Sycrest

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
IAIN/0046	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	07/12/2022		Annex II and PL	
IA/0044	A.7 - Administrative change - Deletion of manufacturing sites	15/12/2021	n/a		

[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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N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2021		PL	
PSUSA/256/202008	Periodic Safety Update EU Single assessment - asenapine	11/03/2021	n/a		PRAC Recommendation - maintenance
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/02/2021		PL	
IB/0040/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	12/02/2021	n/a		
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/01/2021		PL	
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/12/2020	04/02/2021	PL	
IA/0037	A.7 - Administrative change - Deletion of manufacturing sites	28/07/2020	04/02/2021	Annex II and PL	

IA/0036	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)	29/06/2020	n/a		
PSUSA/256/201908	Periodic Safety Update EU Single assessment - asenapine	12/03/2020	n/a		PRAC Recommendation - maintenance
IB/0035	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/01/2020	04/02/2021	SmPC, Annex II, Labelling and PL	
PSUSA/256/201808	Periodic Safety Update EU Single assessment - asenapine	14/03/2019	n/a		PRAC Recommendation - maintenance
IA/0033	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	04/01/2019	n/a		
II/0031/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	17/05/2018	n/a		

	of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/256/201708	Periodic Safety Update EU Single assessment - asenapine	08/03/2018	n/a		PRAC Recommendation - maintenance
II/0030	Update of sections 4.4 and 4.8 of the SmPC to add safety information regarding falls as a result of postmarketing reports and published literature review. The package leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Denmark, Norway, Slovenia and Slovakia in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/02/2018	07/02/2019	SmPC, Annex II, Labelling and PL	Asenapine may cause adverse effects such as somnolence, orthostatic hypotension, dizziness and extrapyramidal symptoms, which may lead to falls and, consequently, fractures or other injuries. Patients at risk for fall should be evaluated prior to prescribing asenapine.
IB/0028	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/07/2017	n/a		
IA/0027	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	09/03/2017	n/a		
PSUSA/256/201608	Periodic Safety Update EU Single assessment - asenapine	09/03/2017	n/a		PRAC Recommendation - maintenance

IAIN/0025/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.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	13/07/2016	31/05/2017	Annex II and PL	
IA/0024	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	03/06/2016	n/a		
PSUSA/256/201508	Periodic Safety Update EU Single assessment - asenapine	17/03/2016	n/a		PRAC Recommendation - maintenance
II/0020	Update of section 4.2 of the SmPC in order to change the starting therapeutic dose to 5mg BID based on the results of an exploratory dose finding study (P05691) conducted to establish the optimal dosing regimen for manic episodes in bipolar disorder. Section 5.1 of the SmpC is updated to reflect the results of the study and minor consequential changes are introduced in sections 4.8 and 5.1 of the SmPC. Section 5.2 of the SmPC is updated in line with CHMP conclusions from variation EMEA/H/C/001177/II/0017. In addition the MAH took	24/09/2015	28/10/2015	SmPC and PL	

	the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0021	Update of sections 4.2, 4.8 and 5.1 of the SmPC with information on long-term safety and efficacy generated in paediatric study P05898, a 50-week open-label, flexible-dose, extension to study P06107 in paediatric subjects with acute manic or mixed episodes associated with bipolar 1 disorder, submitted according to Article 46 of the paediatric regulation. Study P05898 is part of the PIP P/0299/2014. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/10/2015	SmPC	Long term safety in the paediatric population (ages 10 17 years) with manic or mixed episodes associated with bipolar I disorder population was explored in a 50 week, open label, uncontrolled extension study. In this trial, a total of 34.8 % of subjects experienced clinically significant weight increase (i.e., ≥ 7 % increase in body weight at endpoint). Overall mean (SD) weight gain at study endpoint was 3.5 (5.76) kg. The clinically relevant adverse reactions identified in the paediatric trials were generally similar to those observed in the adult trials. However, adverse effects of treatment on weight gain and on plasma lipid profile appeared to be greater than effects observed in the adult trials. Long term efficacy could not be established in the trial.
II/0022	Update of SmPC section 4.8, upon request by the CHMP following the assessment of the renewal application R-19, to revise the frequency classification of some of the already listed adverse drug reactions and to highlight the fact that serious hypersensitivity reactions have been reported. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the UK local representative in the	06/08/2015	28/10/2015	SmPC and PL	Frequency classifications were assigned to the following ADRs as follows: 'Allergic reactions' Uncommon ≥0.1%<1%; 'Restless legs syndrome' Uncommon ≥0.1%<1%; 'Nausea' Common ≥1%<10%; 'Oral mucosal lesions' Uncommon ≥0.1%<1%; 'Salivary hypersecretion' Common ≥1%<10%; 'Drug withdrawal syndrome neonatal' Unknown.

	Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
R/0019	Renewal of the marketing authorisation.	26/02/2015	05/05/2015	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considered that the benefit-risk balance of Sycrest in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/256/201408	Periodic Safety Update EU Single assessment - asenapine	12/02/2015	n/a		PRAC Recommendation - maintenance
II/0017	Update of sections 4.2, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics (SmPC) with pharmacokinetic, safety and efficacy information from studies in the paediatric population. The Package Leaflet has been updated accordingly. Additionally, the MAH took the opportunity to introduce minor editorial changes throughout the annexes. Furthermore, the contact details of the local representatives in the Package Leaflet have been updated. The MAH took this opportunity to amend the Route of Admistration in Annex A from 'Oral use' to 'Sublingual use'. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	20/11/2014	05/05/2015	SmPC, Annex II and PL	Based on the provided data, information related to pharmacokinetics, safety and efficacy in paediatric population was included in the product information of Sycrest. In a PK study using flavoured sublingual tablets, at the 5 mg and 10 mg twice daily dose level, asenapine pharmacokinetics in a paediatric population (10 to 17 years of age, inclusive) are similar to those observed in adults. The 10 mg twice daily dose resulted in an approximate dose proportional increase in asenapine exposure compared to 5 mg twice daily. Based on this small pharmacokinetic study, paediatric patients appeared to be more sensitive to dystonia with initial dosing with asenapine when a gradual up-titration schedule was not followed. The incidence of dystonia in paediatric clinical trials using a gradual up-

	data				titration was similar to that seen in adult trials. The safety and efficacy of Sycrest was evaluated in 403 paediatric patients with bipolar I disorder who participated in a single, 3 week, placebo controlled, double blind trial, of whom 302 patients received Sycrest at fixed doses ranging from 2.5 mg to 10 mg twice daily. Study results showed statistically significant superiority for all three Sycrest doses in improving the Young Mania Rating Scale (YMRS) total score as measured by the change from baseline to Day 21, as compared with placebo. However, the clinical relevance of the efficacy findings has not been established. No long term data are available with regard to the efficacy and the safety of asenapine in this population. The mean change from baseline to endpoint in weight for placebo and asenapine 2.5 mg, 5 mg, and 10 mg twice daily, was 0.48, 1.72, 1.62, and 1.44 kg, respectively. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) was 14.1 % for asenapine 2.5 mg twice daily, 8.9 % for asenapine 5 mg twice daily, and 9.2 % for asenapine 10 mg twice daily, compared to 1.1 % for placebo. Efficacy of Sycrest was not demonstrated in an 8 week, placebo controlled, double blind, randomized, fixed dose trial in 306 adolescent patients aged 12 17 years with schizophrenia at doses of 2.5 and 5 mg twice daily. The clinically relevant adverse experiences identified in the paediatric bipolar and schizophrenia trials were similar to those observed in adult bipolar and schizophrenia trials.

					The most common adverse reactions (≥5 % and at least twice the rate of placebo) reported in paediatric patients with bipolar I disorder were somnolence, sedation, dizziness, dysgeusia, hypoaesthesia oral, paraesthesia oral, nausea, increased appetite, fatigue, and weight increased. The most common adverse reactions (proportion of patients □5 % and at least twice placebo) reported in paediatric patients with schizophrenia were somnolence, sedation, akathisia, dizziness, and hypoaesthesia oral. There was a statistically significant higher incidence of patients with ≥7 % weight gain (from baseline to endpoint) compared to placebo (3.1 %) for Sycrest 2.5 mg twice daily (9.5 %) and Sycrest 5 mg twice daily (13.1 %).
PSUV/0014	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
IG/0404	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	14/02/2014	n/a		
N/0015	The MAH took this opportunity to include the Croatian PI and to introduce the Croatian affiliate in the list of local representatives. Also local representatives for Finland and Greece were corrected together with minor changes in the local representatives address list in the Swedish text. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2014	11/02/2014	PL	

IG/0366	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	08/11/2013	n/a		
II/0012	Update of section 4.8 of the SmPC in order to update the safety information to include 'angioedema' as an adverse reaction, based on post-marketing reports. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	11/02/2014	SmPC, Annex II and PL	Based on post-marketing reports, a safety signal of angioedema was identified by the Marketing Authorisation Holder. Therefore, they proposed to update section 4.8 of the SmPC to include angioedema and the corresponding change to section 4 of the Package Leaflet. The CHMP considered the changes to be acceptable and agreed on the amendments to be introduced.
II/0011	Update of section 4.8 of the SmPC in order to add a new adverse reaction "salivary hypersecretion" based on post marketing reports. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the Annex II is brought in line with the latest QRD template version 8.2. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	11/02/2014	SmPC, Annex II and PL	The CHMP reviewed the post-marketing safety data on salivary hypersecretion and concluded on the need to include the following side-effect in the Product Information: increased saliva (drooling).
IB/0010	Update of section 4.8 of the SmPC in order to add a new adverse reaction "salivary hypersecretion" based on post marketing reports. The Package Leaflet was	17/10/2012	29/10/2012	SmPC and PL	The CHMP reviewed the post-marketing safety data on salivary hypersecretion and concluded on the need to include the following side-effect in the Product Information:

	updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the Annex II is brought in line with the latest QRD template version 8.2. The requested variation introduced amendments to the SmPC, Annex II and Package Leaflet. 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				increased saliva (drooling).
IG/0184	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/08/2012	n/a		
II/0008	Safety update to section 4.8 of the SmPC and section 4 of the PL to include additional adverse reactions. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	Further to CHMP assessement of second PSUR as well as of cumulative review of post-marketing spontaneous reports, this variation is a safety update to section 4.8 of the SmPC and section 4 of the PL to include the following additional side-effects: - anaphylactic/anaphylactoid reactions - ulcers, soreness, redness, swelling and blisters within the mouth - unpleasant sensations in the legs (also called restless legs syndrome) - nausea oral mucosal lesions (ulcerations, blistering and inflammation), nausea and restless Legs syndrome)

IG/0117/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	18/11/2011	18/11/2011	Annex II	
II/0005	Following PhVWP/CHMP conclusions of June 2011, update of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) regarding the use of antipsychotics during the third trimester of pregnancy and risk of abnormal muscle movements and/or withdrawal symptoms in newborns in accordance with the PhVWP/CHMP class labelling recommended wording. In addition, following a modification of the agreed Paediatric Investigation Plan, section 5.1 of the SmPC has been updated to remove the agreed measures related to schizophrenia. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a	22/09/2011	24/10/2011	SmPC and PL	There is evidence to suggest that the newborn babies of mothers treated with antipsychotics during the third trimester of pregnancy may suffer adverse effects (primarily extrapyramidal side effects and/or withdrawal effects). Whilst there is limited data available for some antipsychotics, this is likely to be a class effect. In addition to the inclusion of neonatal drug withdrawal syndrome as listed adverse reaction, section 4.6 of the SmPC and section 2 of the PL were updated in accordance with the PhVWP/CHMP class labelling recommended wording, as follows: SmpC: Neonates exposed to antipsychotics (including [Sycrest]) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and

	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				duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. PL: The following symptoms may occur in newborn babies, of mothers that have used [Sycrest] in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.
II/0003	Update of SPC section 4.8 to include information on hypersensitivity reactions and PL section 4 to provide further information to the physicians and patients. Additionally minor spelling and typo corrections were made to the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/06/2011	27/07/2011	SmPC and PL	Following the review of the post-marketing safety data the Product Information for Sycrest has been updated to reflect the fact that the treatment with asenapine can lead to allergic reactions, such as difficulty in breathing, swollen tongue or throat, skin rash, itching and increased heart rate. Patients must seek medical attention immediately if they experience these symptoms.
IA/0004/G	This was an application for a group of variations. 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.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	20/04/2011	n/a		

N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/01/2011	n/a	Annex II and PL	