Abilify

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
IB/0140	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/03/2022		SmPC and PL	To update SmPC section 4.8 by adding "Blood prolactin decreased" in the tabulated list of all adverse reactions to bring it in line with other parts of the SmPC. In addition the MAH has brought the annexes in line with the excipient guideline on sucrose and SmPC section 4.4 for the

[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).

					1 mg/ml oral solution has additionally be updated to the same guidance regarding hereditary fructose intolerance. The package leaflet has been updated accordingly. Furthermore the MAH has taken this opportunity to make some editorial corrections to the national languages.
N/0139	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2021		PL	
IA/0138	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	13/05/2021	n/a		
PSUSA/234/202007	Periodic Safety Update EU Single assessment - aripiprazole	11/02/2021	n/a		PRAC Recommendation - maintenance
II/0136/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/09/2020	29/09/2021	SmPC and PL	
PSUSA/234/201907	Periodic Safety Update EU Single assessment - aripiprazole	27/02/2020	28/04/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/234/201907.

IB/0134	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/10/2019	28/04/2020	SmPC, Annex II, Labelling and PL	
IAIN/0133	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	18/07/2019	n/a		
PSUSA/234/201807	Periodic Safety Update EU Single assessment - aripiprazole	28/02/2019	29/04/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/234/201807.
T/0131	Transfer of Marketing Authorisation	27/07/2018	23/08/2018	SmPC, Labelling and PL	
IAIN/0130	B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement	26/03/2018	23/08/2018	SmPC and PL	
IA/0129	A.7 - Administrative change - Deletion of manufacturing sites	27/02/2018	23/08/2018	Annex II and PL	
PSUSA/234/201707	Periodic Safety Update EU Single assessment - aripiprazole	08/02/2018	n/a		PRAC Recommendation - maintenance
II/0127	Update of sections 4.4 and 4.8 of the SmPC with further information about the risk of impulse control disorders, and section 4.8 of the SmPC to include the new ADRs 'impulse control disorders', 'binge eating', 'compulsive shopping' and 'poriomania' and to delete	26/10/2017	23/08/2018	SmPC and PL	Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported, include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive

	the ADR 'hyperglycaemia'. The Package Leaflet has been updated accordingly. Further, the MAH has implemented minor editorial changes in section 6.1 of the SmPC, section 6 of the Package leaflet and module 3.2.P.1 to include lactose as one of the components of the excipient vanilla flavour for Abilify orodispersible tablets. In addition, the MAH took the opportunity to align the annexes with the product information of Abilify Maintena and the latest QRD template. 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				behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.
IA/0125	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)	28/04/2017	n/a		
PSUSA/234/201607	Periodic Safety Update EU Single assessment - aripiprazole	09/02/2017	n/a		PRAC Recommendation - maintenance
II/0122	Submission of the final Clinical Study Report of non-interventional, non-imposed PASS study 31-13-300 ("ABILIFY® for the Adolescent Bipolar I Mania Indication Tool Effectiveness Evaluation Survey") to fulfil a post-authorisation measure (MEA 068.2); the Annex II has been updated to delete additional risk minimisation measures based on the	10/11/2016	03/08/2017	Annex II	n/a

	study results and to delete PASS study 31-13-300 included by mistake during variation IB/112/G. Moreover, the updated RMP version 10 has been submitted as part of this application. 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				
II/0110	Update of SmPC sections 4.8 and 5.1 to reflect clinical data generated in paediatric studies 31-09-266 and 31-09-267 submitted according to Article 46 of the paediatric regulation. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/09/2016	03/08/2017	SmPC and PL	For further information, please refer to the scientific discussion "Abilify-H-C-471-II-110".
IB/0121/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.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	24/08/2016	03/08/2017	SmPC, Annex II, Labelling and PL	

	products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products 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.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information				
IA/0120	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	03/06/2016	n/a		
IB/0119	B.II.z - Quality change - Finished product - Other variation	26/05/2016	n/a		
PSUSA/234/201507	Periodic Safety Update EU Single assessment - aripiprazole	25/02/2016	21/04/2016	SmPC and PL	Please refer to Abilify - PSUSA/00000234/201507 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
N/0118	Update of the package leaflet with revised contact details of the local representatives for Cyprus and Greece. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/04/2016	03/08/2017	PL	

IB/0117/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites B.II.z - Quality change - Finished product - Other variation B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	24/02/2016	n/a		
N/0116	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/02/2016	21/04/2016	PL	
IB/0113	B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms	03/09/2015	n/a		
N/0114	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/09/2015	21/04/2016	PL	

IB/0112/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2015	21/04/2016	SmPC, Labelling and PL	
PSUSA/234/201407	Periodic Safety Update EU Single assessment - aripiprazole	26/02/2015	24/04/2015	SmPC and PL	Please refer to Abilify and Abilify Maintena PSUSA/0234/201407 EPAR: Scientific conslusions and grounds recommending the variation to the terms of the marketing authorisation
IAIN/0111/G	This was an application for a group of variations. 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.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.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	15/04/2015	n/a		

IA/0108	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	11/12/2014	n/a		
IA/0106	B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	21/10/2014	n/a		
II/0103	Update of section 4.8 of the SmPC to add diplopia to the list of adverse drug reactions with a frequency 'uncommon' in line with the PRAC recommendation following the assessment of a Eudravigilance signal including 16 relevant case reports. The Package Leaflet is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/09/2014	17/02/2015	SmPC, Labelling and PL	
IA/0105/G	This was an application for a group of variations. 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.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other	21/08/2014	n/a		

	changes to a test procedure (including replacement or addition)				
IAIN/0104	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	04/08/2014	17/02/2015	Labelling	
II/0101	Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) to include information related to studies 31-12-293 and 031-KOA-0703 conducted in patients (6-18 years) with Tourette's disorder (TD). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	17/02/2015	SmPC	The efficacy of aripiprazole was studied in paediatric subjects with Tourette's disorder (aripiprazole: n = 99, placebo: n = 44) in a randomised, double-blind, placebo controlled, 8 week study using a fixed dose weight-based treatment group design over the dose range of 5 mg/day to 20 mg/day and a starting dose of 2 mg. Patients were 7 17 years of age and presented an average score of 30 on Total Tic Score on the Yale Global Tic Severity Scale (TTS-YGTSS) at baseline. Aripiprazole showed an improvement on TTS-YGTSS change from baseline to Week 8 of 13.35, for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg) as compared with an improvement of 7.09 in the placebo group. The efficacy of aripiprazole in paediatric subjects with Tourette's syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated over a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10 week, randomised, double blind, placebo-controlled study conducted in Korea. Patients were 6 18 years and presented an average score of 29 on TTS-YGTSS at baseline. Aripiprazole group showed an improvement of 14.97 on TTS-YGTSS change from baseline to Week 10 as compared with an improvement of 9.62 in the placebo group.

					In both of these short term trials, the clinical relevance of the efficacy findings has not been established, considering the magnitude of treatment effect compared to the large placebo effect and the unclear effects regarding psycho-social functioning. No long term data are available with regard to the efficacy and the safety of aripiprazole in this fluctuating disorder. Overall, the safety and efficacy of ABILIFY in children and adolescents 6 to 18 years of age have not yet been established. No recommendation on a posology can be made. This updated information is based on the results of studies submitted in accordance with Article 46 of the Paediatric Regulation (EC) No 1901/2006.
N/0102	Update of details for local representatives in Annex IIIB. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/03/2014	17/02/2015	PL	
N/0100	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/03/2014	17/02/2015	PL	
II/0096/G	This was an application for a group of variations. Group of variations related to the introduction of a new manufacturing site for the finished product including the following changes: B.II.b.1.d – addition of an alternative site responsible for the manufacture and quality control testing of the bulk finished product (orodispersible tablets and oral solution)	20/03/2014	17/02/2015	SmPC and PL	

	B.II.a.3.a.1 - changes in the composition of the flavouring agent (vanilla flavour) used in orodispersible tablets B.II.b.3.a – minor changes to the manufacturing process of the finished product (orodispersible tablets and oral solution) at the alternative site. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
PSUV/0098	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance
IAIN/0099/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	16/01/2014	10/04/2014	Annex II and PL	

IB/0097/G	This was an application for a group of variations. Group of variations consisting of : 1) a change of the address of the MAH and 2) the implementation of the agreed wording related to the incidence of low prolactinaemia in section 4.8 of the SmPC as an outcome of the assessment of article 46 paediatric study 31-05-243 (P46 066.1). Details of the local representatives were also updated in the Package Leaflet. A.1 - Administrative change - Change in the name and/or address of the MAH 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	21/11/2013	10/04/2014	SmPC, Labelling and PL	
IB/0095	Update of section 5.1 of the Summary of Product Characteristics (SmPC) following the assessment of the paediatric study results CN138603 (P46-65), submitted under article 46 of the Regulation (EC) No 1901/2006. Furthermore, update of the product information according to the QRD template (version 9) including linguistic amendments. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	31/07/2013	10/04/2014	SmPC, Annex II, Labelling and PL	

IAIN/0094	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	27/06/2013	10/04/2014	Annex II and PL	
IB/0093	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	03/05/2013	n/a		
II/0084	Update of section 4.4 of the SmPC to add information on the risk of suicidality in paediatric patients based on the results of the epidemiological study CN138598. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	10/04/2014	SmPC	Based on review of the results from a clinical study conducted in paediatric patients, the CHMP concluded that these data were insufficient to evaluate the risk of suicide with aripiprazole compared to other antipsychotics in patients below 18 years of age, but there is evidence that the risk persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole. This updated warning is based on the results of a study submitted in accordance with Article 46 of the Paediatric Regulation No 1901/2006.
N/0092	The Marketing Authorisation Holder (MAH) took the opportunity to update details of local representatives in Annex IIIB. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/03/2013	13/06/2013	PL	
N/0090	The Marketing Authorisation Holder (MAH) took the opportunity to update details of local representatives in Annex IIIB. Minor change in labelling or package leaflet not	14/03/2013	13/06/2013	PL	

	connected with the SPC (Art. 61.3 Notification)				
IAIN/0091	A.1 - Administrative change - Change in the name and/or address of the MAH	01/02/2013	13/06/2013	SmPC, Labelling and PL	
IAIN/0089	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/12/2012	n/a		
II/0082	Extension of indication to include the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	13/12/2012	24/01/2013	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion Abilify-H-000471-II-0082-AR.
II/0086	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) to include information on pathological gambling following CHMP conclusions on PSUR 15. Sections 2 and 4 of the Package Leaflet (PL) have been amended 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	18/10/2012	19/11/2012	SmPC, Annex II and PL	On the basis of the data submitted, the CHMP considered that this application fulfilled their request for updating the Product Information regarding pathological gambling. The following information has been included in the SmPC: - section 4.4: Pathological gambling: post-marketing reports of pathological gambling have been reported among patients prescribed ABILIFY, regardless of whether these patients had a prior history of gambling. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully (see section 4.8). - section 4.8: pathological gambling (under the postmarketing table) Sections 2 and 4 of the PL were amended accordingly.

IA/0088/G	This was an application for a group of variations. 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	19/10/2012	n/a		
IA/0087/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	19/09/2012	n/a		
IAIN/0085/G	This was an application for a group of variations. B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	29/08/2012	n/a		

IAIN/0083/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.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.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	29/03/2012	10/05/2012	Annex II and PL	
IB/0081	Following the CHMP conclusions on Antipsychotics and Use during the third trimester of pregnancy and risk of abnormal muscle movements and/or withdrawal symptoms in newborns, dated 23 June 2011, the MAH is amending the Summary of Product Characteristics (SmPC) and Package Leaflet (PIL) with the PhVWP/CHMP recommended wording. In addition the MAH takes the opportunity to introduce minor linguistic amendments in the texts of the Product Information, including editorial updates of the list of local representatives in the Package Leaflet. Furthermore the MAH is deleting the suffix to the MA numbers for Iceland and Norway, since these are no longer required. C.I.3.a - Implementation of change(s) requested	21/09/2011	n/a	SmPC and PL	

	following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
IB/0080	B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms	10/08/2011	n/a		
IA/0079	A.7 - Administrative change - Deletion of manufacturing sites	08/04/2011	n/a		
IA/0078	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	16/03/2011	n/a		
II/0074	Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) to include information related to study CN138-189 (a trial of adjunctive aripiprazole to lithium or valproate) submitted as part of FUM 39. Annex II has also been amended to delete the version number of the detailed description of pharmacovigilance system (DDPS). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	21/01/2011	SmPC and Annex II	Based on the review of FUM 39 further investigating in clinical trials (CN138-189 and CN138-392), the efficacy of aripiprazole in combination with mood stabilizers (lithium and valproate) or lamotrigine in the recurrence prevention of manic episodes in patients with Bipolar I Disorder, the CHMP recommended to update section 4.2 of the SPC clarifying that the therapy should continue at the same dose for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy. In addition, results from study CN138-189 were reflected in section 5.1 as follows:

					In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores ? 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania). In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer. Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate. The Kaplan-Meier rates for recurrence to any mood episode f
IA/0077	A.7 - Administrative change - Deletion of manufacturing sites	10/01/2011	n/a		
N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/12/2010	n/a	PL	

II/0073	Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) to include information related to studies CN138-178, CN138-179, and CN138-180 conducted in patients (6-17 years) with irritability associated with autistic disorder (IAD) following CHMP conclusions on article 46 of Paediatric Regulation (P46-FUM 054). C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/09/2010	05/11/2010	SmPC	On the basis of the submitted data, the CHMP recommended to reflect the following information: Section 4.2: Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established in irritability associated with autistic disorder. Currently available data are described in section 5.1 but no recommendation on a posology can be made. Section 5.1: Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

II/0072	Further to the assessment of FUM 47, section 4.8 of the SmPC was revised to reflect the rates of low serum prolactin levels observed in the schizophrenia adolescent population. Further to the assessment of FUM 44.1, section 2 of the Package Leaflet was amended to add symptoms of hyperglycaemia. The EMA name and website were updated throughout the Product Information. Annex II was updated with respect to the new version identifier of the latest RMP. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/09/2010	05/11/2010	SmPC, Annex II and PL	Further to the assessment of MAH´s analysis of safety parameters in paediatric population treated with aripiprazole, the MAH revised section 4.8 of the SmPC to reflect the rates of low serum prolactin levels observed in the schizophrenia adolescent population. The following text was added to section 4.8 of the SPC: "In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ ml) and males (<2 ng/ ml) was 29.5% and 48.3%, respectively." Further, the MAH took the opportunity to update the Package Leaflet in Section 2 to highlight to patients the importance of informing physicians about any symptoms suggestive of diabetes (symptoms of high blood sugar). In addition, the EMA name and website were updated throughout the Product Information and Annex II was updated with respect to the new version identifier of the latest Risk Management Plan.
IA/0075	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	04/08/2010	n/a	Annex II	
II/0069	Update of section 4.4 of the Summary of Product Characteristics (SPC) to include a wording on risk of suicidality in patients with schizophrenia based on the results of epidemiological study CN 138-537. Additionally, the Product Information was updated in accordance with the latest QRD template (version 7.3 dated October 2009).	18/02/2010	23/03/2010	SmPC, Annex II and PL	In study CN138-537 (extension of epidemiological study CN138-458 including patients with schizophrenia), aripiprazole users did not have an increased risk of suicide events compared with users of atypical antipsychotics combined. The CHMP recommended therefore an update of the warning on the occurrence of suicidal behaviour to reflect that the study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics

	Update of Summary of Product Characteristics and Package Leaflet				among patients with schizophrenia.
IA/0071/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	08/03/2010	n/a	Annex II	
N/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/03/2010	n/a	Labelling and PL	
II/0068	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) in relation to a class-labelling on risk of venous thromboembolism (VTE) associated with antipsychotics at the CHMP request. The introductory paragraph in section 4.8 of the SPC was also updated. Relevant sections of the Package Leaflet (PL) were amended accordingly. In addition, the name of the Marketing Authorisation Holder was shortened to "Otsuka" in the relevant section of the Labelling. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/09/2009	05/11/2009	SmPC, Labelling and PL	The Pharmacovigilance Working Party (PhVWP) considered a national review from a Member State on spontaneous reporting data and world-wide published literature on antipsychotics and the risk of venous thromboembolic events (VTE). Despite the limitations of both sources of information (data from literature is limited by the lack of randomised controlled trial data and the heterogeneity of completed published studies; post marketing data is limited by potential confounding factors such as sedation and weight gain which are commonly present in antipsychotic users), the PhVWP concluded that an association between VTE and antipsychotics cannot be excluded. The PhVWP concluded that it was not possible to distinguish risk between different drugs and therefore there was no justification for warnings for VTE just for a few drugs. Following the PhVWP

					conclusions, the CHMP recommended the inclusion of the proposed PhVWP class labelling into the Abilify SPC/PL. The ADRs table was updated to replace thromboembolic events by venous thromboembolism (including pulmonary embolism and deep vein thrombosis) and the following new warning was included in the SPC: - Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ABILIFY and preventive measures undertaken. Furthermore, the introductory paragraph in section 4.8 of the SPC was also updated to align it with the information reflected in the Adverse Drug Reactions (ADRs) table.
II/0048	Extension of indication for Abilify to include "treatment of schizophrenia in adolescents 15 years and older". In addition, details of the local representatives for Estonia, Belgium and Luxembourg were also updated. Extension of indication Update of Summary of Product Characteristics and Package Leaflet	27/07/2009	21/08/2009	SmPC, Annex II and PL	Please refer to the scientific discussion Abilify H-471-II-4-AR.
II/0067	Update of sections 4.6 and 4.8 of the Summary of Product Characteristics to include safety information on congenital anomalies and dystonia in line with the CHMP conclusions on the 9th PSUR. Section 4.8 was also updated to add a brief introduction summarising the safety profile of aripiprazole.	29/05/2009	07/07/2009	SmPC	Based on the review of the 9th PSUR, the CHMP recommended an update of the Product Information in relation to section 4.6 of the Summary of Product Characteristics (SPC). A significant number of congenital anomalies were reported for which causality could not be attributable with certainty but numerically, these reports

	Update of Summary of Product Characteristics				were of concern. Additionally the CHMP requested an update of the information in relation to dystonia. In line with the CHMP conclusions on the 9th PSUR, the MAH amended the Product Information to introduce the following: - Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. - Dystonia: Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.
II/0065	Update of sections 4.8 and 5.1 of the Summary of Product Characteristics (SPC) for Abilify, with information related to the lack of effect of aripiprazole on lipid parameters (dyslipidaemia) as compared to placebo. Update of Summary of Product Characteristics	23/04/2009	08/06/2009	SmPC	On 16 July 2008, the MAH submitted the results of a pharmacovigilance analysis of the post marketing safety data and the meta-analysis of completed, controlled clinical trials of aripiprazole, with respect to parameters relevant to the evaluation of dyslipidaemia, as proposed in the Risk Management Plan and following CHMP's request. In the pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and fasting LDL. The following was added to the SPC: -Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (? 6.22 mmol/l) was 2.5% for

					aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo. -Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (? 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo. -HDL: incidence of changes in levels from normal (? 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo. -Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (? 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo. The above results showed that in studies available and as group means, aripiprazole is neutral in these parameters. The CHMP considered that an update of the SPC to reflect this information was acceptable.
II/0064	Update of section 4.5 of the Summary of Product Characteristics (SPC) to reflect the absence of interaction with lamotrigine following a drug interaction study (CN 138402).	23/04/2009	08/06/2009	SmPC	Study CN1384021 was designed to investigate the effect of aripiprazole on the steady state pharmacokinetics of lamotrigine. Results indicated that there were no clinically important changes in lamotrigine pharmacokinetics when co-administered with aripiprazole. On this basis, the CHMP

	Update of Summary of Product Characteristics				considered acceptable to reflect the absence of interaction with lamotrigine into the SPC, given that combination therapy is commonly used for the treatment of bipolar disorder and therefore it is likely that aripiprazole is co-administered with lamotrigine, a drug used for the recurrence prevention of mood episodes (i.e. depression, mania, hypomania, and mixed episodes).
R/0059	Renewal of the marketing authorisation.	19/02/2009	21/04/2009	SmPC and PL	
IA/0066	IA_09_Deletion of manufacturing site	03/03/2009	n/a		
II/0060	Update of Detailed Description of the Pharmacovigilance System Changes to QPPV Update of DDPS (Pharmacovigilance)	22/01/2009	24/02/2009	Annex II	The Detailed Description of the Pharmacovigilance System has been updated (Version 3.0) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
II/0056	The Marketing Authorisation Holder applied to add an additional site for manufacture, primary packaging, quality control testing and release of Abilify 7.5 mg/ml solution for injection. Quality changes	22/01/2008	11/02/2009		
IA/0062	IA_09_Deletion of manufacturing site	10/12/2008	n/a		
IA/0061	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	10/12/2008	n/a	SmPC and PL	

N/0057	Update of the list of local representative in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/10/2008	n/a	PL	
IA/0058	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	02/10/2008	n/a		
II/0055	Update of section 4.4 of the Summary of Product of Characteristics (SPC) to include information on risk of suicidality in patients with Bipolar Disorder as requested by the CHMP following the assessment of epidemiological study CN138-458. Update of Summary of Product Characteristics	24/07/2008	25/08/2008	SmPC	In study CN138-458, the unadjusted suicide event rate was 20.69 per 1,000 person years in current aripiprazole users (n=2,751). Compared with current users of other atypical antipsychotics combined, current aripiprazole users did not have an increased risk of suicide events (adjusted HR= 0.69, 95% CI, 0.42-1.14). Since study CN138-458 mainly included patients with Bipolar Disorder (i.e 85%), the CHMP recommended to reflect these results for this population. Thus, the warning on occurrence of suicidal behaviour has been updated to include that results of an epidemiological study found that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with bipolar disorder.
II/0041	Extension of indication for Abilify 7.5mg/ml solution for injection to include 'rapid control of agitation and disturbed behaviours in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.' Extension of Indication	24/04/2008	20/06/2008	SmPC and PL	Please refer to the scientific discussion Abilify H-471-II-41-AR.

IB/0054	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	13/05/2008	n/a		
IB/0049	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	07/05/2008	n/a		
IA/0053	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	17/04/2008	n/a		
IA/0052	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	17/04/2008	n/a		
IA/0050	IA_32_a_Change in batch size of the finished product - up to 10-fold	15/04/2008	n/a		
II/0039	Extension of indication for Abilify to include the treatment of moderate to severe manic episodes in Bipolar I disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment. Extension of Indication	21/02/2008	31/03/2008	SmPC, Annex II and PL	Please refer to the scientific discussion Abilify H-471-II-39 AR.
II/0042	Update of section 4.8 of the Summary of Product Characteristics (SPC) to add diarrhoea and increased alkaline phosphatase further to the CHMP conclusions on the sixth PSUR. Section 4 of the Package Leaflet (PL) has been amended accordingly. Details of the local representatives for Romania and Latvia were also updated.	24/01/2008	29/02/2008	SmPC and PL	Based on the sixth periodic safety update report (PSUR), the MAH proposed to add diarrhoea and increased alkaline phosphatase as postmarketing adverse events. The CHMP considered these changes to be acceptable.

	Update of Summary of Product Characteristics and Package Leaflet				
II/0046	Quality changes	21/02/2008	25/02/2008		
IB/0044	IB_33_Minor change in the manufacture of the finished product	13/12/2007	n/a		
IA/0047	IA_27_a_Change to test proc. of immediate packaging - minor change to approved test procedure	12/12/2007	n/a		
IB/0043	IA_37_a_Change in the specification of the finished product - tightening of specification limits IB_38_c_Change in test procedure of finished product - other changes	28/11/2007	n/a		
IA/0045	IA_05_Change in the name and/or address of a manufacturer of the finished product	26/11/2007	n/a		
II/0040	Quality changes	01/09/2007	29/10/2007	SmPC	
IA/0038	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	26/06/2007	n/a		
II/0037	Update of section 4.8 of the Summary Product Characteristics (SPC) to add anxiety, abdominal and stomach discomforts, hyperhidrosis, peripheral oedema, thromboembolic events further to the CHMP conclusions on the fifth PSUR. Update of section 4.4 of the SPC to add a general warning on hypersensitivity.	26/04/2007	05/06/2007	SmPC, Labelling and PL	Based on the fifth periodic safety update report (PSUR), the MAH proposed to add safety-related information into the relevant sections of the SPC and PL, including: - anxiety, abdominal and stomach discomforts, hyperhidrosis, peripheral oedema, thromboembolic events as postmarketing adverse events;

	Section 4 of the Package Leaflet (PL) has been amended accordingly. In addition, update of the Product Information according to the latest QRD templates. Update of Summary of Product Characteristics, Labelling and Package Leaflet				- a general warning on hypersensitivity. The CHMP considered these changes to be acceptable.
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/04/2007	n/a	Labelling and PL	
IB/0033	IB_37_a_Change in the specification of the finished product - tightening of specification limits	09/02/2007	n/a		
IA/0035	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	07/02/2007	n/a		
IB/0032	IB_19_a_Change in specification of an excipient - tightening of specification limits	31/01/2007	n/a		
IA/0034	IA_47_b_Deletion of a strength	31/01/2007	n/a	SmPC, Labelling and PL	
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2007	n/a	PL	
IB/0028	IB_37_b_Change in the specification of the finished product - add. of new test parameter IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	10/01/2007	n/a		

IA/0030	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	14/12/2006	n/a		
IA/0029	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	14/12/2006	n/a		
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/12/2006	n/a	PL	
II/0024	This variation refers to an update of sections 4.4, 4.5, 4.8 and 4.9 of the Summary of Product Characteristics (SPC) to add safety-related information further to the CHMP conclusions on the third and fourth periodic safety update reports (PSUR). Sections 2 and 4 of the Package Leaflet (PL) have been amended accordingly. Furthermore, the PL was updated to include all relevant warnings, precautions and interactions in accordance to the SPC. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	28/11/2006	SmPC and PL	Based on the third and fourth periodic safety update reports (PSUR), the MAH proposed to add safety-related information into the relevant sections of the SPC and PL, including: - special warnings and precautions for use related to patients with known cardiac and vascular disorders (including blood pressure disorders and QT prolongation), weight gain and dysphagia; neuroleptic malignant syndrome (NMS), hyperglycaemia and diabetes mellitus; - information on concomitant use with weak inhibitors of CYP3A4 or CYP2D6 (e.g.: When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.), with medicines known to cause QT prolongation or electrolyte imbalance; - post-marketing adverse events: leukopenia, neutropenia, thrombocytopenia, allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritis, or urticaria), hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma, weight gain, weight decreased, anorexia, hyponatremia, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion, QT prolongation, ventricular

					arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia, hypertension, oropharyngeal spasm, laryngospasm, aspiration pneumonia, dysphagia, jaundice, hepatitis, rash, photosensitivity reaction, alopecia, rhabdomyolysis, myalgia, stiffness, urinary incontinence, urinary retention, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased; - overdose: update of post-marketing events seen in adults (lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting) and children (somnolence, transient loss of consciousness and extrapyramidal symptoms) and change in reported estimated dose for overdosage in adults. The CHMP considered these changes to be acceptable.
X/0016	Annex I_2.(e) Change or addition of a new route of administration Annex I_2.(d) Change or addition of a new pharmaceutical form	27/07/2006	04/10/2006	SmPC, Labelling and PL	The MAH submitted an extension application (EMEA/H/C/471/X/16) to add a new pharmaceutical form and a new route of administration. It is a ready-to-use solution for injection 7.5 mg/ml for intramuscular use. Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Abilify 7.5 mg/ml solution for injection in the rapid control of agitation and disturbed behaviours in patients with schizophrenia, when oral therapy is not appropriate was favourable.
II/0015	This variation refers to an extension of indication of Abilify in the treatment of rapid control of agitation and disturbed behaviours in patients with schizophrenia, when oral therapy is not appropriate.	27/07/2006	04/10/2006	SmPC, Labelling and PL	Please refer to Scientific Discussion H-471-II-15.

	Extension of Indication				
IA/0026	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	19/09/2006	n/a		
II/0023	This variation refers to an update of section 5.3 of the Summary Product Characteristics (SPC) to change the safety ratios animal/human exposure further to the CHMP conclusions on the review of bioanalytical results impacting on plasma concentration measurement in initial pivotal non clinical studies. Update of Summary of Product Characteristics	27/07/2006	07/09/2006	SmPC	The CHMP concluded that the safety ratio (animal/human exposure) at the tumorigenic dose of 60 mg/kg/day in female rats be changed from the original '14 times' to '10 times' to accurately reflect the week 68 toxicokinetic data from the 70-week investigative study in rats. In addition, the CHMP requested the MAH to include a reference to the safety margin of 7 in relation to the maximum non tumorigenic dose. The MAH submitted this type II variation to update section 5.3 of the SPC accordingly. The CHMP considered these changes to be acceptable.
II/0022	This variation refers to an update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) to include information on the risk of suicide and suicide related events in connection with aripiprazole treatment. Sections 2 and 4 of the Package Leaflet (PL) were amended accordingly. In addition, editorial corrections were made in section 4.8 of the SPC and section 6 of the PL for Abilify 1mg/ml oral solution and in section 5.1 of the SPC for all pharmaceutical forms.Annex II was amended to be in line with the QRD templates. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	07/09/2006	SmPC, Annex II and PL	In PSUR 2, 32 initial cases of suicidal ideation were reported, of which 7 were fatal. Further to additional spontaneous cases reported in the Europan Union, the CHMP requested the Marketing Authorisation Holder (MAH) to provide all data related to the risk of suicide and suicide-related events in connection with aripiprazole treatment. The CHMP concluded that the association of aripiprazole with a higher risk of suicidality is possible. However, the magnitude of the risk is not possible to establish and it is also not possible to establish if the risk is different from other antipsychotic drugs. The CHMP considered an update of sections 4.4 and 4.8 of the SPC was necessary to reflect this information. Therefore, the MAH submitted a type II variation to update the SPC and also amend sections 2 and 4 of the PL. In addition, editorial corrections were made in section 4.8 of the

					SPC and section 6 of the PL for Abilify 1mg/ml oral solution and also in section 5.1 of the SPC for all pharmaceutical forms. Furthermore, Annex II was amended to be in line with the QRD templates.The CHMP considered these changes to be acceptable.
IA/0025	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	16/08/2006	n/a		
II/0019	The MAH applied for an update of section 4.5 of the Summary of Product Characteristics to reflect the absence of interaction when aripiprazole was administered concomitantly with either valproate or lithium, further to the adoption of the CHMP conclusions on the interaction studies with valproate (CN138-126) and lithium (CN138 127). Additionally, the Product Information has been amended in accordance with the latest QRD templates (version 7, July 2005) and a correction in the Package Leaflet to add 'chest pain' was proposed. Update of the Product Information of Abilify oral solution to include changes already approved for Abilify tablets and orodispersible tablets was also made. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/04/2006	31/05/2006	SmPC, Labelling and PL	Based on its review of the interaction studies of aripiprazole on valproate (CN138-126) and lithium (CN138-127), the CHMP concluded that these studies were specifically done to assess such interactions and the medicines targeted were very relevant in the indication for which aripiprazole is approved. These studies have shown that aripiprazole had no significant effect on the steady-state pharmacokinetics of either valproate or lithium and the CHMP agreed to include these data into the Summary of Product Characteristics (SPC). Therefore, the MAH submitted this type II variation to update section 4.5 of the SPC in order to reflect the absence of interaction when aripiprazole was administered concomitantly with either valproate or lithium. Additionally, the Product Information has been amended in accordance with the latest QRD templates (version 7, July 2005) and a correction in the Package Leaflet to add 'chest pain' was proposed. Update of the Product Information of Abilify oral solution to include changes related to starting and maintenance doses (see variation EMEA/H/C/000471/II/0007) and related to safety (see variation EMEA/H/C/000471/II/0008), already approved for Abilify tablets and orodispersible tablets was also made.

IA/0021	IA_01_Change in the name and/or address of the marketing authorisation holder	31/05/2006	n/a	SmPC, Labelling and PL	
IA/0020	IA_28_Change in any part of primary packaging material not in contact with finished product	28/04/2006	n/a		
II/0017	Change in formulation	23/03/2006	27/04/2006	SmPC, Labelling and PL	
IB/0018	IB_17_a_Change in re-test period of the active substance	22/02/2006	n/a		
IB/0014	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	13/01/2006	n/a	SmPC	
II/0008	Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	07/11/2005	SmPC and PL	The section 4.4 of the SPC was updated to include information from clinical trials on that elderly patients with dementia-related psychosis treated with aripiprazole (note: non-approved indication) are at increased risk of death compared to placebo, that the rate of death in aripiprazole-treated elderly patients with dementia-related psychosis was 3.5% compared to 1.7% in the placebo group and that although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. In section 4.8 of the SPC the increased mortality in elderly demented patients was further mentioned. Furthermore, three adverse reactions reported during post-marketing surveillance in PSUR 1 and PSUR 2 (priapism, temperature regulation disorder and increased Gamma

					Glutamyl Transferase (GGT)) was added to the section 4.8. In the section 4.9 of the SPC more detailled information on the symptoms seen in patients who have taken overdoses, such as lethargy, increased blood pressure, and somnolence, were mentioned following PSUR 2. Furthermore, the codification system for adverse events from clinical trials mentioned in section 4.8 was changed from COSTART to MedDRA.
II/0007	Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	07/11/2005	SmPC and PL	The section 4.2 of the SPC was updated with new information from a short-term placebo-controlled trial evaluating 3 fixed doses of aripiprazole (2 mg, 5 mg and 10 mg) in patients with acute schizophrenia in order to better characterise the minimum effective dose. The recommended starting dose is set at 10-15 mg. The maintenance dose remains on 15 mg, as long-term efficacy of the 10 mg dose has not been studied.
X/0004	Addition of a new oral solution form. X-3-iv_Change or addition of a new pharmaceutical form	27/07/2005	28/10/2005	SmPC, Annex II, Labelling and PL	The overall benefit/risk assessment for the oral solution was considered positive with an established bioequivalence between the tablet and oral solution formulation. The oral solution may be used as an alternative to Abilify tablets for patients who have difficulty in swallowing tablets.
IB/0011	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	19/08/2005	n/a		
IA/0012	IA_32_a_Change in batch size of the finished product - up to 10-fold	09/08/2005	n/a		
IA/0010	IA_05_Change in the name and/or address of a manufacturer of the finished product	02/08/2005	n/a		

IA/0009	IA_05_Change in the name and/or address of a manufacturer of the finished product	02/08/2005	n/a		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/07/2005	n/a	PL	
X/0001	Addition of a new orodispersible form. Annex I_2.(d) Change or addition of a new pharmaceutical form	16/03/2005	20/06/2005	SmPC, Labelling and PL	The overall benefit/risk assessment for the orodispersible tablet was considered positive with an established bioequivalence between the tablet and orodispersible formulations. The orodispersible tablets may be used as an alternative to Abilify tablets for patients who have difficulty in swallowing tablets.
II/0003	Update of sections 4.2, 4.4, 4.8 and 4.9 of the SPC and corresponding sections of the PL with safety information based on the PSUR 1, inclusion of a warning concerning cerebrovascular adverse events in elderly patients with psychosis associated with Alzheimer's disease, as well as information on overdose experience. Update of Summary of Product Characteristics, Labelling and Package Leaflet	17/02/2005	30/03/2005	SmPC, Labelling and PL	Following placebo-controlled trials of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, information was added to section 4.4 of the SPC on cerebrovascular adverse events, e.g. stroke, transient ischemic attacks, reported in elderly patients with dementia-related psychosis. It should be noted that Abilify is not approved for the treatment of dementia-related psychosis.Information was added to section 4.4 of the SPC on hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, reported in patients treated with atypical antipsychotic agents. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse events (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with Abilify and with other atypical antipsychotic agents are not available to allow direct comparisons. Thus, patients treated with any antipsychotic

					agents, including Abilify, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.Cerebrovascular adverse events in elderly demented patients, hyperglycaemia and diabetes mellitus, as well as dyskinesia was added to section 4.8 of the SPC.Information was added to section 4.9 of the SPC on from clinical trials, accidental or intentional acute overdosage of aripiprazole identified in patients with estimated doses up to 1080 mg with no fatalities. The reported signs and symptoms observed with aripiprazole overdose included nausea, vomiting, asthenia, diarrhoea, and somnolence. During post-marketing experience, the reported signs and symptoms observed in adult patients who overdosed with aripiprazole alone
IB/0005	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	23/03/2005	n/a	SmPC	
II/0002	Additional manufacturing site of the active substance. Change(s) to the manufacturing process for the active substance	20/01/2005	24/01/2005		