Aclasta

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/0072	Further to assessment of study ZOL446H2337 (a randomised, double-blind, placebo-controlled efficacy and safety study of intravenous zoledronic acid administered twice yearly compared to placebo in children with glucocorticoid-induced osteoporosis (GIO)), sections 4.2 and 5.1 of the SmPC have been updated with final results from the study. Currently available literature together with the results of study H2337, do not support the indication of zoledronic acid	27/06/2019	31/07/2019	SmPC 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).

	in paediatric patients with GIO. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. 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				
IB/0073/G	This was an application for a group of variations. B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	18/07/2019	n/a		
PSUSA/9334/ 201808	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for Osteoporosis)	11/04/2019	n/a		PRAC Recommendation - maintenance
II/0069	Submission of the final 5-year report from study (ZOL446H2422) listed as a category 3 study in the RMP. This is a non-interventional post-authorisation safety study using health registries to compare safety of Aclasta against oral bisphosphonates and untreated population controls. C.I.13 - Other variations not specifically covered	04/10/2018	n/a		The risk of heart failure was found to be higher in the zolendronic acid group compared with subjects treated with oral bisphosphonates, (HR 1.21 95% CI 1.09;1.34) and compared with matched, untreated background population subjects (HR 1.39 95% CI 1.25;1.55). The association remained with a similar magnitude when adjusted for age, previous fractures, comorbidities and previous medication (HR 1.31; 95% CI: 1.15, 1.49). Considering the modest risk

	elsewhere in this Annex which involve the submission of studies to the competent authority				estimates and likely remaining unmeasured confounding in this observational study, the totality of the data is not sufficient to conclude that the risk of heart failure is possibly related to Aclasta use or to support an increase in other cardiovascular outcomes associated with Aclasta. The incidence of fracture non-union/delayed union in the observational study was over three times higher compared to untreated subjects and did not substantially change after adjustments of previous fractures. Currently, fracture non-union/delayed union is an important potential risk in the Aclasta risk management plan. Higher baseline risk of fractures inflates the apparent risk of fracture complications such as fracture nonunion or delayed union. Consequently, the increased risk of fracture non-union or delayed union in the actual study cannot be related to Aclasta with such reasonable possibility that would require change in the product information. The risk of osteonecrosis of the jaw (ONJ) was higher in zoledronic acid treated patients compared to oral bisphosphonates initiators. This is in line with the current information in the Aclasta SmPC regarding considerations when evaluating a patient's risk of developing ONJ. In addition, the current additional risk minimisation measures for Aclasta include a patient reminder card on ONJ. Cardiovascular mortality was not reported with an increased frequency in zoledronic acid users either in the pooled randomised clinical trials or in the observational study ZOL446H2422. In contrast, all-cause mortality was slightly increased in zoledronic acid treated subjects compared to oral bisphosphonates inhibitors HR 1.15 (1.07-1.24) and also compared to untreated subjects HR 1.1 (1.02-1.18) in the selected model in ZOL446H2422. The estimates suggesting

					an increased risk for all-cause mortality are weak and consequently sensitive to remaining confounding from patient frailty. The data suggest some remaining imbalance between the compared groups in fracture history. The mortality analyses in detail from the two large pivotal studies 2301 and 2310 do not provide sufficient support for a causal link to increased all-cause mortality. Based on the review of the study results, the benefit/risk balance of zolendronic acid (Aclasta) remains unchanged for the approved indications and no changes are warranted in the product information.
T/0070	Transfer of Marketing Authorisation	20/03/2018	19/04/2018	SmPC, Labelling and PL	
II/0068	Update of section 4.8 of the SmPC in order to add the adverse reaction hypophosphataemia with a frequency 'rare' based on post-marketing spontaneous reports and internal databases. The package leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to remove the lower level term 'shoulder pain' in the SmPC which is covered by the corresponding preferred term 'musculosketal pain', to update the list of local representatives in the Package Leaflet and to bring the product information in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	07/03/2018	SmPC, Annex II, Labelling and PL	

WS/1016/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	15/12/2016	n/a		
IG/0705/G	This was an application for a group of variations. 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	08/08/2016	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
N/0066	Update of the package leaflet with revised contact details of the local representatives for France and Spain. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/07/2016	02/12/2016	PL	
IB/0063/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	31/03/2016	n/a		

	product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
PSUSA/9334/ 201508	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for Osteoporosis)	17/03/2016	n/a		PRAC Recommendation - maintenance
II/0056	Submission of a revised RMP (version 11.2) in order to introduce a Patient Reminder Card as an additional risk minimisation measure for the existing identified risk of osteonecrosis of the jaw and to propose indicators to measure the effectiveness of this new measure. Furthermore, the clinical trial exposure data from the Aclasta study ZOL446H2301E2 has been updated. In addition, the MAH took the opportunity to comply with the EMA Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk Management Systems (EMA/838713/2011) and the Guidance on format of the risk management plan (RMP) in the EU (EMA/718034/2012).	25/02/2016	n/a		

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IA/0064	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)	22/02/2016	n/a		
IAIN/0062	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/12/2015	02/12/2016	SmPC and PL	
IB/0061	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/12/2015	n/a		
IG/0611	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	07/09/2015	n/a		
IG/0574/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 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 B.I.b.2.a - Change in test procedure for AS or starting	13/08/2015	n/a		

	material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised				
PSUSA/9334/ 201408	Periodic Safety Update EU Single assessment - zoledronic acid (indicated for Osteoporosis)	26/03/2015	28/05/2015	SmPC, Annex II and PL	Please refer to Aclasta PSUSA-9334-201408 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IAIN/0055	A.1 - Administrative change - Change in the name and/or address of the MAH	02/03/2015	28/05/2015	SmPC, Labelling and PL	
IB/0054	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/02/2015	n/a		
IG/0524	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	10/02/2015	n/a		
R/0051	Renewal of the marketing authorisation.	20/11/2014	19/01/2015	SmPC, Annex II, Labelling and PL	Based on the review of available information, the CHMP is of the opinion that the quality, safety and efficacy of Aclasta continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The product information has been updated to align with QRD templates, including paediatric information.

					The CHMP recommends that the renewal be granted with unlimited validity.
PSUV/0047	Periodic Safety Update	25/04/2014	11/07/2014		Please refer to Aclasta-EMEA-H-C-000595-PSUV-0047 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
WS/0522	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of a new specification parameter and limits to the specification of a solvent used in the manufacturing process of the active substance. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	22/05/2014	n/a		
IA/0050/G	This was an application for a group of variations. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a	05/05/2014	n/a		

	new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method 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) 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)				
II/0045	Submission of a final clinical study report. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/02/2014	n/a		A final study report was submitted for a 3-year international, multicenter, randomized, double-blind extension study carried out in order to further assess the efficacy and long term safety of zoledronic acid in postmenopausal women with osteoporosis after taking up to 9 annual doses of Aclasta (Group Z9) as well as to characterize the durability of effect in patients who have received up to 6 annual doses of zoledronic acid followed by up to 3 annual doses of placebo (Group Z6P3). Comparisons were made between the continuous use of zoledronic acid for 9 years (Z9 treatment group) and the use of zoledronic acid for 6 years followed by 3 years of placebo (Z6P3 treatment group). Treatment differences in total hip BMD and femoral neck BMD were numerically in favor of the Z9 treatment group compared to the Z6P3 group but differences were small and not likely to be clinically important. No significant differences

					were observed between Z9 and Z6P3 treatment groups in the risk of clinical, vertebral, non-vertebral and morphometric vertebral fractures. Post-dose symptom adverse events (AEs), Cardiac arrhythmia AEs and renal laboratory abnormality were more frequent in the Z9 treatment group compared to the Z6P3 group. These adverse events are labelled. No new safety findings have been identified. The benefit/risk balance remains unchanged. The small number of patients in the study may have limited the ability to detect differences in efficacy parameters between the treatments. A positive benefit/risk balance of continuing zoledronic acid treatment past 6 years cannot be considered proven. The current SmPC states in 4.2: “The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Aclasta on an individual patient basis, particularly after 5 or more years of use.” The current wording is sufficient to inform the prescribers about the uncertainties of long-term use of Aclasta.
II/0044	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/02/2014	n/a		
IG/0394/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	19/12/2013	n/a		

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
IB/0043	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	24/09/2013	n/a		
IA/0042	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits	14/08/2013	n/a		
II/0041	Update of SmPC section 4.4 Special warnings and precautions as requested by the CHMP further to assessment of PSUR 9: alignment of SmPC with the Company Core Data Sheet to include observation of acute renal failure after a single administration, and to advise calculation of creatinine clearance based upon actual body weight using the Cockroft -Gault formula prior to each dose. Accordingly update of physician educational material, also reflecting increased risk in subjects of advanced age. Furthermore, the PI is being brought in line with the latest QRD Template version 9, including editorial changes to improve readability. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet (Croatia, Luxemburg and Malta). The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.	25/07/2013	11/07/2014	SmPC, Annex II, Labelling and PL	In the CHMP conclusion on the assessment of the ninth Aclasta Periodic Safety Update Report (PSUR 9), the MAH was requested to further align the SmPC information with the US Product Information (USPI) and with the company Core Data Sheet (CDS) with the following information: 1) to report the observation of acute renal failure after a single administration; 2) to advise the calculation of CrCl based upon actual body weight using the Cockcroft-Gault formula before each Aclasta dose. The MAH was also asked to reflect in the physician educational material the increased risk for subjects of advanced age and the advice to calculate CrCl using the Cockcroft-Gault formula prior to each dose. These changes to the Product information and educational key messages were agreed by the CHMP during the current variation. The CHMP also agreed to the proposed changes to align with the latest QRD Template (version 9), editorial changes, and update of the local representatives.

	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				
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details 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	17/08/2012	n/a		
IAIN/0037/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary 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 A.7 - Administrative change - Deletion of manufacturing sites	26/07/2012	n/a		

IG/0180	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	22/05/2012	n/a		
II/0034	Update of SmPC sections 4.2 and 5.1 to include a recommendation and information on the re-treatment of patients with Paget`s disease of the bone, who have been previously treated with zoledronic acid, based mainly on results of a newly completed re-treatment clinical study CZOL446K2418. The Package Leaflet was updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/03/2012	20/04/2012	SmPC and PL	This update to the product information is supported mainly by results of study CZOL446K2418, an open label Aclasta re-treatment study of relapsed patients with Paget`s disease of the bone who participated in the main registration studies studies CZOL446K2304 and K2305 and data from the Extended Observation Period (EOP) to studies K2304 and K2305 on patients that had not relapsed in the pivotal trials. The CHMP agreed to update of SmPC sections 4.2 and 5.1 to include a recommendation and information on the re-treatment of patients with Paget`s disease of the bone, who have been previously treated with zoledronic acid ; the update of the Package Leaflet was agreed accordingly. The benefit-risk balance for Aclasta is not changed by data presented in this variation.
IG/0148/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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	22/02/2012	n/a		

II/0028	Update of SmPC section 4.3 to include 'Severe renal impairment with creatinine clearance < 35 ml/min' as a contraindication due to increased risk of renal failure in this population. The corresponding information is also included in sections 4.2, 4.4 and 5.2. Minor editorial changes in section 4.8. The Annex II, Package Leaflet and Annex 127a is updated in accordance; the format of annex II and annex 127a was adapted in line with the latest QRD template. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet (Poland and Romania). The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II: "The MAH should submit an updated Risk Management Plan reflecting "atypical femoral fractures" as potential risk. The Risk Management plan should be submitted by 6 October 2011." The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/12/2011	06/02/2012	SmPC, Annex II and PL	This application was submitted as a single Type II variation mainly to update SmPC section 4.3 to include 'Severe renal impairment with creatinine clearance < 35 ml/min' as a contraindication due to increased risk of renal failure in this population. The information is also included in sections 4.2, 4.4 and 5.2. Minor editorial changes have also been implemented in section 4.8. Renal dysfunction has been reported in a number of cases after zoledronic acid infusion. Advanced age and comorbidities are reported as risk factors. Cumulatively, 265 spontaneous reports of renal dysfunction have been received. The product information has been amended to alert physicians to the risk of renal impairment, including renal failure requiring dialysis, occurring especially in patients with pre-existing renal compromise or other risk factors including concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration. The Annex II, Package Leaflet and Annex 127a is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet (Poland and Romania). These amendments to the product information do not alter the benefit/risk balance for the product, which is still considered positive.
IA/0033	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	05/01/2012	n/a		Application withdrawn

IG/0135/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	16/12/2011	n/a		
IG/0088/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the	11/07/2011	n/a		

	DD 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				
A20/0026	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 19 October 2010, the opinion of the CHMP on measures necessary to ensure the safe use of the above mentioned medicinal product further to the CHMP review on the currently available data in relation to the incidence of atypical stress fractures and its impact on the risk-benefit balance.	14/04/2011	29/06/2011	SmPC, Annex II and PL	Please refer to the Assessment Report: H-595-RAR-A20-0026-en
II/0027/G	This was an application for a group of variations. A rapid microbiological test method as an alternative sterility test method for the finished product release testing is proposed. To update to the calculation of the degradation products so it does not include one by-product of the manufacturing process of the active substance. 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	17/03/2011	13/04/2011		

IG/0041/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	08/02/2011	n/a		
IG/0032/G	This was an application for a group of variations. To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement.	21/12/2010	n/a	Annex II	

	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.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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				
IB/0025/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological 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	17/08/2010	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites				
II/0024	Update of section 4.8 of the SPC with information on eye disorders (scleritis and orbital inflammation), vascular disorders (hypotension), musculoskeletal and connective tissue disorders (osteonecrosis of the jaw), renal and urinary disorders (renal impairment) and general disorders (dehydration), upon request by CHMP following the assessment of PSUR 6 and update of sections 4.2, 4.4 and 4.5 of the SPC with information regarding renal impairment in line with a recent CDS update. Further, update of SPC section 5.2 with a statement related to the uptake of zoledronic acid into bone upon request by CHMP following the assessment of a follow-up measure. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	12/05/2010	SmPC and PL	The terms "scleritis and orbital inflammation", "hypotension", "osteonecrosis of the jaw", "renal impairment (including rare cases of renal failure)" and "dehydration" were added to the table of adverse reactions, and "concomitant diuretic therapy" was added under class effects in section 4.8 of the SPC. The safety information regarding renal impairment in the SPC was updated in sections 4.2 (deletion of "limited experience in patients with renal impairment"), 4.4 (strengthening of warnings and precautions) and 4.5 (addition of "In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase"). Further, addition to SmPC section 5.2 of a statement related to the retention time of zoledronic acid in bone. The Package Leaflet has been updated accordingly.
II/0023	Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	29/04/2010	Annex II	
R/0022	Renewal of the marketing authorisation.	20/01/2010	30/03/2010	SmPC, Annex II, 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 Aclasta continues to be favourable. Because of several safety concerns, such as adverse effects

					on renal function and the potential risks of osteonecrosis of the jaw and atypical stress fractures with long term treatment, the benefit-risk balance of Aclasta should be re-evaluated on a regular basis in PSURs or when new relevant information becomes available. The MAH should submit 1- yearly PSURs Therefore, based on the safety profile of Aclasta, which requires submission of 1-yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0021	Change to the specification of a raw material Change to the test procedure and/or specification of a raw material	24/09/2009	29/09/2009		
II/0017	Extension of Indication to include treatment of -osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk for fracture. Extension of Indication	23/04/2009	22/06/2009	SmPC, Annex II, Labelling and PL	For further information please refer to the Scientific Discussion: Aclasta-H-595-II-17-AR
II/0020	The MAH applied for changes in the in-process controls used in the manufacturing of the active substance. Quality changes	19/12/2008	23/03/2009		
II/0016	To include treatment of osteoporosis in post-menopausal women and men at increased risk of	24/07/2008	26/09/2008	SmPC, Annex II, Labelling	Please refer to the scientific discussion: Aclasta-H-595-II-16-AR

	fracture, including those with a recent low-trauma hip fracture. Extension of Indication			and PL	
IA/0019	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	17/09/2008	n/a		
IB/0018	IB_17_a_Change in re-test period of the active substance	16/04/2008	n/a		
II/0014	To update section 4.8 of the SPC in accordance with the Company Core Data Sheet following the evaluation of safety data from a 3-year clinical trial in women with postmenopausal osteoporosis. In addition, the contact details of the local representatives in Iceland and Latvia are amended. Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	03/10/2007	SmPC and PL	Results from a randomised, double-blind, placebo-controlled multicentre study to evaluate the safety and efficacy of zoledronic acid in the treatment of osteoporosis in postmenopausal women 65-89 years of age (n=7,736) were submitted in support of this variation. The results showed that patients treated with zoledronic acid exhibited a threefold greater incidence of atrial fibrillation (AF) reported as a serious adverse event compared to patients receiving placebo. A statistically significant increase in the risk of all atrial fibrillation events (serious and non-serious) was not demonstrated, and an ECG study in a subgroup of patients did not reveal any differences between the zoledronic acid and placebo groups. The events did not occur early after infusion, when drug concentrations in serum were the highest. It was however considered unlikely that this finding was due to chance considering the size of the study. Post-marketing reports cannot be considered a sensitive measure for this adverse event, as AF is very common in the elderly population and until now would not have been suspected to be related to bisphosphonates. Section 4.8 of the SPC was

					updated to reflect this finding.
II/0010	To include treatment of osteoporosis in post-menopausal women at increased risk of fracture. Extension of Indication	19/07/2007	03/10/2007	SmPC, Annex II, Labelling and PL	For further information please refer to the Scientific Discussion: EMEA-H-595-II-10-AR
IA/0013	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/05/2007	n/a		
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/05/2007	n/a	PL	
IB/0012	IB_33_Minor change in the manufacture of the finished product	13/11/2006	n/a		
IB/0011	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	13/11/2006	n/a	SmPC	
II/0008	Update of Sections 4.3 and 4.8 of the SPC following a review of the Core Data Sheet and a literature search for zoledronic acid. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	24/10/2006	SmPC and PL	Summary of the adopted changes in the SPC: 4.3 Contraindications Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates. 4.8 Undesirable effects Local reactions: Local reactions at the infusion site such as redness, swelling and/or pain have been observed following the administration of zoledronic acid. Iritis/uveitis/episcleritis/conjunctivitis: Cases of iritis, uveitis, episcleritis and conjunctivitis have been reported in patients treated with bisphosphonates.

					The Package leaflet has been updated accordingly.
II/0007	Update of Sections 4.4 and 4.8 of the SPC to implement the labelling proposed by the PhVWP and adopted by the CHMP for biphosphonates on osteonecrosis of the jaw. The Package Leaflet has been updated accordingly. In addition a statement regarding the availability of pack sizes has been added in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	24/10/2006	SmPC and PL	Summary of the changes in SPC and PL: Summary of Product Characteristics Section 4.4 Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedure, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. Section 4.8 :

					Uncommonly, cases of osteonecrosis (primarily of the jaw) have been reported, predominantly in cancer patients treated with bisphosphonates. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing dental disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4). The Package L
IA/0009	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	18/08/2006	n/a	Annex II and PL	
IA/0006	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/06/2006	n/a		
IB/0005	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	01/03/2006	01/03/2006	SmPC, Labelling and PL	
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	27/01/2006	n/a		
IA/0002	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	19/09/2005	n/a		

N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/06/2005	n/a	Labelling and PL	