Xagrid

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/0100/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.1 - Administrative change - Change in the name	16/02/2023		SmPC, Annex II, Labelling and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	and/or address of the MAH				
N/0097	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2022	03/02/2023	PL	
IB/0096	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	31/08/2022	n/a		
IA/0095	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	22/04/2022	n/a		
II/0091	C.I.4 Update of sections 4.2, 4.4, 4.8 and 4.9 of the SmPC in order to add a new warning on the risks of fatal thrombotic complications associated with abrupt treatment discontinuation based on new Pharmacovigilance data. The Package Leaflet is updated accordingly. is recommended for approval. Amendments to the marketing authorisation In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB are recommended. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/01/2022	28/02/2022	SmPC, Labelling and PL	The table in Module 8b of the EPAR will be updated as follows: Scope Please refer to the Recommendations section above Summary SmPC new text Sections 4.2, and 4.9 A cross reference to section 4.4 is added to highlight the risks in the case of treatment discontinuation. Section 4.4 the following text is added: Thrombotic Risk Abrupt treatment discontinuation should be avoided due to the risk of sudden increase in platelet counts, which may lead to potentially fatal thrombotic complications, such as cerebral infarction. Patients should be advised how to recognize early signs and symptoms suggestive of

					thrombotic complications, such as cerebral infarction, and if symptoms occur to seek medical assistance. Treatment discontinuation In the event of dosage interruption or treatment withdrawal, the rebound in platelet count is variable, but the platelet count will start to increase within 4 days of stopping treatment with anagrelide and will return to pre-treatment levels within 10 to 14 days, possibly rebounding above baseline values. Therefore, platelets should be monitored frequently (see section 4.2). Section 4.8 Cerebral infraction is added as an AE with frequency unknown under Nervous system disorders with a cross-reference to section 4.4 For more information, please refer to the Summary of Product Characteristics. A Direct Healthcare Professional Communication (DHPC) was considered necessary by the CHMP to communicate on the risk of cerebral infarction following an abrupt treatment
IAIN/0094	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	16/02/2022	03/02/2023	Annex II and PL	
IA/0093/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 importer, batch release	07/02/2022	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
T/0092	Transfer of Marketing Authorisation	23/11/2021	03/12/2021	SmPC, Labelling and PL	
PSUSA/208/202009	Periodic Safety Update EU Single assessment - anagrelide	09/04/2021	n/a		PRAC Recommendation - maintenance
II/0089	C.I.4, Update of sections 4.5. and 5.2 of the SmPC in order to add drug-drug interaction information with omeprazole, and update pharmacokinetics, based on final results from clinical study SPD-422-113 a Drug-Drug interaction (DDI) study with Xagrid (anagrelide hydrochloride) assessing the effect of multiple doses omeprazole on anagrelide and 3-OH anagrelide exposure; The study was agreed as a commitment in variation EMEA/H/C/000480/II/0075. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/11/2020	18/11/2021	SmPC	SmPC new text: Section 4.5, CYP1A2 inducers. Reference to section 5.2 for further information is added. Section 5.2 Pharmacokinetic Properties, Biotransformation The effect of omeprazole, a CYP1A2 inducer, on the pharmacokinetics of anagrelide was investigated in 20 healthy adult subjects following multiple, once daily 40 mg doses. The results showed that in the presence of omeprazole, AUC(0-∞), AUC(0-t), and Cmax of anagrelide were reduced by 27%, 26%, and 36%, respectively; and the corresponding values for 3 hydroxy anagrelide, a metabolite of anagrelide, were reduced by 13%, 14%, and 18%, respectively. For more information, please refer to the Summary of Product Characteristics.
PSUSA/208/201909	Periodic Safety Update EU Single assessment - anagrelide	17/04/2020	n/a		PRAC Recommendation - maintenance
II/0086	C.I.4 - Change(s) in the SPC, Labelling or PL due to	30/01/2020	18/06/2020	SmPC, Annex	

	new quality, preclinical, clinical or pharmacovigilance data			II, Labelling and PL	
IA/0087/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/10/2019	n/a		
IAIN/0085/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	26/08/2019	n/a		
IAIN/0084/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 -	08/07/2019	18/06/2020	Annex II and PL	

	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				
PSUSA/208/201809	Periodic Safety Update EU Single assessment - anagrelide	11/04/2019	n/a		PRAC Recommendation - maintenance
T/0082	Transfer of Marketing Authorisation	06/08/2018	23/08/2018	SmPC, Labelling and PL	
S/0081	13th Annual Re-assessment	26/04/2018	11/07/2018	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that the Marketing Authorisation of Xagrid should be maintained. The CHMP also considered that all specific obligations have been fulfilled, that data on efficacy and safety can be considered now as comprehensive and therefore that the Marketing Authorisation should be switched, from a Marketing Authorisation under exceptional circumstances to a full Marketing Authorisation. Xagrid is also removed from the additional monitoring list as the conditions to the marketing authorisation have been fulfilled.
PSUSA/208/201709	Periodic Safety Update EU Single assessment - anagrelide	12/04/2018	n/a		PRAC Recommendation - maintenance

IAIN/0079	A.1 - Administrative change - Change in the name and/or address of the MAH	11/08/2017	11/07/2018	SmPC, Labelling and PL	
PSUSA/208/201609	Periodic Safety Update EU Single assessment - anagrelide	21/04/2017	16/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/208/201609.
IA/0078/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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	30/05/2017	n/a		
II/0075	Update of sections 4.4, 4.5 and 5.1 of the SmPC in order to change the terminology of myeloproliferative disorders to myeloproliferative neoplasms, add text regarding platelet count rebound above baseline following dosage interruption, incorporate a section in drug interactions on CYP1A2 inducers and update information on the mode of action. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, correct	21/04/2017	16/06/2017	SmPC and PL	The platelet count will increase within 4 days of stopping treatment with anagrelide and will return to pre-treatment levels within 10 to 14 days, possibly rebounding above baseline values. Therefore platelets should be monitored frequently. CYP1A2 inducers (such as omeprazole) could decrease the exposure of anagrelide increasing its main active metabolite. The consequences on the safety and efficacy profile of anagrelide are not established. Therefore, clinical and biological monitoring is recommended in patients taking concomitant CYP1A2 inducers. If needed, anagrelide

	typographical errors and bring the PI in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				dose adjustment could be made. The precise mechanism by which anagrelide reduces blood platelet count is unknown. In cell culture studies, anagrelide suppressed expression of transcription factors including GATA-1 and FOG-1 required for megakaryocytopoiesis, ultimately leading to reduced platelet production.
S/0077	Annual re-assessment.	23/03/2017	n/a		
II/0074	Submission of the final Clinical Study Report of the study SPD422-403, a phase IIIb, randomised, open-label study conducted as a specific obligation to compare the safety, efficacy, and tolerability of anagrelide hydrochloride versus hydroxyurea in high-risk essential thrombocythaemia patients. No changes to the approved product information have been requested as a consequence of this study report. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/01/2017	n/a		The primary objective of study SPD422-403 was to compare the safety of anagrelide and hydroxyurea in short and long term usage of up to three years with particular reference to cardiovascular safety (as assessed by echocardiography). Results confirmed observations in the previous 126-month safety update report. Reduction of platelet count under 600 G/l was obtained with anagrelide and hydroxyurea. The decrease in median platelet count was faster and tended to be more marked in the hydroxyurea group. Safety data submitted in the final safety report are in line with the known safety profile of Anagrelide and the CHMP considered that no changes to the approved product information were necessary based on this report.
PSUSA/208/201509	Periodic Safety Update EU Single assessment - anagrelide	14/04/2016	n/a		PRAC Recommendation - maintenance
S/0072	11th Annual Re-assessment	01/04/2016	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation

					of Xagrid should be maintained under exceptional circumstances.
S/0064	10th Annual Re-assessment.	19/11/2015	18/01/2016	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Xagrid should be maintained under exceptional circumstances.
IA/0073	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	04/01/2016	n/a		
IA/0070	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	10/12/2015	n/a		
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/11/2015	18/01/2016	PL	
IG/0621	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	16/10/2015	n/a		
IA/0067	A.7 - Administrative change - Deletion of manufacturing sites	03/09/2015	n/a		
IA/0066/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of	23/07/2015	n/a		

	the AS - Minor change in the manufacturing process of the AS B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits				
II/0062	Update of section 4.6 of the SmPC with new information regarding breast-feeding and fertility and update of section 5.3 of the SmPC based on new non-clinical data. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet and to update the contact details of the local representatives in the Package Leaflet. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	23/04/2015	18/01/2016	SmPC and PL	Breast-feeding: It is unknown whether anagrelide /metabolites are excreted in human milk. Available data in animals have shown excretion of anagrelide/metabolites in milk. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with anagrelide. Fertility: No human data on the effect of anagrelide on fertility are available. In male rats, anagrelide at oral doses up to 240 mg/kg/day (>1000 times a 2mg/day dose, based on body surface area) was found to have no effect on fertility and reproductive performance. In female rats increases in pre- and post-implantation losses and a decrease in the mean number of live embryos was observed at 30 mg/kg/day. The NOEL (10mg/kg/day) to this effect was 143, 12 and 11-fold higher than the AUC in humans administered a dose of anagrelide 2 mg/day, and the metabolites BCH24426 and RL603, respectively. Embryofoetal development studies: Maternally toxic doses of anagrelide (60 mg/kg/day and above) in rats and rabbits were associated with increased embryo resorption and foetal mortality. In a pre- and post-natal development study in female rats, anagrelide at oral doses of ≥10 mg/kg produced a non-adverse increase in gestational duration. At the NOEL dose (3mg/kg/day), the AUCs for anagrelide and the metabolites BCH24426 and RL603 were 14, 2 and 2-

					fold higher than the AUC in humans administered an oral dose of anagrelide 2mg/day. Anagrelide at ≥60 mg/kg increased parturition time and mortality in the dam and foetus respectively. At the NOEL dose (30mg/kg/day), the AUCs for anagrelide and the metabolites BCH24426 and RL603 were 425-, 31- and 13-fold higher than the AUC in humans administered an oral dose of anagrelide 2 mg/day, respectively. Repeated dose toxicity: Following repeated oral administration of anagrelide in dogs, at doses of 1 mg/kg/day or higher, subendocardial haemorrhage and focal myocardial necrosis was observed at 1mg/kg/day or higher in males and females with males being more sensitive occurred in dogs. The no observed effect level (NOEL) for male dogs (0.3mg/kg/day) corresponds to 0.1, 0.1, and 1.6-fold the AUC in humans for anagrelide at 2mg/day, and the metabolites BCH24426 and RL603, respectively.
IAIN/0065/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible 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)	15/04/2015	18/01/2016	Annex II and PL	
PSUSA/208/201409	Periodic Safety Update EU Single assessment - anagrelide	10/04/2015	n/a		PRAC Recommendation - maintenance

II/0059	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/09/2014	07/11/2014	SmPC and PL	
R/0060	Renewal of the marketing authorisation.	22/05/2014	18/07/2014	SmPC	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit/risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk balance of Xagrid continues to be favourable. The CHMP recommends a renewal of the Marketing Authorisation for Xagrid under exceptional circumstances with unlimited validity. The outstanding clinical data that will be generated by the ongoing studies, included as part of the Specific Obligations, will provide additional efficacy and/or safety information. The MAH will continue to submit PSURs annually until otherwise specified by the CHMP. Following the recommendation from the CHMP, changes were made to the Product Information in section 4.4 to include a warning on the drug interaction with acetylsalicylic acid and alignment of the information in section 5.2 with the latest QRD template.
PSUSA/208/201309	Periodic Safety Update EU Single assessment - anagrelide	26/06/2014	n/a		PRAC Recommendation - maintenance
S/0057	9th Annual Re-assessment.	20/03/2014	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the

					product remains favourable. The MAH is asked to provide further data concerning an excess of non-haematological malignancies observed in the HU treatment arm in the study SPD422-401. The deadline for the submission of the data is October 2014.
IAIN/0058/G	This was an application for a group of variations. 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 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) 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	30/01/2014	18/07/2014	Annex II and PL	
II/0056	Update of the SmPC and PL following the outcome of study SPD422-111 in order to add a warning on QT prolongation, include a new adverse event of torsade de pointes and further information on the study Section 4.4 has been amended to include monitoring of electrolytes and additional QT/QTc results, section 4.8 was updated to include a new ADR of torsades de pointes and a description of results of the TQT study	21/11/2013	18/07/2014	SmPC and PL	Study SPD422-111 was a double blind and randomised study in healthy men and women with anagrelide that included a placebo and a positive control. Two single oral doses of 0.5mg and 2.5mg anagrelide were investigated. An effect on the mean QT/QTc interval > 5 ms was observed for QTcNi at 1, 1.5 and 2 hour and at 2 and 2.5 hour for 2.5mg and 0.5 mg, respectively, and for QTcF at 1 and 1.5 hour after administration for the 2.5mg dose. Post-

	has been included in section 5.1 of the SmPC. The MAH also took the opportunity to make some corrections to section 4.5 with a more appropriate CYP1A2 inhibitor. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				marketing data has also retrieved 3 reported Torsade de pointes, 2 Ventricular tachycardia and 1 prolonged QT interval, case reports for ventricular fibrillation, sudden death, seizures and syncope were retrieved.
IA/0055	A.7 - Administrative change - Deletion of manufacturing sites	10/06/2013	n/a		
IA/0054	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/05/2013	n/a		
S/0053	8th Annual Re-assessment	21/03/2013	16/05/2013	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
S/0048	7th Annual Re-assessment.	15/11/2012	14/01/2013	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the

					product remains favourable.
IA/0052	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/11/2012	n/a		
IA/0051/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms 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.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	11/10/2012	n/a		
IG/0216	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/09/2012	n/a		
IA/0049	A.7 - Administrative change - Deletion of manufacturing sites	16/07/2012	n/a		
IA/0047/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	28/07/2011	n/a		

	and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products				
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/05/2011	n/a	Labelling and PL	
S/0043	6th Annual Re-assessment	17/02/2011	06/05/2011	SmPC and Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable and that the marketing authorization remains under exceptional circumstances. Annex II.C has been updated to reflect the current status of the specific obligations. In addition, in light of the safety data provided from study SPD422-401 where 16 major haemorrhagic events were reported in patients receiving concomitantly Xagrid and aspirin, section 4.5 of the SmPC was updated upon request from CHMP, to reflect this information. Section 2 of the Package Leaflet was amended accordingly.
IA/0045/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	18/02/2011	n/a	Annex II and PL	

	site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing				
IB/0044	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk, other change	16/02/2011	n/a		
IB/0037/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	07/12/2010	n/a		
II/0036	Update of section 4.8 of the SmPC in order to add ''tubulointerstitial nephritis'' with frequency ''not known'' based on a safety review conducted by the MAH. The PL has been updated acccordingly. Furthermore, the MAH took the opportunity to update the details of the local representatives and to make some typographical changes to the SmPC and PL. Finally, a correction to the greek translation of	21/10/2010	26/11/2010	SmPC and PL	Based on the results of a cumulative safety review performed by the MAH, section 4.8 of the SmPC and section 4 of the PL are updated to include tubulointerstitial nephritis (TIN). The safety review which was conducted using the cut-off date of April 30 2010 included 11 case reports of TIN. Overall, causal relationship between anagrelide and TIN could not be excluded in 6 of the documented reports. The data suggested at least a possible

	the PL has been made to bring it in line with the approved english text. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				causal relationship in 5 reports and a probable causal relationship in a report describing positive dechallenge and rechallenge. The provided data strongly suggested a role for anagrelide in causing tubular necrosis. However, there was no specific clinical pattern identified from the reviewed reports.
IB/0042	Change in the specification parameters of the finished product B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	18/11/2010	n/a		
IA/0040/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	22/10/2010	n/a		
IA/0041	B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling	20/10/2010	n/a		
IA/0039/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	15/10/2010	n/a		

	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0038	B.II.c.3.a.1 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents NOT used in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	14/10/2010	n/a		
IA/0035/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	17/06/2010	n/a		

	material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
S/0033	Annual re-assessment.	18/02/2010	26/05/2010	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that amendments of Annexes I, II and IIIB of the Commission Decision are necessary and that the Marketing Authorisation remains under exceptional circumstances.
IB/0034	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	20/04/2010	n/a	SmPC	
II/0032	Update of section 4.8 of the SmPC to include information regarding hepatitis, upon request by CHMP following the assessment of the 4th annual reassessment (S-29) and the renewal (R-30). Section 4 of the Package Leaflet has been updated accordingly. Minor editorial changes were also introduced. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	26/03/2010	SmPC and PL	This type II variation concerns an update to section 4.8 in the Summary of Product Characteristics (SmPC) regarding the cumulative review of hepatobiliary disorders cases. The change in Section 4.8 'Undesirable effects' 'Rare side effects' is to add 'hepatitis' under the sub-heading 'Hepatobiliary disorders' with frequency 'Not known'. In addition, section 4 of the PL was updated to add reference to hepatitis and allergic alveolitis.

N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/12/2009	n/a	Labelling and PL	
R/0030	Renewal of the marketing authorisation.	20/08/2009	30/10/2009	SmPC, Annex II and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit/risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of Xagrid continues to be favourable. The CHMP recommends a renewal of the Marketing Authorisation for Xagrid under exceptional circumstances. The outstanding clinical data that will be generated by the ongoing studies, included as part of the Specific Obligations, will provide additional efficacy and/or safety information. Following the assessment of the latest 6-monthly safety update report for these ongoing studies and following the assessment of the 6th PSUR, the data presented did not modify the benefit/risk of Xagrid. However, considering the adverse events reported the MAH was requested to closely monitor all cases of hepatic disorders, vasculitis, pulmonary fibrosis/interstitial lung disease, as well as all cases of benign or malignant neoplasms (including myelofibrosis), thrombohaemorrhagic events and cardiovascular events and to discuss such cases in future PSURs. The MAH will continue to submit PSURs annually until

					otherwise specified by the CHMP. Therefore, based on the above presented Pharmacovigilance grounds, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time. During the renewal procedure, changes were made to the Product Information to bring it in line with the current EMEA/QRD template, SPC guideline and other relevant guideline(s), which were reviewed by QRD and accepted by the CHMP.
S/0029	Annual re-assessment.	19/02/2009	30/04/2009	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of Annexes I and III of the Commission Decision is necessary and that the Marketing Authorisation remains under exceptional circumstances. Annex II.C has been amended according to the conclusions reached during the CHMP discussion.
II/0028	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	22/01/2009	26/02/2009	SmPC and PL	This type II variation concerns an update of sections 4.4 and 4.5 of the SPC regarding the effects of anagrelide in combination with acetylsalicylic acid on platelet aggregation in line with the results of study SPD422-110. This study was performed in healthy subjects and showed that co-administration of repeat-dose anagrelide 1mg once daily and acetylsalicylic acid 75mg once daily may enhance the anti-platelet aggregation effects of each drug compared

					with administration of acetylsalicylic acid alone. Therefore, due to the lack of data in ET patients, the potential risks of the concomitant use of anagrelide with acetylsalicylic acid should be assessed, particularly in patients with a high risk profile for haemorrhage before treatment is initiated. Further, two paragraphs were deleted in section 4.5 of the SPC; one concerning an interaction study in the dog as results from experimental studies carried out in animals should not be included in this section according to the SPC Guideline; and one related to potential food interaction with grapefruit juice as it is a well known strong CYP3A4 inhibitor, and not a CYP1A2 inhibitor. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details for Belgium and Estonia in the list of local representatives in the Package Leaflet.
II/0026	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	23/10/2008	25/11/2008	SmPC and PL	This variation concerns an update of sections 4.2 and 5.2 of the SPC with information on elderly patients based on the results of study SPD422-203. Pharmacokinetic data from fasting elderly patients with essential thrombocythaemia (ET) (age range 65-75 years) compared to fasting adult patients (age range 22-50 years) indicate that the Cmax and AUC of anagrelide were 36% and 61% higher respectively in elderly patients, but that the Cmax and AUC of the active metabolite, 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline, were 42% and 37% lower respectively in the elderly patients. These differences were likely to be caused by lower presystemic metabolism of anagrelide to 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline in the elderly patients. The observed pharmacokinetic differences between elderly

					and young patients with ET do not warrant using a different starting regimen or different dose titration step to achieve an individual patient-optimised anagrelide regimen. Further, the MAH has made editorial changes and updated the list of local representatives in the Package Leaflet.
IA/0027	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	22/10/2008	n/a		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/08/2008	n/a	Annex II and PL	
IB/0022	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	17/06/2008	n/a		
S/0020	Annual Reassessment	19/03/2008	21/05/2008	Annex II	3rd Annual Reassessment The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of Annexes I and III of the Commission Decision is necessary and that the Marketing Authorisation remains under exceptional circumstances. Annex II.C has been amended according to the conclusions reached during the CHMP discussion
II/0021	Update of or change(s) to the pharmaceutical documentation	24/04/2008	30/04/2008		
IA/0024	IA_22_a_Submission of TSE Ph. Eur. certificate for	09/04/2008	n/a		

	exc. - Approved/new manufacturer				
IA/0023	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	09/04/2008	n/a		
II/0019	Update of Summary of Product Characteristics, Labelling and Package Leaflet	13/12/2007	28/01/2008	SmPC, Labelling and PL	This type II variation concerns an update of section 5.3 of the SPC based on the results of Study R00812-SPD422, a 104-week oral (dietary) administration oncogenicity study in the rat. Further, the Marketing Authorisation Holder took the opportunity to update the ATC code in section 5.1 of the SPC, to revise the contact details for Austria, Cyprus and Germany in the list of local representatives in the Package Leaflet and to update the annexes in line with the latest QRD template version 7.2. In this two-year rat carcinogenicity study, non-neoplastic and neoplastic findings were observed and related or attributed to an exaggerated pharmacological effect. Among them, the incidence of adrenal phaeochromocytomas was increased relative to control in males at all dose levels (3 mg/kg/day) and in females receiving 15 mg/kg/day and above. The lowest dose in males (3 mg/kg/day) corresponds to 37 times the human AUC exposure after a 1 mg twice daily dose. Uterine adenocarcinomas, of epigenetic origin, could be related to an enzyme induction of CYP1 family. They were observed in females receiving 30 mg/kg/day, corresponding to 572 times the human AUC exposure after a 1 mg twice daily dose. Currently, there is no clinical evidence that these findings are of relevance to human use.

IA/0018	IA_13_a_Change in test proc. for active substance - minor change	18/06/2007	n/a		
IA/0017	IA_13_a_Change in test proc. for active substance - minor change	18/06/2007	n/a		
IA/0016	IA_13_a_Change in test proc. for active substance - minor change	18/06/2007	n/a		
IA/0015	IA_13_a_Change in test proc. for active substance - minor change	18/06/2007	n/a		
S/0013	Annual re-assessment.	22/02/2007	15/05/2007	Annex II	2nd Annual Reassessment Taking into account the data provided as part of this 2nd Annual Re-assessment, it can be concluded that the Benefit/Risk balance for Xagrid remains unchanged. The Marketing Authorisation should be maintained under exceptional circumstances until the pending specific obligations are fulfilled.
IA/0014	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	04/05/2007	n/a		
II/0012	Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/02/2007	28/03/2007	SmPC, Labelling and PL	The MAH applied for a type II variation, upon request by CHMP following the assessment of the 3rd PSUR, to include the ADR "allergic alveolitis" in section 4.8 of the SPC and to add the standard EU excipient warning for the lactose content to section 4.4 of the SPC. The Package Leaflet and the labelling have been updated accordingly. Further, the MAH proposed to implement minor editorial changes to sections 4.1, 4.2, 4.4, 4.6, 4.8, 4.9 and 5.1 of the SPC. In

					addition, the MAH took the opportunity to add the contact details for Bulgaria and Romania to the list of local representatives in the Package Leaflet.
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/09/2006	n/a	PL	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	28/06/2006	07/08/2006	SmPC and PL	The MAH applied for a type II variation, upon request by CHMP, to include "pulmonary hypertension" and "hepatic enzymes increased" in section 4.8 of the SPC, to include information on two cases of intentional overdose in section 4.9 and to update the recommendations on renal impairment in section 4.2 of the SPC. The Package Leaflet (PL) has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes to sections 4.8 and 5.1 of the SPC and sections 2 and 4 of the PL. With reference to the post-marketing case reports of intentional overdose with anagrelide, the reported symptoms include sinus tachycardia and vomiting. Symptoms resolved with conservative management.
S/0006	Annual re-assessment.	23/03/2006	19/05/2006	Annex II	1st Annual Reassessment On the basis of the submitted data, the CHMP, having reviewed the compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, is of the opinion that the quality, safety and efficacy continues to be to be favourable for Xagrid in the approved indication. It is recommended that the marketing authorisation remain

					under exceptional circumstances.
IA/0010	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/05/2006	n/a		
IA/0009	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/05/2006	n/a		
IA/0008	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/05/2006	n/a		
II/0004	Update of Summary of Product Characteristics and Package Leaflet	26/01/2006	28/02/2006	SmPC and PL	The MAH applied for a type II variation to add the ADR "Cardiomyopathy" to section 4.8 of the SPC. The Package Leaflet has been amended accordingly. In addition, the MAH took the opportunity to make an editorial change to the Local Representative in Greece.
IA/0005	IA_13_a_Change in test proc. for active substance - minor change	21/12/2005	n/a		
II/0003	Update of Summary of Product Characteristics	15/09/2005	07/11/2005	SmPC	The MAH applied for a type II variation to update sections 4.2, 4.3, 4.4 and 5.2 of the SPC to include revised recommendations for use in patients with hepatic and renal impairment, including the impact of food. These changes were based on results from Study: SPD422-103 (severe renal impairment), Study: SPD422-104 (moderate hepatic impairment) and Study: SPD422-109 (Fed/fast states). Editorial changes have also been implemented. Anagrelide is contraindicated in patients with moderate or severe hepatic impairment and in patients with moderate or severe renal impairment (creatinine clearance <50

					ml/min). The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced. It is not recommended in patients with elevated transaminases (>5 times the upper limit of normal). Pharmacokinetic data from healthy subjects established that food decreases the Cmax of anagrelide by 14% but increases the AUC by 20%. Food had a more significant effect on the active metabolite and decreased the Cmax by 29% although it had no effect on the AUC.
II/0001	Update of Summary of Product Characteristics	27/07/2005	08/09/2005	SmPC	The MAH applied for a type II variation to update section 5.1 (Pharmacodynamic properties) of the SPC to include revised recommendations for use in children based on the results of study SPD 422-202 (Children study). "An open label clinical study with a 3 month treatment period did not raise any safety concerns for anagrelide in 17 children/adolescent patients with ET (age range 7-14 years) compared to 18 adult patients. Earlier during clinical development a limited number (12) of children (age range 5-17 years) with essential thrombocythaemia were treated with anagrelide." Further the MAH introduced consequential changes to section 5.2 (Pharmacokinetic properties): "Pharmacokinetic data from fasting children and adolescents (age range 7-14 years) with essential thrombocythaemia indicate that dose and body weight

					normalized exposure, Cmax and AUC, of anagrelide were lower in children/adolescents compared to adults. There was also a trend to lower exposure to the active metabolite. These observations may be a reflection of more efficient metabolic clearance in younger subjects."