Iressa

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
II/0034	Update of section 4.8 of the SmPC in order to add Palmar-plantar erythrodysaesthesia syndrome to the list of adverse drug reactions (ADRs) with frequency uncommon; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1.	14/01/2021		SmPC, Annex II, Labelling and PL	

[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).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0035	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	17/12/2020	n/a		
II/0033	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	03/09/2020	n/a		
IAIN/0032/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	27/03/2019	09/03/2020	Annex II and PL	
PSUSA/1518/201807	Periodic Safety Update EU Single assessment - gefitinib	14/02/2019	n/a		PRAC Recommendation - maintenance

IA/0030	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	27/07/2018	n/a		
IB/0029	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/04/2018	08/04/2019	SmPC, Labelling and PL	
IA/0028	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	23/06/2017	n/a		
II/0026	Update of section 4.1 of the SmPC in order to specify that Iressa should be used as monotherapy and not in combination with other medicines in its approved indication based on the submission of the final study report of the IMPRESS (D791LC00001) study following the PRAC recommendation in conclusion to the assessment of the 8th PSUR. The RMP was updated in consequence in order to add as identified risk the continuation of gefitinib as add-on to chemotherapy in patients with secondary resistance to gefitinib (agreed version 10.0). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/02/2017	29/03/2017	SmPC	
II/0027	Update of section 5.1 of the SmPC in order to update	26/01/2017	29/03/2017	SmPC	Most NSCLC tumours with sensitising EGFR kinase

	information on mechanisms of resistance to gefitinib in patients with EGFR mutation positive Non-Small Cell Lung Cancer (NSCLC) as proposed during assessment of LEG 21. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce some editorial changes in the SmPC 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				mutations eventually develop resistance to IRESSA treatment, with a median time to disease progression of 1 year. In about 60% of cases, resistance is associated with a secondary T790M mutation for which T790M targeted EGFR TKIs may be considered as a next line treatment option. Other potential mechanisms of resistance that have been reported following treatment with EGFR signal blocking agents include: bypass signalling such as HER2 and MET gene amplification and PIK3CA mutations. Phenotypic switch to small cell lung cancer has also been reported in 5-10% of cases.
II/0025	Update of section 4.8 of the SmPC in order to update the safety information on allergic reaction amending the frequency from Uncommon to Common. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to align the Package leaflet with the SmPC adding dry mouth as a common side effects in section 4. The MAH took also the opportunity to introduce minor editorial changes, to update the list of local representatives for Poland in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	29/03/2017	SmPC, Labelling and PL	
II/0024	Update of section 5.3 of the SmPC in order to update information that the clinical experience has not	15/09/2016	29/03/2017	SmPC	

	shown a causal association between QT prolongation and gefitinib. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/1518/ 201507	Periodic Safety Update EU Single assessment - gefitinib	14/01/2016	n/a		PRAC Recommendation - maintenance
IA/0022	B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	08/01/2016	n/a		
IG/0633	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	09/12/2015	n/a		
IA/0021	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	02/12/2015	n/a		
PSUSA/1518/ 201407	Periodic Safety Update EU Single assessment - gefitinib	12/02/2015	n/a		PRAC Recommendation - maintenance
IA/0018	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)	23/12/2014	n/a		

II/0016	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	15/10/2015	SmPC	
R/0012	Renewal of the marketing authorisation.	20/02/2014	23/04/2014	SmPC and PL	The CHMP, having reviewed the available information on the status of the fulfilment of post-authorisation measures and having confirmed the positive benefit/risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of Iressa, subject to the Conditions as laid down in Annex II to the Opinion. The CHMP recommends that the renewal be granted with unlimited validity.
IB/0014/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 importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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.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	28/02/2014	n/a		

IG/0402	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	27/02/2014	n/a		
PSUV/0013	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance
II/0011	Update of section 5.1 of the SmPC in order to reflect the results of study D791AC00014 (IFUM). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	27/06/2013	23/04/2014	SmPC, Annex II and PL	This variation reflects the results from the IRESSA Follow-Up Measure (IFUM) study (D791AC00014) on the efficacy and safety of gefitinib (250 mg orally once daily) as first-line treatment in Caucasian patients with activating sensitising EGFR mutation-positive (EGFR M+) locally advanced or metastatic NSCLC. Results of this study are consistent with the results from the pivotal trial conducted in Asian patients which is reflected in section 5.1 of the SmPC.
IG/0273	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/02/2013	n/a		
IB/0009/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.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	30/11/2012	n/a		

IA/0008	A.7 - Administrative change - Deletion of manufacturing sites	31/07/2012	n/a		
II/0005	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on the development of keratitis and ulcerative keratitis. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the Product Information was brought in line with the latest QRD template version 8. 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	15/03/2012	20/04/2012	SmPC, Annex II, Labelling and PL	The PhVWP, having reviewed reports of keratitis and ulcerative keratitis across EGFR inhibitors class of products, recommended a warning in the SmPC, which was endorsed by the CHMP. Following a request from the CHMP, the MAH submitted a variation to add the warning of keratitis and ulcerative keratitis and provided additional analyses from the FDA's safety database, the WHO Vigibase and the MAH's worldwide safety database. The MAH reported 13 events of keratitis and 1 event of ulcerative keratitis with the use of gefitinib. The product information has been amended with a warning in section 4.4 and 4.8 of the SmPC.
IG/0124/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	18/11/2011	n/a		
II/0004	In this variation the MAH has updated the section 5.1 of the SmPC based on updated overall survival (OS)	23/06/2011	01/08/2011	SmPC and PL	Section 5.1 of the SmPC has been updated with a new analysis of overall survival (OS) data from the IPASS

	data from the IPASS study further to the request of the CHMP following the assessment of FUM 002. In addition to this, the MAH updated the section 5.1 of the SmPC with the efficacy outcomes of the EGFR mutation-unknown subgroup of patients from this study. The MAH also took the opportunity to update the list of the local representatives in the Package Leaflet.				Study. In the IPASS trial, IRESSA demonstrated superior PFS, ORR, QoL and symptom relief with no significant difference in OS compared to carboplatin/paclitaxel in previously untreated patients, with locally advanced or metastatic NSCLC, whose tumours harboured activating mutations of the EGFR tyrosine kinase.
IG/0035	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	07/01/2011	n/a	Annex II	
II/0003/G	This was an application for a group of variations. This was an application for a group of variations. Update of section 4.8 of the Summary of Product Characteristics (SmPC) to update the frequency of hepatitis and to add the adverse reactions gastrointestinal perforation, skin fissures, bullous conditions, cutaneous vasculitis, cystitis and haemorrhagic cystitis further to safety reviews conducted by the Marketing Authorisation Holder (MAH). Section 4.4 of the SmPC was also updated to reflect the information relative to hepatitis and gastrointestinal perforation. The Package Leaflet was amended accordingly.	21/10/2010	26/11/2010	SmPC, Annex II, Labelling and PL	The Product information of Iressa is updated with recent safety information obtained from clinical trials and post marketing surveillance. Based on five reports of hepatitis identified in clinical trials, the frequency of hepatitis has been revised to uncommon adverse reaction. Analysis of the MAH safety database also showed that few reports, all containing confounding factors, resulted in hepatic failure associated in some cases with a fatal outcome. Therefore, this information has been included in the existing warning related to hepatitis. Gastro-intestinal (GI) perforation has been observed in clinical studies and post-marketing surveillance. Based on 5 reports of GI perforation observed in clinical trials, the

	The MAH also updated section 4.9 "overdose" of the SmPC based on new available data from a high dose study. The EU RMP has been revised accordingly and its version number (version 6) has been updated in Annex II. In addition, details of the blister and aluminium laminate foil flow-wrap have been combined under Annex IIIA and minor changes were made to the list of representatives in Annex IIIB. Lastly, minor editorial changes and updates based on the latest QRD template (version 7.3.1.) were made through the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				frequency has been defined as uncommon. The overall safety results showed that use of Iressa is a relevant co-factor which together with other risk factors is associated with an increased risk of gastro-intestinal perforation. Based on the results of the safety reviews, cystitis and haemorrhagic cystitis have been included in section 4.8 of the SmPC with the frequency of "common" and "rare" respectively. In relation to skin reactions, a review of the safety data indicated that skin fissures, bullous conditions and cutaneous vasculitis have been observed. Therefore, these adverse reactions have been added to the SmPC. Lastly, safety data from a phase I dose escalation study evaluating high dose of Iressa (1,500 to 3,500 mg) have shown consistent results with the established safety profile of Iressa, which was generally well tolerated, with no unexpected safety or tolerability concerns identified. The overdose section 4.9 of the SmPC has been updated accordingly.
II/0002	Update of the Detailed Description of Pharmacovigilance System (DDPS). Consequently, Annex II has been revised with the new version number of the agreed DDPS (version 10). Minor updates were implemented in the Risk Management Plan. Update of Summary of Product Characteristics	17/12/2009	19/01/2010	Annex II	The Detailed Description of Pharmacovigilance System (DDPS) was updated and consequently, Annex II has been revised with the new version number of the agreed DDPS (version 10). Minor updates were implemented in the Risk Management Plan. The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person

					responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
IA/0001	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	17/09/2009	17/09/2009	SmPC, Labelling and PL	