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*Certificate Granted* pending  
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*Inventor* Glaxo Group  
*International* EU107440001/NO-002/NO  
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*Current Expiry* 08/01/19  
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*Inventor* GLAXO GROUP  
*International* EU/1/07/440/001  
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*Extension Granted* pending  
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*Current Expiry Date* 08/01/19

*Country* Switzerland  
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*Patent Title* BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS  
*Inventor* GLAXO GROUP LIMITED  
*International* 57937  
*Certificate Number* C01047694/01  
*Certificate Date* 22/08/07  
*Extension Granted* yes  
*Delivery Date* 31/03/09

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<i>Current Expiry Date</i>	22/05/22
<i>Country</i>	UK
<i>Patent Number</i>	EP1047694
<i>Original Expiry Date</i>	08/01/19
<i>Certificate Application</i>	yes
<i>Certificate Granted</i>	yes
<i>Current Expiry Date</i>	08/01/19
<i>Patent Title</i>	Bicyclic heteroaromatic compounds as proteintyrosine kinase inhibitors
<i>Inventor</i>	Glaxo Group Limited
<i>International</i>	EU/1/07/440/001-002
<i>Certificate Number</i>	GB08/044
<i>Certificate Date</i>	09/09/08
<i>Extension Granted</i>	yes
<i>Original Expiry Date</i>	08/01/19
<i>Current Expiry Date</i>	08/01/19
<i>Country</i>	USA
<i>Patent Number</i>	Product Exclusivity Data
<i>Current Expiry Date</i>	13/03/12
<i>Brand</i>	TYKERB
<i>Inventor</i>	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE
<i>International</i>	022059/001
<i>Current Expiry Date</i>	13/03/12
<i>Country</i>	USA
<i>Patent Number</i>	Product Exclusivity Data
<i>Current Expiry Date</i>	29/01/13
<i>Brand</i>	TYKERB
<i>Inventor</i>	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE
<i>International</i>	022059/001
<i>Current Expiry Date</i>	29/01/13
<i>Country</i>	USA
<i>Patent Number</i>	US6391874
<i>Certificate Granted</i>	yes
<i>Current Expiry Date</i>	11/07/17
<i>Brand</i>	TYKERB
<i>Inventor</i>	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE
<i>International</i>	022059/001
<i>Extension Granted</i>	yes

*Current Expiry Date* 11/07/17

*Country* USA  
*Patent Number* US6713485  
*Certificate Granted* yes  
*Current Expiry Date* 29/09/20  
*Brand* TYKERB  
*Inventor* SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE  
*International* 022059/001  
*Extension Granted* yes  
*Current Expiry Date* 29/09/20

*Country* USA  
*Patent Number* US6727256  
*Certificate Granted* yes  
*Current Expiry Date* 08/01/19  
*Brand* TYKERB  
*Inventor* SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE  
*International* 022059/001  
*Extension Granted* yes  
*Current Expiry Date* 08/01/19

*Country* USA  
*Patent Number* US6828320  
*Certificate Granted* yes  
*Current Expiry Date* 11/07/17  
*Brand* TYKERB  
*Inventor* SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE  
*International* 022059/001  
*Extension Granted* yes  
*Current Expiry Date* 11/07/17

*Country* USA  
*Patent Number* US7157466  
*Certificate Granted* yes  
*Current Expiry Date* 19/11/21  
*Brand* TYKERB  
*Inventor* SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE  
*International* 022059/001  
*Extension Granted* yes  
*Current Expiry Date* 19/11/21