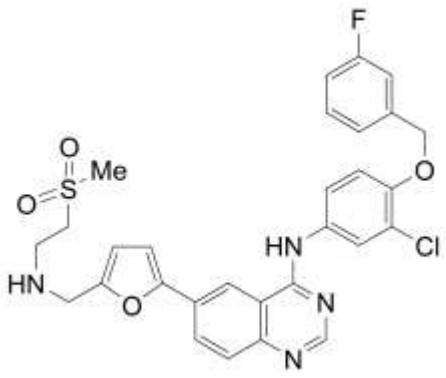
Product **Lapatinib**



Nomenclature	N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine
OtherNames	Lapatinib Ditosylate (USAN)
DevelopmentCode	GW-572016 ; GW572016 ; GW-2016 ; GW2016 ; GW-572016F ; GW572016F ; GSK-572016 ; GSK572016 ; 572016
Brand	Tyverb (GSK: EU) Tykerb (GSK: USA)
RN	231277-92-2 ; 388082-78-8
GeneralFormula	C29H26ClFN4O4S
MW	581,1
PriorityDate	1998
LaunchingDate	2007
LastUpdate	2011/01
Patent Info	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)

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Schmidt C.
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Konecny GE. et al., Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells, Cancer Res. 2006 Feb 1;66(3):1630-9.

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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Xia W. et al., Combining lapatinib (GW572016), a small molecule inhibitor of ErbB1 and ErbB2 tyrosine kinases, with therapeutic anti-ErbB2 antibodies enhances apoptosis of ErbB2-overexpressing breast cancer cells, Oncogene. 2005 Sep 15;24(41):6213-21.

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Originator GlaxoSmithKline (GSK)

Developer	GlaxoSmithKline (GSK)
Market	Launched
Uses	Antineoplastic High Potency Drug
BioClass	Cytotoxic ; Apoptotic ; Antiproliferative
Reactions & Technology	Iodination Chlorination N-Arylation Palladium catalyzed coupling Reductive Amination Diazotation Sandmeyer Reaction O-Alkylation Nitro Reduction Nitration Lithiation Boric acid Synthesis
	High Potency Drug Technology
Comments	Lapatinib is a dual kinase inhibitor indicated for the treatment of breast cancer and several othe 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 clinicals 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.

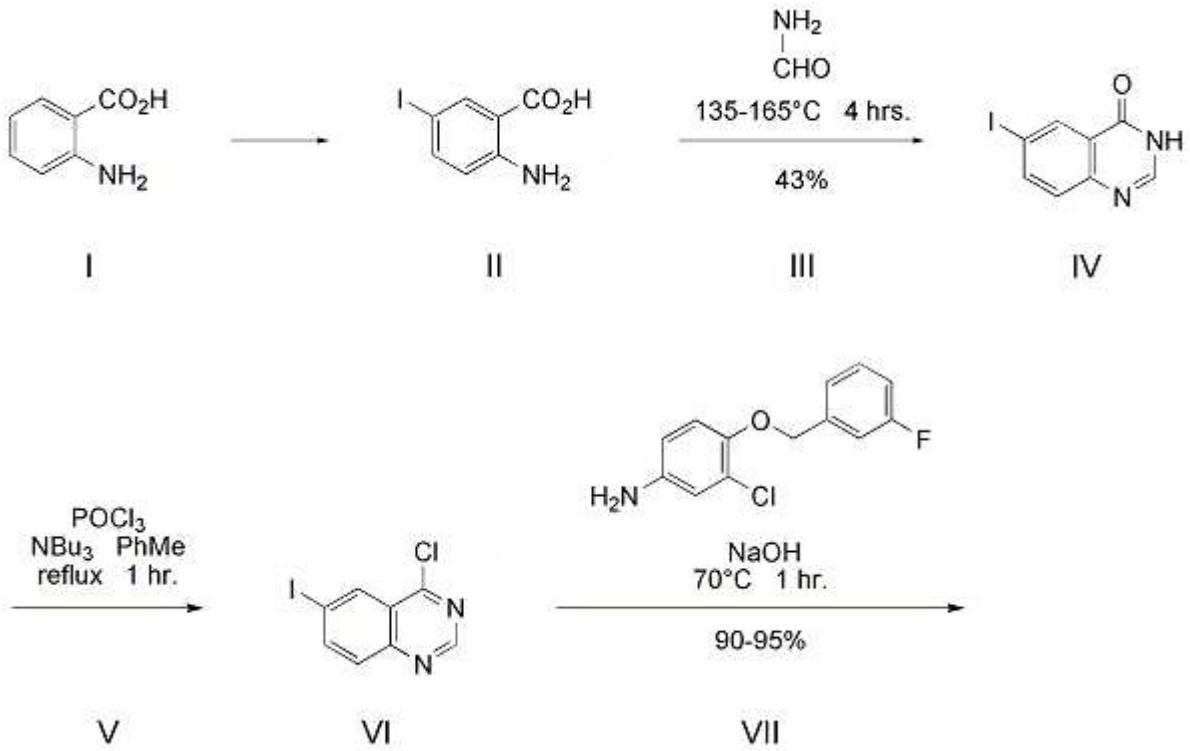
2003: Phase III

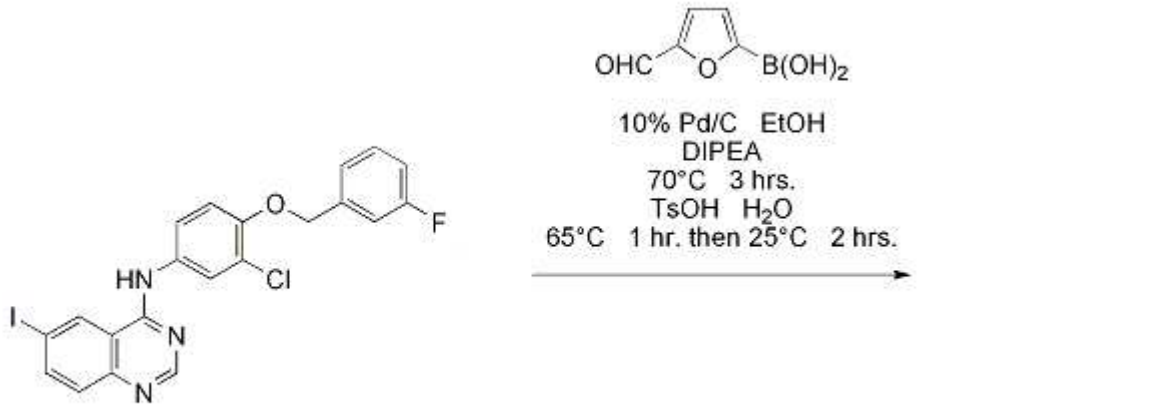
The compound is developed as the ditosylate salt (CAS-RN: 388082-78-8)

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.

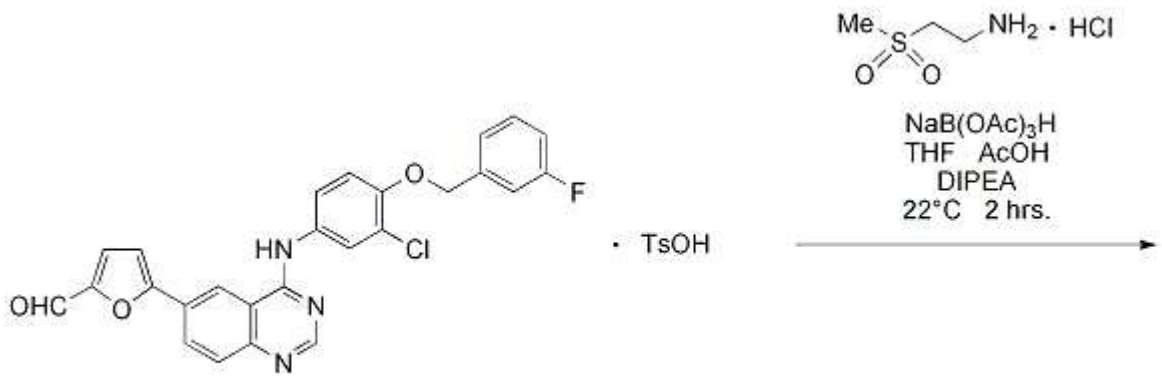
Tyverb is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

- 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

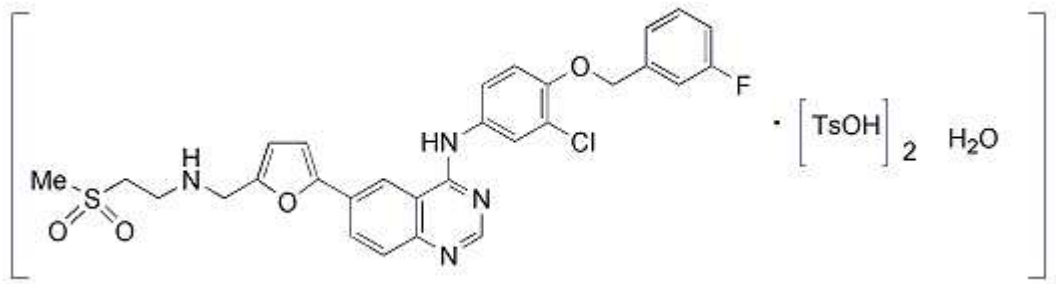


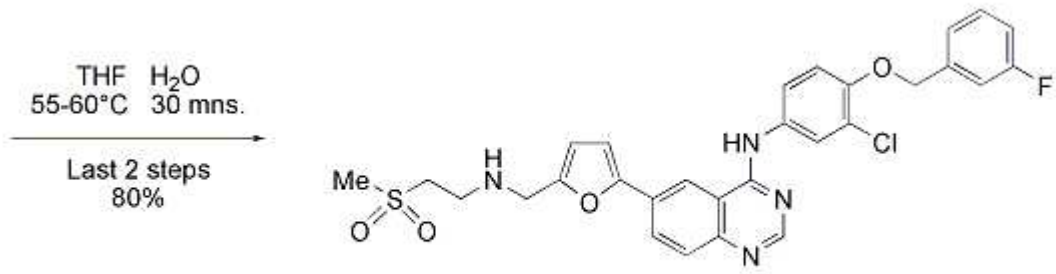


VIII IX



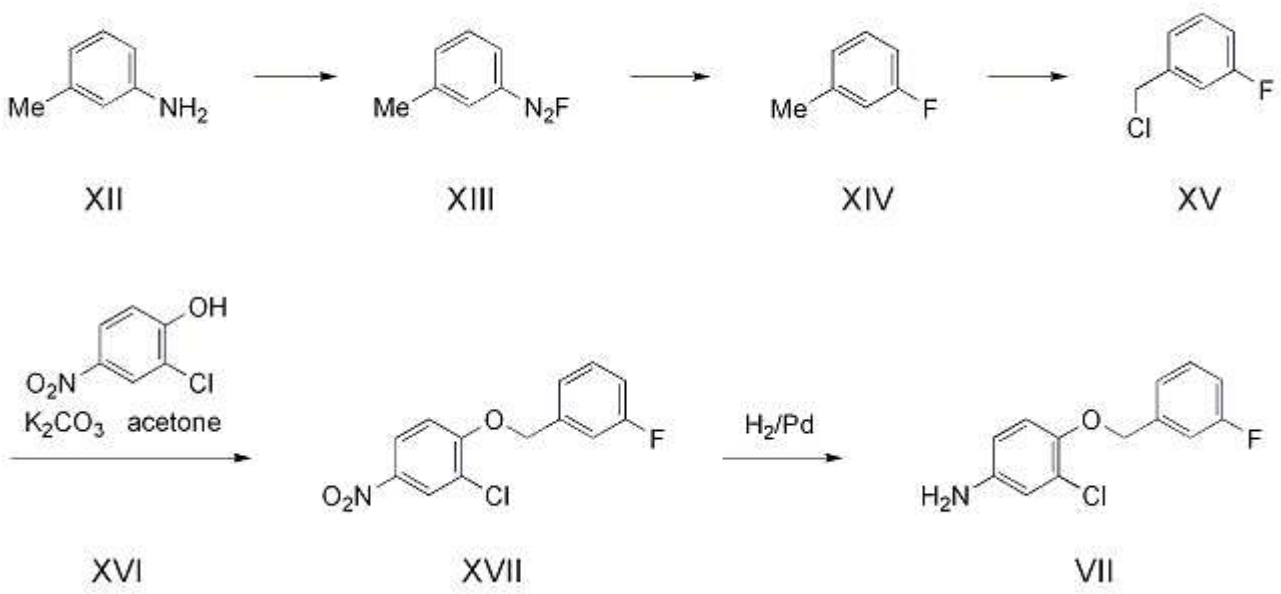
X XI





Lapatinib

Preparation of VII



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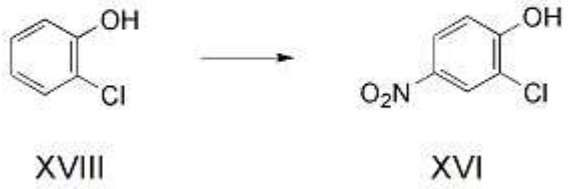

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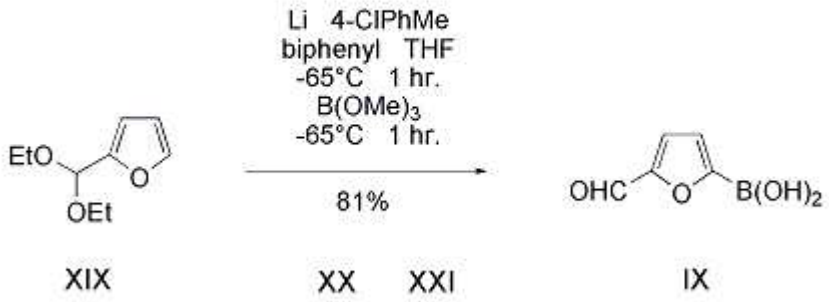

Intermediates List

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

Brand	*Year*	*Currency*	*Sales (millions)*	*Region*	*Volumes (kg)*
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

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

Dosage

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

SPC

Country	*Patent Number*	*Original Expiry*	*Brand*	*Certificate Granted*	*Current Expiry*
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

Country	Australia
Patent Number	AU749549B
Original Expiry	08/01/19
Certificate Application	yes
Certificate Granted	yes
Current Expiry	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	08/01/19
Certificate Application	yes
Certificate Granted	yes
Current Expiry	10/06/23
Patent Title	Bicyclic heteroaromatic compounds as protein
Inventor	GLAXO GROUP
International	EU/1/07/440/001-002
Certificate Number	SZ 37/2008
Certificate Date	17/10/08
Extension Granted	yes
Delivery Date	15/01/09
Original Expiry Date	08/01/19
Current Expiry Date	10/06/23

Country	Belgium
Patent Number	EP1047694
Original Expiry	08/01/19
Certificate Application	yes
Certificate Granted	yes
Current Expiry	11/06/23
Patent Title	Bicyclic heteroaromatic compounds as protein
Inventor	GLAXO GROUP LIMITED
International	EU/1/07/440/001
Certificate Number	2008C/035
Certificate Date	09/10/08
Extension Granted	yes
Delivery Date	03/02/09
Original Expiry Date	08/01/19
Current Expiry Date	11/06/23

Country	Denmark

Patent Number	EP1047694
Original Expiry	08/01/19
Certificate Application	yes
Certificate Granted	pending
Current Expiry	08/01/19
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
Certificate Date	23/10/08
Extension Granted	pending
Original Expiry Date	08/01/19
Current Expiry Date	08/01/19

Country	Estonia
Patent Number	EE4616
Original Expiry	08/01/19
Certificate Application	yes
Certificate Granted	yes
Current Expiry	10/06/23
Brand	Tyverb
Patent Title	BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS
Inventor	Glaxo Group Limited
International	C(2008)2742
Certificate Number	C20080005
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Extension Granted	yes
Delivery Date	15/02/09
Original Expiry Date	08/01/19
Current Expiry Date	10/06/23

Country	Finland
Patent Number	EP1047694
Original Expiry	08/01/19
Certificate Application	yes
Certificate Granted	pending
Current Expiry	08/01/19
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
Extension Granted	pending
Original Expiry Date	08/01/19
Current Expiry Date	08/01/19

Country	France
Patent Number	EP1047694
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
International	EU/1/07/440/001
Certificate Number	08C0038
Certificate Date	01/10/08
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
Current Expiry	08/01/19
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
Current Expiry	10/06/23
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
Certificate Date	12/09/08
Extension Granted	yes
Delivery Date	15/02/09
Original Expiry Date	27/06/20
Current Expiry Date	10/06/23

Country	Ireland
Patent Number	EP1047694
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
Certificate Date	17/09/08
Extension Granted	pending
Original Expiry Date	08/01/19
Current Expiry Date	08/01/19

Country	Netherlands
Patent Number	EP1047694
Original Expiry	08/01/19
Certificate Application	yes
Certificate Granted	yes
Current Expiry	09/06/23
Patent Title	BICYCLIC HETEROAROMATIC COMPOUNDS AS PROTEIN TYROSINE KINASE INHIBITORS
Inventor	Glaxo Wellcome House
International	EU/1/07/440/001-002
Certificate Number	300360
Certificate Date	12/09/08
Extension Granted	yes

Delivery Date	04/12/08
Original Expiry Date	08/01/19
Current Expiry Date	09/06/23

Country	Norway
Certificate Application	yes
Certificate Granted	pending
Brand	TYVERG
Inventor	Glaxo Group
International	EU107440001/NO-002/NO
Certificate Number	2008017
Certificate Date	13/11/08
Extension Granted	pending

Country	Sweden
Patent Number	EP1047694
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
International	EU/1/07/440/001
Certificate Number	0890036-7
Extension Granted	pending
Original Expiry Date	08/01/19
Current Expiry Date	08/01/19

Country	Switzerland
Patent Number	EP1047694
Original Expiry	08/01/19
Certificate Application	yes
Certificate Granted	yes
Current Expiry	22/05/22
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

Original Expiry Date	08/01/19
Current Expiry Date	22/05/22

Country	UK
Patent Number	EP1047694
Original Expiry	08/01/19
Certificate Application	yes
Certificate Granted	yes
Current Expiry	08/01/19
Patent Title	Bicyclic heteroaromatic compounds as proteintyrosine kinase inhibitors
Inventor	Glaxo Group Limited
International	EU/1/07/440/001-002
Certificate Number	GB08/044
Certificate Date	09/09/08
Extension Granted	yes
Original Expiry Date	08/01/19
Current Expiry Date	08/01/19

Country	USA
Patent Number	Product Exclusivity Data
Current Expiry	13/03/12
Brand	TYKERB
Inventor	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE
International	022059/001
Current Expiry Date	13/03/12

Country	USA
Patent Number	Product Exclusivity Data
Current Expiry	29/01/13
Brand	TYKERB
Inventor	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE
International	022059/001
Current Expiry Date	29/01/13

Country	USA
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Certificate Granted	yes
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Inventor	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE
International	022059/001
Extension Granted	yes

Current Expiry Date	11/07/17

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Patent Number	US6713485
Certificate Granted	yes
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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	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	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	19/11/21
Brand	TYKERB
Inventor	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE
International	022059/001
Extension Granted	yes
Current Expiry Date	19/11/21