Jinarc

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/0036	Submission of an updated RMP version 15.0 in order to reflect the outcome of the substantial amendment to the protocol of the category 1 PASS study (156-12-299) as concluded in (PSA/S/0078.1). The Annex II is updated accordingly. In addition, the MAH took the opportunity to correct an oversight/editorial	01/09/2022		Annex II and PL	Within the procedure EMEA/H/C/PSA/S/0078, the MAH submitted two proposed versions B and C amendment 4 of PASS protocol Post-authorisation Safety Study, 156-12-299, which is an obligation in the Marketing Authorisation, Annex II of the Product Information with Jinarc. The MAH justified to amend the PASS protocol by reducing

[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).

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	error in the Package Leaflet relevant to (II/0033/G). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				the sample size from 3000 to 2100 patients and reducing the length of the study duration from 3 years to 2 years of follow-up and the PRAC agreed (EMEA/H/C/PSA/S/0078.1). Consequently, The MAH submitted an update of the EU Risk Management Plan v.15.0 within this type II variation to update milestones of the PASS study 156-12-299 (dates for study closure, Last Patient Last Visit (LPLV) and final study report submission) as committed in the outcome of above-mentioned procedure. Annex II of Product Information is also updated accordingly. The MAH has also submitted an amended Package Leaflet to align the information with that in the SmPC. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10395 /202105	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	02/12/2021	n/a		PRAC Recommendation - maintenance
II/0033/G	This was an application for a group of variations. Update of section 4.5 of the SmPC in order to update the safety information based on final results from study 156-201-00233 and 156-201-00234; the Package Leaflet is updated accordingly. 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	09/09/2021	22/03/2022	SmPC and PL	Drug-drug interaction study 156-201-00233 was designed to investigate BCRP inhibitory potential of tolvaptan and the potential inhibitory effect of tolvaptan metabolite DM-4103 on an OATP1B1 transporter substrates. Drug-drug interaction study 156-201-00234 was designed to investigate OAT3 inhibitory potential of tolvaptan metabolite DM-4103. Co-administration of tolvaptan (90 mg) with rosuvastatin (5 mg), a BCRP substrate, increased rosuvastatin Cmax and AUCt of 54% and 69%, respectively. If BCRP substrates (e.g. sulfasalazine) are co-administered with tolvaptan, patients must be managed cautiously and evaluated for excessive effects of these medicinal products. Administration of

					rosuvastatin (OATP1B1 substrate) or furosemide (OAT3 substrate) to healthy subjects with elevated oxobutyric acid metabolite (inhibitor of OATP1B1 and OAT3) plasma concentrations did not meaningfully alter the pharmacokinetics of rosuvastatin or furosemide. Statins commonly used in the tolvaptan phase 3 pivotal trial (e.g. rosuvastatin and pitavastatin) are OATP1B1 or OATP1B3 substrates, however no difference in adverse events profile was observed during the phase 3 pivotal trial for tolvaptan in ADPKD. If OCT1 substrates (e.g. metformin) are co-administered with tolvaptan, patients must be managed cautiously and evaluated for excessive effects of these medicinal products.
IA/0034	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	02/07/2021	n/a		
II/0029	To update the RMP for Jinarc to version 14.4 to include dehydration and pregnancy prevention programme as requiring additional risk minimisation measures in accordance with Annex II. 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	09/04/2021	22/03/2022	SmPC	The RMP is updated to include the following changes: • Additional risk minimisation measures are included in relation to the safety concerns of dehydration (important identified risk) and pregnancy (missing information) • Removal of of "Too Rapid Rise of Serum Sodium and Neurologic Sequelae (encephalopathy, osmotic demyelination" and "Interaction with CYP3A4 Inhibitors" from the important identified risks • Removal of "glaucoma" and "basal cell carcinoma" from the important potential risks. • Removal of "Use in ADPKD patients with renal function other than CKD stage 1-4" and "paediatric use" from

					the missing information Section 5.3 of the SmPC is updated with exposure margins on reprotoxicity based on exposure margins at NOAELs from clinical study 156-09-285 in ADPKD patients Jinarc: Teratogenicity was noted in rabbits given 1,000 mg/kg/day (2.6-times the exposure at the maximum human recommended dose of 120 mg/day). No teratogenic effects were seen in rabbits at 300 mg/kg/day (1.2-times the exposure at the maximum human recommended dose of 120 mg/day). [..] The no observed adverse effect level (NOAEL) for reproduction in females (100 mg/kg/day) was about 4.4 times the exposure at the maximum human recommended dose of 120 mg/day.
PSUSA/10395 /202005	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	28/01/2021	31/03/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10395/202005.
II/0031	Update of sections 4.2 and 4.4 of the SmPC in order to include information on patients with CKD late stage 4 based on final results from study 156-12-211 listed as a category 3 study in the RMP; this is a Phase 3b, Multicenter, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/03/2021	22/03/2022	SmPC, Annex II and PL	No new safety signals have emerged based on the newly submitted data. The aquaretic effect of tolvaptan gave rise to the majority of reported AEs. Liver toxicity remains among the common main adverse reactions. The risk of glaucoma and skin neoplasm associated to tolvaptan remains uncertain; additional results from routine further pharmacovigilance activities are needed before making definitive conclusions. Information on pregnancy is very limited and further monitoring is required. Finally, information became available in the subpopulation within stage 4 CKD. The safety profile of this patient subcategory was consistent with the profile described for the overall population. A post-hoc analysis for efficacy was conducted

					within this patient subcategory and showed beneficial effects on annual eGFR slope. The availability of clinical data in this patient subgroup is now reflected in the updated SmPC as follows: Section 4.2 of the SmPC is updated to state that limited data are available for patients with CKD late stage 4 (eGFR < 25 mL/min/1.73 m2). Section 4.4 of the SmPC is updated to state that there are limited safety and efficacy data available for Jinarc in patients with CKD late stage 4 (eGFR< 25 mL/min/1.73 m2) and that there are no data in patients with CKD stage 5.
IA/0032/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	04/03/2021	22/03/2022	Annex II and PL	
R/0027	Renewal of the marketing authorisation.	30/01/2020	03/04/2020	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Jinarc in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation to be granted with unlimited validity, subject to the conditions as detailed in Annex II.
PSUSA/10395 /201905	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	28/11/2019	n/a		PRAC Recommendation - maintenance
IA/0028	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	24/10/2019	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release)				
IB/0025	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/08/2019	09/12/2019	Annex II	
PSUSA/10395 /201811	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	14/06/2019		SmPC and PL	PRAC Recommendation - maintenance
IB/0022	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/04/2019	n/a		
IAIN/0024/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.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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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	08/03/2019	n/a		

	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.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
PSUSA/10395 /201805	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	13/12/2018	12/02/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10395/201805.
IAIN/0021/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets,	19/12/2018	09/12/2019	SmPC, Labelling and PL	

	ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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				
T/0020	Transfer of Marketing Authorisation	18/10/2018	12/11/2018	SmPC, Labelling and PL	

II/0015	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information on acute liver failure requiring liver transplantation, based on post-marketing experience with tolvaptan in autosomal dominant polycystic kidney disease (ADPKD). The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/09/2018	12/11/2018	SmPC and PL	The product information has been updated to add a warning to section 4.4 of the SmPC under 'Idiosyncratic hepatic toxicity' which explains that liver failure requiring liver transplantation has been reported post-marketing in association with the ADPKD indication. Wording in Section 4.8 of the SmPC under the 'not known' frequency now mentions 'acute hepatic failure' as a suspected adverse event (with a footnote that it was 'observed in post-marketing with tolvaptan in ADPKD. Liver transplantation was necessary'). The PL was updated accordingly.
II/0009	Extension of Indications to the treatment of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 4, based on the results of a completed Post Authorisation Efficacy Study (PAES, Trial 156-13-210). Trial 156-13-210 is a Phase 3b, Multi-centre, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease. Submission of these results fulfils the corresponding condition mandated by Annex II of the Product Information for tolvaptan (ANX 006). Sections 4.1, 4.8 and 5.1 of the SmPC and the package leaflet were updated accordingly. Changes in line with QRD template and other minor additional editorial changes were also carried out.	28/06/2018	26/07/2018	SmPC, Annex II and PL	Please refer to Scientific Discussion : Jinarc EMEA/H/C/002788/II/0009 AR

	Version 13.3 of the RMP, updated to reflect the study results, was approved. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0018	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	20/07/2018	12/11/2018	Annex II and PL	
IAIN/0017	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	20/07/2018	12/11/2018	Annex II and PL	
II/0016	Update of sections 4.3 and 4.4 of the SmPC in order to add a contraindication and a warning on hypersensitivity to benzazepine derivatives, thus aligning the product information to the patient population studied in clinical trials and the RMP for Jinarc. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/05/2018	29/06/2018	SmPC and PL	The product information has been updated to add a contraindication for patients with hypersensitivity to benzazepine derivatives using tolvaptan. This corresponds to an existing contraindication in the risk management plan deriving from an exclusion from clinical trials of this group of patients during the development of tolvaptan. A warning has also been added to underline that severe sensitivity reactions or anaphylaxis can occur in patients with benzazepine or benzazepine derivative hypersensitivity.
PSUSA/10395	Periodic Safety Update EU Single assessment -	14/06/2018	n/a		PRAC Recommendation - maintenance

/201711	tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))				
IB/0014	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	15/05/2018	29/06/2018	SmPC, Labelling and PL	
II/0010	Update of Section 4.5 of the SmPC to modify the existing warning regarding co-administration of tolvaptan with CYP3A inhibitors based on data from a completed PK study 156-14-216, a Phase 1, Single centre, Open-label, drug interaction trial to Investigate the Effect of Oral Fluconazole, a Moderate CYP3A4 Inhibitor, on Tolvaptan Pharmacokinetics in Healthy Adult Subjects (MEA 003). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/04/2018	29/06/2018	SmPC	Co-administration of tolvaptan and fluconazole, a moderate CYP3A inhibitor, produced a 200% and 80% increase in tolvaptan AUC and Cmax, respectively.
IA/0012	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	15/02/2018	n/a		
IA/0008	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)	14/12/2017	n/a		

PSUSA/10395 /201705	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	30/11/2017	n/a		PRAC Recommendation - maintenance
II/0006	Update of section 5.1 of the SmPC based on final results from study 156-08-271 (TEMPO 4:4) listed as a PAES in Annex II (ANX 005). This study is a multicentre, open-label, extension study of trial 156-04-251 to evaluate the long-term safety and efficacy of oral tolvaptan tablet regimens in patients with autosomal dominant polycystic. It provides data for Jinarc treatment of autosomal dominant polycystic kidney disease (ADPKD) over 5 years. Annex II of the Product Information has been updated accordingly. Editorial changes have been made to the SmPC to align the Product Information with the latest QRD template v.10 to include the first date of authorisation for the Jinarc MA (27/05/2015) and the combination of the 15mg and 30mg strengths into one SmPC. In addition, the Marketing authorisation holder (MAH) took the opportunity to add the current ATC code applicable for tolvaptan as it has been assigned by WHO. The RMP version 13.1 has also been submitted to reflect the completion of the 156-08-271 study. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/07/2017	11/09/2017	SmPC and Annex II	TEMPO 4:4 is an open-label extension study that included 871 subjects that completed TEMPO 3:4 from 106 centres across 13 countries. This trial evaluated the effects of tolvaptan on safety, TKV and estimated Glomerular Filtration Rate (eGFR) in subjects receiving active treatment for 5 years (early-treated), compared with subjects treated with placebo for 3 years, then switched to active treatment for 2 years (delayed-treated). The primary end point for total kidney volume (TKV) did not distinguish a difference in change (-1.7%) over the 5 year treatment between early- and delayed-treated subjects at the pre-specified threshold of statistical significance (p=0.3580). Both groups' TKV growth trajectory was slowed, relative to placebo in the first 3 years, suggesting both early- and delayed- tolvaptan treated subjects benefitted to a similar degree. A secondary endpoint testing the persistence of positive effects on renal function indicated that the preservation of eGFR observed by the end of the TEMPO 3:4 pivotal trial (3.01 to 3.34 mL/min/1.73m2 at follow-up visits 1 and 2) could be preserved during open-label treatment. This difference was maintained in the pre-specified Mixed effect Model Repeated Measures (MMRM) analysis (3.15 mL/min/1.73m2, 95%CI 1.462 to 4.836, p=0.0003) and with sensitivity analyses where baseline eGFR data were carried forward (2.64 mL/min/1.73m2, 95%CI 0.672 to 4.603, p=0.0086). These data suggest that Jinarc can slow

					the rate of renal function decline, and that these benefits persist over the duration of therapy. Longer term data are not currently available to show whether long-term therapy with Jinarc continues to slow the rate of renal function decline and affect clinical outcomes of Automosal Dominant Polycystic Kidney Disease (ADPKD), including delay in the onset of end-stage renal disease. Genotyping for PKD1 and PKD2 genes was conducted in a majority of patients entering the open-label extension study (TEMPO 4:4) but the results are not yet known.Following an additional 2 years of tolvaptan treatment, resulting in a total of 5 years on tolvaptan therapy no new safety signals were identified.
PSUSA/10395 /201611	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	09/06/2017	n/a		PRAC Recommendation - maintenance
PSUSA/10395 /201605	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	12/01/2017	n/a		PRAC Recommendation - maintenance
II/0003	To update the Summary of Product Characteristics (section 4.3 contraindications) and the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	11/09/2017	SmPC and PL	
IB/0002	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	14/07/2016	n/a		

	authorisation, including the RMP - Other variation				
PSUSA/10395 /201511	Periodic Safety Update EU Single assessment - tolvaptan (indicated for adults with autosomal dominant polycystic kidney disease (ADPKD))	09/06/2016	n/a		PRAC Recommendation - maintenance