Tarceva

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
T/0073	Transfer of Marketing Authorisation	24/10/2024	14/11/2024	SmPC, Labelling and PL	
PSUSA/1255/ 202311	Periodic Safety Update EU Single assessment - erlotinib	11/07/2024	n/a		PRAC Recommendation - maintenance

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

II/0071	Please refer to the Recommendations section above C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	16/03/2023	14/03/2024	SmPC and PL	Not applicable
PSUSA/1255/ 202111	Periodic Safety Update EU Single assessment - erlotinib	21/07/2022	19/09/2022		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1255/202111.
IA/0069	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	09/02/2022	n/a		
IA/0068	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	14/07/2021	18/02/2022	SmPC, Annex II, Labelling and PL	
IB/0067	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/02/2021	18/02/2022	SmPC and PL	
PSUSA/1255/ 201911	Periodic Safety Update EU Single assessment - erlotinib	09/07/2020	n/a		PRAC Recommendation - maintenance
IA/0065/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-	30/04/2020	n/a		

	sterile medicinal products B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
IA/0063	A.7 - Administrative change - Deletion of manufacturing sites	02/10/2019	n/a		
IB/0062/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.II.z - Quality change - Finished product - Other variation	29/04/2019	n/a		
IB/0061/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/01/2019	n/a		

II/0058	Update of sections 4.2, 4.5 and 5.1 of the SmPC based on phase III clinical study MO22162 (CURRENTS) comparing a higher dose of Tarceva (300 mg) over the recommended daily dose (150 mg) in current smokers with locally advanced or metastatic non-small cell lung cancer (NSCLC) in the second-line setting after failure of chemotherapy. The Package Leaflet is updated accordingly. The RMP version 7.1 has been agreed, as part of this application. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in sections 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC. Moreover, Annex II has been updated, as additional risk minimisation measures (educational material) have been deleted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/11/2018	07/02/2019	SmPC, Annex II and PL	EGFR mutation testing should be performed in accordance with the approved indications. In a double-blind, randomised phase III study (MO22162, CURRENTS) comparing two doses of Tarceva (300 mg versus 150 mg) in current smokers (mean of 38 pack years) with locally advanced or metastatic NSCLC in the second-line setting after failure on chemotherapy, the 300 mg dose of Tarceva demonstrated no PFS benefit over the recommended dose (7.00 vs 6.86 weeks, respectively). Secondary efficacy endpoints were all consistent with the primary endpoint and no difference was detected for OS between patients treated with erlotinib 300 mg and 150 mg daily (HR 1.03, 95% CI 0.80 to 1.32). Safety data were comparable between the 300 mg and 150 mg doses; however, there was a numerical increase in the incidence of rash, interstitial lung disease and diarrhoea, in patients receiving the higher dose of erlotinib. Based on the data from the CURRENTS study, no evidence was seen for any benefit of a higher erlotinib dose of 300 mg when compared with the recommended dose of 150 mg in active smokers. Patients in this study were not selected based on EGFR mutation status.
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	07/02/2019	PL	
IA/0059/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	02/08/2018	n/a		

	specification parameter to the specification with its corresponding test method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
PSUSA/1255/ 201711	Periodic Safety Update EU Single assessment - erlotinib	14/06/2018	n/a		PRAC Recommendation - maintenance
T/0057	Transfer of Marketing Authorisation	20/02/2018	06/04/2018	SmPC, Labelling and PL	
II/0052	Update of section 4.4 of the SmPC in order to include recommendations on Epidermal Growth Factor Receptor (EGFR) mutation status testing, to be in line with current technical and scientific progress. In addition, the Marketing authorisation holder (MAH) took the opportunity to make a minor correction in section 4.2 of the SmPC and minor editorial changes and to bring the PI in line with the latest QRD template version 10. Furthermore, the Annex II has been corrected, as requested by the EMA, to include Educational Material as an additional risk minimisation measure, which are already included in the RMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2018	07/02/2019	SmPC and Annex II	When considering the use of Tarceva as a first line or maintenance treatment for locally advanced or metastatic NSCLC, it is important that the EGFR mutation status of a patient is determined. A validated, robust, reliable and sensitive test with a prespecified positivity threshold and demonstrated utility for the determination of EGFR mutation status, using either tumor DNA derived from a tissue sample or circulating free DNA (cfDNA) obtained from a blood (plasma) sample, should be performed according to local medical practice. If a plasma-based cfDNA test is used and the result is negative for activating mutations, perform a tissue test wherever possible due to the potential for false negative results from a plasma-based test.
IG/0887	A.5.b - Administrative change - Change in the name	29/01/2018	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
II/0051	Update of section 4.1 of the SmPC in relation to the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen based on a review of relevant literature, Real World Data Reports (BIOMARQUEURS FRANCE CSR and ESCAP-2011-CPHG CSR) and a new CSR Addendum of the previously submitted relevant pivotal study BR.21, as requested by the CHMP following assessment of variation EMEA/H/C/000618/II/0043 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/11/2017	11/12/2017	SmPC	Tarceva is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In patients with tumours without EGFR activating mutations, Tarceva is indicated when other treatment options are not considered suitable.
IA/0054	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	08/12/2017	n/a		
PSUSA/1255/ 201611	Periodic Safety Update EU Single assessment - erlotinib	06/07/2017	n/a		PRAC Recommendation - maintenance
IA/0053	A.7 - Administrative change - Deletion of manufacturing sites	23/06/2017	n/a		
IA/0049	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	21/11/2016	n/a		

IB/0048	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	12/11/2016	30/10/2017	SmPC	
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/07/2016	30/10/2017	Labelling	
IA/0046	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	20/06/2016	n/a		
PSUSA/1255/ 201511	Periodic Safety Update EU Single assessment - erlotinib	09/06/2016	n/a		PRAC Recommendation - maintenance
II/0045	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/05/2016	n/a		
II/0043	Modification of the indication to limit maintenance treatment to NSCLC patients with an EGFR-activating mutation and stable disease after first-line chemotherapy based on the data from study BO25460 (IUNO). Consequently, SmPC sections 4.1, 4.8 and 5.1 have been updated. The Package leaflet is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/12/2015	25/01/2016	SmPC and PL	Please refer to the Scientific Discussion Tarceva-II-43.

IG/0573	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	01/07/2015	n/a		
PSUSA/1255/ 201411	Periodic Safety Update EU Single assessment - erlotinib	11/06/2015	n/a		PRAC Recommendation - maintenance
IB/0040/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	07/01/2015	n/a		
IG/0497	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	18/11/2014	n/a		
PSUV/0036	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance

IA/0038	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	16/04/2014	n/a		
IA/0037	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	25/02/2014	n/a		
II/0034	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/01/2014	n/a		
IB/0035	B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	18/12/2013	n/a		
II/0033	Update of section 4.8 of the SmPC to add the adverse reaction uveitis with a frequency very rare. The Package Leaflet was updated accordingly. Minor editorial or typographical corrections have been implemented throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2013	08/10/2014	SmPC and PL	Following a recommendation from the CHMP the MAH has been closely monitoring events of uveitis, in order to determine whether an update to the existing safety information wording on ocular events would be required. Further to the review of the available safety data, clinical data and literature, it is considered that uveitis may have a causal relationship with erlotinib treatment. Consequently, the product information of Tarceva has been updated to add the adverse reaction uveitis with a frequency very rare.
II/0032	Update of section 5.1 of the SmPC in order to include updated efficacy results from study ML20650 (EURTAC) of erlotinib in the first-line treatment of patients with locally advanced or metastatic non-	24/10/2013	08/10/2014	SmPC	As a part of the approval of the indication of erlotinib in the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)−activating

	small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) - activating mutations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				mutations the MAH committed to provide updated Overall survival and Progression free survival data from study ML20650 (EURTAC) as the approval was based on interim data. These updated results are in line with the results seen in the interim analysis and confirm the clinical benefit of Tarceva in this indication.
IB/0030/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	22/02/2013	n/a		

	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0031	Update of section 4.8 of the SmPC in order to include the adverse reaction Palmar-Plantar Erythrodysaesthesia Syndrome (PPES) as requested by the PRAC. The Package Leaflet has been updated accordingly. Furthermore, the PI has been brought in line with the latest QRD template version 8.3. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/02/2013	26/08/2013	SmPC, Annex II and PL	Following a Pharmacovigilance Risk Assessment Committee (PRAC) review of cases of Palmar-plantar erythrodysaesthesia syndrome (PPES) for Tarceva, the MAH has updated section 4.8 of the SmPC in order to include PPES as an adverse reaction with a frequency of rare. In addition, the Package Leaflet has been updated to describe the rare adverse reaction as "flushed or painful palms or soles" accordingly. Editorial amendments to the product information in line with updated templates have also been introduced.
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
IAIN/0028/G	This was an application for a group of variations. B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition	27/09/2012	29/10/2012	SmPC and PL	

	of inks used for product marking - Changes in imprints, bossing or other markings A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
II/0027	Update of section 4.8 of the SmPC to add the adverse reactions folliculitis and acne/dermatitis acneiform further to a review of infections in skin, subcutaneous tissue and mucosa performed by the MAH at the request of the CHMP in the assessment of the renewal. The Package Leaflet was updated accordingly. The MAH also took the opportunity to update the product information in line with QRD template version 8.1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	21/06/2012	SmPC, Annex II, Labelling and PL	Further to the CHMP request, the MAH conducted a review of skin infection events reported during with erlotinib in clinical studies, post-marketing experience as well as a review of epidemiology data and literature. Based on the reviewed data, a casual relationship exists between some skin infections (acne, dermatitis acneiform, folliculitis, cellulitis and paronychia). The SmPC already contained wording on skin infection manifested as severe infection including cellulitis, paronychia and rash including dermatitis acneiform. As a consequence, the SmPC was further updated to add the adverse reactions folliculitis and acne/dermatitis acneiform with a common frequency.
II/0020	Extension of indication of Tarceva for the first-line treatment of locally advanced or metastatic NSCLC with EGFR activating mutations. The MAH also applied to revise the warnings on keratitis in section 4.4 of the SmPC and sections 2, 4 of the Package Leaflet following a request from the CHMP to harmonise the wording across EGFR inhibitor products. Annex II has also been updated to reflect the latest Risk Management Plan version	21/07/2011	24/08/2011	SmPC, Annex II and PL	Please see Scientific discussion H-618-II-0020.

	number (RMP v. 3.1). The MAH took the opportunity to introduce amendments to the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0026	Update of section 5.3 of the SmPC following the completion of the 2 year carcinogenicity studies conducted with erlotinib in rats and mice. In addition to this, further to the assessment of FUM 32 (user testing) the MAH took the opportunity to include some minor layout changes to the sections 2 and 4 of the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	18/05/2011	SmPC and PL	Update of section 5.3 of the SmPC following the completion of the 2 year carcinogenicity studies conducted with erlotinib in rats and mice. In addition to this, further to the assessment of FUM 32 (user testing) the MAH took the opportunity to include some minor layout changes to the sections 2 and 4 of the PL.
IB/0024/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	03/09/2010	n/a		

IB/0023/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	03/09/2010	n/a		
IA/0025	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/08/2010	n/a		
IB/0021	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	12/08/2010	n/a	SmPC	

IA/0022	B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	03/08/2010	n/a		
R/0018	Renewal of the marketing authorisation.	22/04/2010	02/07/2010	SmPC, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Tarceva continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation with unlimited validity.
II/0019/G	This was an application for a group of variations. Update of section 4.5 of the Summary of Product Characteristics (SmPC) to revise the wording of the interaction with coumarins-derivative anticoagulants and to include interaction with statins. In addition to this, sections 4.4 and 4.8 of the SmPC have been updated to include fatal diarrhoea. All the above changes were requested further to the assessment of the 6th PSUR. The Package Leaflet has been updated accordingly. Furthermore, sections 4.4 and 4.8 of the SmPC have been updated in order to include the fatal outcome of cases with gastrointensinal perforation based on a safety review conducted by the MAH. In addition, section 4.8 of the SmPC has been updated to include skin fissures.	20/05/2010	01/07/2010	SmPC and PL	This group of type II variations concerns an update of section 4.5 of the SPC to revise the wording of the interaction with coumarins-derivative anticoagulants and to include interaction with statins, upon request by CHMP following the assessment of the 6th PSUR. In addition to this, sections 4.4 and 4.8 of the SmPC have been updated to include fatal diarrhoea. Furthermore, sections 4.4 and 4.8 of the SmPC have been revised to include the possibility of the fatal outcome of gastrointestinal bleeding and gastrointestinal perforation based on a safety review conducted by the MAH. Finally the adverse reaction of skin fissures has been included in the table of adverse reactions under section 4.8 of the SmPC. The Package Leaflet has been updated accordingly.

	The Package Leaflet has been updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0017	Extension of the indication for use as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, Annex II has been updated in order to include the agreed Risk Management Plan. Extension of Indication	18/03/2010	27/04/2010	SmPC, Annex II and PL	See Scientific Discussion H-618-II-0017-SD.
II/0016	Update to sections 4.4 (special warnings and precautions for use) and 4.8 (undesirable effects) of the SPC with new safety information on corneal perforation, GI perforation and serious skin conditions. The Package Leaflet has been updated accordingly. The contact details of the Latvian local representative has also been updated in the Package	23/04/2009	28/05/2009	SmPC and PL	The following warnings have been included in the product information of Tarceva: Very rare cases of corneal perforation or ulceration have been reported during use of Tarceva. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with Tarceva treatment which are also risk factors for

	Leaflet. Update of Summary of Product Characteristics and Package Leaflet				corneal perforation/ulceration. Tarceva therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain. Patients receiving Tarceva are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Tarceva should be permanently discontinued in patients who develop gastrointestinal perforation. Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.
II/0014	Update of section 4.2, 4.5 and 5.1 of the SPC with the results of studies BP21502 (interaction with ranitidine) and OSI-774-107, (PK in smokers) which were part of the follow-up measures and addition of the term alveolitis under section 4.4 of the SPC as requested from the CHMP following the latest PSUR assessment. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	27/01/2009	SmPC and PL	As a consequence of finalising one post authorisation study in smokers and an interaction study with ranitidine the marketing authorisation holder has applied to introduce amendments to section 4.2, (posology), 4.5 (Interactions) and 5.2 (Pharmacokinetic Properties) of the Summary of Product Characteristics. Additional information relating to alveolitis has been put in to section 4.4 as consequential to the assessment of the 5th PSUR which is also satisfactory.
IA/0015	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	17/12/2008	n/a		

IA/0013	IA_09_Deletion of manufacturing site	04/08/2008	n/a		
II/0012	Update of section 4.2 and 5.2 of the SPC with information on the use of Tarceva in patients with hepatic impairment and amendment of section 4.8 of the SPC with updated information on adverse events. The package leaflet has been revised accordingly. The MAH has also applied to amend the Labelling with the information given in Braille and to make several editorial changes to the Package Leaflet to improve readability as well as to update the contact details in the list of local representatives for Estonia and Finland. Update of Summary of Product Characteristics, Labelling and Package Leaflet	13/12/2007	18/01/2008	SmPC, Labelling and PL	As a part of the opinion for the original application for Tarceva in June 2005 the MAH committed to provide the final study report for study OSI-774-104, entitled: "An Open-Label Study to Characterize the Pharmacokinetic Parameters of Erlotinib (Tarceva®, OSI-774) in Cancer Patients with Advanced Solid Tumors with Adequate and Moderately Impaired Hepatic Function". Based on these available study results the MAH applied for an update of section 4.2 and 5.2 of the SPC. SPC sections 4.2 and 5.2 as well as the respective PL sections have been updated appropriately to reflect the results of study OSI-774-104 investigating the pharmacokinetic parameters of a single oral 150 mg dose of erlotinib in cancer patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) compared to patients with adequate hepatic function. The pharmacokinetic and safety profile of erlotinib in moderately hepatic-impaired patients suggest that initiation of erlotinib treatment at a reduced dose is not required in cancer patients with moderate hepatic impairment. Nevertheless caution is advised when Tarceva is administered to patients with moderately impaired hepatic function, reflecting the limited clinical data available. Within the scope of this variation it is also proposed to update section 4.8 of the SPC with new information in relation to hair and nail changes as an association of certain hair and nail changes such as paronychia, hirsutism, eyelash/eyebrow changes, brittle and loose nails with

					erlotinib is suspected. The MAH also applied to update the Labelling to include information in Braille. The package leaflet was updated accordingly to reflect the SPC changes. In addition, editorial changes to the Package Leaflet were introduced to improve readability and to update the contact details in the list of local representatives for Estonia and Finland.
IA/0011	IA_39_Change/addition of imprints, bossing or other markings	21/09/2007	n/a	SmPC and PL	
II/0010	Update of section 4.5 of the SPC with information on the interactions with omeprazole and ciprofloxacin. The Package Leaflet has also been updated accordingly. In addition, the new ATC code was implemented in section 5.1 of the SPC. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	The marketing authorisation holder has conducted an adequately designed interaction study evaluating the effect of ciprofloxacin 750 mg BID on a single dose of 100 mg erlotinib. Ciprofloxacin leads to a significant increase in erlotinib AUC while no statistically significant changes in Cmax were found. The active metabolite exposure also increased about 60% and 48% for the AUC and Cmax respectively. These results were adequately reflected in the SPC. The marketing authorisation holder has also conducted an adequately designed interaction study evaluating the effect of omeprazole 40 mg daily for 7 days on a single dose of 150 mg erlotinib. AUC exposure was reduced by about 46 and 58% for erlotinib and metabolite, respectively. For Cmax reductions of 61 and 69% for erlotinib and the primary metabolite, respectively, was found. No adverse reactions could be attributed to the combination of drugs. These reductions are of a moderate to substantial order of magnitude. The clinical significance is unknown, but a reduced clinical effect cannot be excluded as in practise the

					outcome of the interaction study, leads to the advice to avoid concomitant use of PPIs. This would mean that certain gastrointestinal conditions may be undertreated when Tarceva is to be administered. It can be considered that the general risk of underexposure to Tarceva used for the treatment of life threatening conditions (non-small cell lung cancer or pancreatic cancer) outweighs the risk of undertreatment of e.g. acid burn, ulcus ventriculi, reflux-oesophagitis, reflux and dyspepsia, particularly in light of the fact that alternative treatment regimens could be envisaged for these diseases. Depending on the severity of the upper GI condition opposite the need to treat the underlying cancer (NSCLC or pancreatic cancer) effectively, the treating physician may still assess the risk/benefit for their individual patient and give appropriate treatment guidance. The ATC code for Tarceva changed from
II/0008	The Marketing Authorisation Holder (MAH) has applied for a type II variation, upon request by the CHMP following the assessment of the 3rd Periodic Safety Update Report (PSUR), to update section 4.4 of the SPC with clarification on events of dehydration, and section 4.8 of the SPC with information regarding severe infections and the adverse drug reactions (ADRs) 'dehydration', 'hypokaliemia', 'renal failure', 'alopecia' and 'dermatitis acneiform'. Furthermore, sections 4.4 and 4.8 of the SPC and section 4 of the Package Leaflet were also updated with information on hepatic failure. In addition, the MAH made minor editorial changes to the SPC and Package Leaflet.	24/01/2007	27/02/2007	SmPC and PL	Upon request by the CHMP in September 2006 following the assessment of the 3rd Periodic Safety Update Report (PSUR) covering period 18 November 2005 - 17 May 2006, the Marketing Authorisation Holder (MAH) applied for a type II variation to update section 4.4 and 4.8 of the SPC. The MAH also proposed to update section 4.4 and 4.8 of the SPC and section 4 of the Package Leaflet with information on hepatic failure. In addition, the MAH made minor editorial changes to the SPC and Package Leaflet. The MAH proposed to update sections 4.4 and 4.8 of the SPC to include clarification on events of dehydration, hypokalaemia and renal failure. 'Alopecia' has been added as a common undesirable effect in section 4.8 of the SPC.

	Update of Summary of Product Characteristics and Package Leaflet				Further details are provided in section 4.8 of the SPC with regards to "infection" where severe infections, with or without neutropenia, have included pneumonia, sepsis and cellulitis. In section 4.8 of the SPC, it was clarified that the term 'rash' included dermatitis acneiform. Information on rare cases of hepatic failure is also added in sections 4.4 and 4.8 of the SPC and section 4 of the Package Leaflet. The CHMP considers that sections 4.4 and 4.8 of the SPC have been updated appropriately to reflect the outcome of the 3rd PSUR assessment. The additional information included in section 4.4 and section 4.8 of the SPC and section 4 of the Package Leaflet in relation to hepatic failure is also considered acceptable.
II/0007	The Marketing Authorisation Holder (MAH) applied for a type II variation, upon request by the CHMP following the assessment of a follow-up measure (FUM 008), to update section 4.5 of the Summary of Product Characteristics (SPC) to reflect the results of interaction studies of erlotinib with capecitabine, carboplatin/paclitaxel CYP3A4 substrates rifampicin. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/01/2007	27/02/2007	SmPC and PL	The Marketing Authorisation Holder (MAH) applied for a type II variation, upon request by the CHMP following the assessment of a Follow-Up Measure (FUM 008), to update section 4.5 of the Summary of Product Characteristics (SPC) to reflect the results of interaction studies OSI-774-151-152, OSI-774-151-153, NP17536 and OSI-774-105. The Package Leaflet has been updated accordingly. Based on the results of these interaction studies, the MAH proposed to include the following statements in section 4.5 of the SPC: 'Pretreatment or coadministration of Tarceva did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam by up to 24%. In another clinical study, erlotinib was shown not to affect

					pharmacokinetics of the concomitantly administered CYP3A4/2C8 substrate paclitaxel. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely.' [_] 'Co-administration of rifampicin with a single 450 mg dose of Tarceva resulted in a mean erlotinib exposure (AUC) of 57.5% of that after a single 150 mg Tarceva dose in the absence of rifampicin treatment. Co-administration of Tarceva with CYP3A4 inducers should therefore be avoided. For patients who require concomitant treatment with Tarceva and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety (including renal and liver functions and serum electrolytes) is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring.' [_] 'Erlotinib increases platinum concentrations. In a clinical study, the concomitant use of erlotinib with carboplatin and paclitaxel led to an increase of total platinum AUC0-48 of 10.6%. Although statistically significant, the magnitude of this difference is not considered to be clinically relevant. In clinical practice, there may be othe
II/0002	This is an extension of the indication of Tarceva (erlotinib hydrochloride) in combination with gemcitabine in first-line treatment of patients with metastatic pancreatic cancer. When prescribing Tarceva, factors associated with prolonged survival should be taken into account. No survival advanatage could be shown for patients	14/12/2006	24/01/2007	SmPC, Labelling and PL	This is an extension of the indication of Tarceva (erlotinib hydrochloride) in combination with gemcitabine in first-line treatment of patients with metastatic pancreatic cancer. When prescribing Tarceva, factors associated with prolonged survival should be taken into account. No survival advanatage could be shown for patients with locally advanced disease.

	with locally advanced disease. Extension of Indication				Please also refer to the Scientific Discussion AR-H-618-II-02.
IA/0009	IA_05_Change in the name and/or address of a manufacturer of the finished product	01/12/2006	n/a	Annex II and PL	
II/0006	Update of the SPC sections 4.4, 4.5 and 5.2 with the results of the final report of a clinical interaction study evaluating the effect of smoking on erlotinib pharmacokinetics. The Package Leaflet has also been updated accordingly. In addition an amendment to section 4.8 was introduced. The MAH has also taken the opportunity to update the annexes according to the latest QRD template Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/10/2006	22/11/2006	SmPC, Labelling and PL	The MAH has applied to update the SPC sections 4.4, 4.5 and 5.2 with the results of the final report of a clinical interaction study evaluating the effect of smoking on erlotinib pharmacokinetics. In addition minor amendments to sections 4.4 and 4.8 were introduced.
II/0005	Quality changes	16/11/2006	21/11/2006		
IB/0004	IB_37_b_Change in the specification of the finished product - add. of new test parameter	06/04/2006	n/a		
II/0003	The MAH applied to update section 4.4 of the SPC and accordingly sections 2 and 4 of the Package Leaflet with information on secondary effects of severe diarrhoea; dehydration, hypokaleamia and acute renal failure Update of Summary of Product Characteristics and Package Leaflet	23/02/2006	22/03/2006	SmPC and PL	The MAH applied to update section 4.4 of the SPC and accordingly sections 2 and 4 of the Package Leaflet with information on secondary effects of severe diarrhoea: dehydration, hypokaleamia and acute renal failure as requested by the CHMP in December 2005 following their review of the MAH's safety report.

IA/0001	IA_01_Change in the name and/or address of the marketing authorisation holder	10/10/2005	n/a	SmPC, Labelling and PL	