Adenuric

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IB/0069	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/08/2022		SmPC and PL	To update section 5.1 of the SmPC in order to correct a discrepancy between the SmPCs of the two dosages. In addition, the list of local representatives in the PL has been updated.
IB/0067/G	This was an application for a group of variations.	29/04/2022	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).

	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation 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.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				

IB/0066	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	21/12/2021	n/a		
II/0061	C.I.4 - Update of sections 4.4, 4.8 and 5.1 of the SmPC based on the final results from study FAST (Febuxostat versus Allopurinol Streamlined Trial) listed as a category 3 study in the RMP; this is an interventional study investigating the cardiovascular safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia. The Package Leaflet is updated accordingly. The RMP version 8.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to update the warning relevant to the content of sodium according to the Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use'. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/12/2021		SmPC and PL	FAST study was a prospective, randomised, open-label, blinded-endpoint study comparing the cardiovascular (CV) safety profile of febuxostat versus allopurinol in patients with chronic hyperuricaemia (in conditions where urate deposition had already occurred) and CV risk factors (i.e. patients 60 years or older and with at least one other CV risk factor). In this study, treatment with febuxostat was not associated with an increase in CV death or all-cause death, overall or in the subgroup of patients with a baseline history of myocardial infarction, stroke or unstable angina. Nevertheless, considering that a higher number of fatal cardiovascular events were observed with febuxostat when compared to allopurinol in patients with pre-existing major cardiovascular diseases during the development of the product and in one post registrational study (CARES), treatment of this patient group should be exercised cautiously and they should be monitored regularly. For more information, please refer to the Summary of Product Characteristics.
PSUSA/1353/ 202104	Periodic Safety Update EU Single assessment - febuxostat	02/12/2021	n/a		PRAC Recommendation - maintenance
II/0062	C.I.4 - Update of sections 4.4 and 4.5 of the SmPC in order to amend an existing warning on the drug-drug interaction information with mercaptopurine/azathioprine based on final results	11/11/2021		SmPC	The results of study FAI-01 has confirmed the adequacy of the currently recommended dose adjustment that in case of concomitant administration with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to 20% or

	from study FAI-01 listed as a category 3 study in the RMP; this is a phase I, drug-drug interaction study investigating the PK profile of 6-mercaptopurine following coadministration of two doses febuxostat and azathioprine in healthy subjects. The RMP version 9.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				less of the previously prescribed dose. This recommendation was initially based on a modelling and simulation analysis from preclinical data in rats. For more information, please refer to the Summary of Product Characteristics.
IB/0065	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	13/08/2021	n/a		
IA/0063/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.c - Change in test procedure for AS or	29/06/2021	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
IA/0060/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.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites A.4 - Administrative change - Change in the name	11/01/2021	n/a		

	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				
IB/0059	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/01/2021	n/a		
PSUSA/1353/ 202004	Periodic Safety Update EU Single assessment - febuxostat	26/11/2020	n/a		PRAC Recommendation - maintenance
IB/0058	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	16/07/2020	n/a		
II/0056	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	17/04/2020	n/a		
PSUSA/1353/ 201904	Periodic Safety Update EU Single assessment - febuxostat	31/10/2019	n/a		PRAC Recommendation - maintenance
II/0051	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to include the results of the post authorisation safety study CARES (TMX-67_301) to compare the cardiovascular outcomes of febuxostat and allopurinol in subjects with gout and cardiovascular comorbidities. This was a Multicenter, Randomized, Active-Control, Phase IIIB Study conducted at the	27/06/2019	31/07/2019	SmPC and PL	CARES Study was a multicenter, randomized, double-blind, non inferiority trial comparing CV outcomes with febuxostat versus allopurinol in patients with gout and a history of major CV disease including MI, hospitalization for unstable angina, coronary or cerebral revascularization procedure, stroke, hospitalized transient ischemic attack, peripheral vascular disease, or diabetes mellitus with evidence of

	request of the FDA. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. At the CHMP request, the RMP has been updated (version 7.0) and a DHPC was agreed to inform prescribers of the findings of the CARES study. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				microvascular or macrovascular disease. To achieve sUA less than 6 mg/dL, the dose of febuxostat was titrated from 40 mg up to 80 mg (regardless of renal function) and the dose of allopurinol was titrated in 100 mg increments from 300 to 600 mg in patients with normal renal function and mild renal impairment and from 200 to 400 mg in patients with moderate renal impairment. The primary endpoint in CARES was the time to first occurrence of Major Adverse Cardiovascular Events (MACE), a composite of non-fatal MI, non-fatal stroke, CV death and unstable angina with urgent coronary revascularization. The endpoints (primary and secondary) were analysed according to the intention-to-treat (ITT) analysis including all subjects who were randomized and received at least one dose of double-blind study medication. Overall 56.6% of patients discontinued trial treatment prematurely and 45% of patients did not complete all trial visits. In total, 6,190 patients were followed for a median of 32 months and the median duration of exposure was 728 days for patients in febuxostat group (n 3098) and 719 days in allopurinol group (n 3092). The primary MACE endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8% vs. 10.4% of patients, respectively; hazard ratio [HR] 1.03; two-sided repeated 95% confidence interval [CI] 0.87-1.23). In the analysis of the individual components of MACE, the rate of CV deaths was higher with febuxostat than allopurinol (4.3% vs. 3.2% of patients; HR 1.34; 95% CI 1.03-1.73). The rates of the other MACE events were

					similar in the febuxostat and allopurinol groups, i.e. non-fatal MI (3.6% vs. 3.8% of patients; HR 0.93; 95% CI 0.72-1.21), non-fatal stroke (2.3% vs. 2.3% of patients; HR 1.01; 95% CI 0.73-1.41) and urgent revascularization due to unstable angina (1.6% vs. 1.8% of patients; HR 0.86; 95% CI 0.59-1.26). The rate of all-cause mortality was also higher with febuxostat than allopurinol (7.8% vs. 6.4% of patients; HR 1.22; 95% CI 1.01-1.47), which was mainly driven by the higher rate of CV deaths in that group. Rates of adjudicated hospitalization for heart failure, hospital admissions for arrhythmias not associated with ischemia, venous thromboembolic events and hospitalization for transient ischemic attacks were comparable for febuxostat and allopurinol." Based on these results sudden cardiac death was added as a rare adverse reactions and the following recommendation was made: Treatment with febuxostat in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina) should be avoided, unless no other therapy options are appropriate. In the post registrational CARES trial the rate of MACE events was similar in febuxostat versus allopurinol treated patients (HR 1.03; 95% CI 0.87-1.23), but a higher rate of cardiovascular deaths was observed (4.3% vs. 3.2% of patients; HR 1.34; 95% CI 1.03-1.73). The PL has been updated accordingly.
IB/0054	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	21/05/2019	n/a		

IA/0053/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	10/04/2019	n/a		
IAIN/0052	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	10/12/2018	22/05/2019	SmPC and PL	
PSUSA/1353/201804	Periodic Safety Update EU Single assessment - febuxostat	31/10/2018	n/a		PRAC Recommendation - maintenance

II/0047	Update of sections 4.4,4.5 and 5.3 of the SmPC in order to reflect the results of preclinical study MRPO-2015-PKM-005 "Pharmacokinetic of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol" and clinical study REP-POPPK-MRP-2015-PKM-005 "population pharmacokinetic analysis from study titled pharmacokinetic of azathioprine in the rat after one-week daily oral treatment at three different dosages and with the concomitant oral administration of febuxostat or allopurinol", investigating the drug-drug interaction with azathioprine when co-administered with febuxostat. The RMP version is updated to version 6.1. In addition, the MAH took the opportunity to correct the typing errors and to bring the PI in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/05/2018	22/05/2019	SmPC, Labelling and PL	Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity. No interaction studies have been performed in humans. Where the combination cannot be avoided, a reduction of the dose of mercaptopurine/azathioprine is recommended. Based on modelling and simulation analysis of data from a pre-clinical study in rats, when coadministered with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to the 20% or less of the previously prescribed dose in order to avoid possible haematological effects. The patients should be closely monitored and the dose of mercaptopurine/azathioprine should be subsequently adjusted based on the evaluation of the therapeutic response and the onset of eventual toxic effects.
PSUSA/1353/201704	Periodic Safety Update EU Single assessment - febuxostat	14/12/2017	05/03/2018	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1353/201704.
IB/0048	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	06/02/2018	n/a		

IA/0049/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	16/01/2018	n/a		
IA/0045/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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	04/07/2017	n/a		
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/03/2017	05/03/2018	PL	
PSUSA/1353/201604	Periodic Safety Update EU Single assessment - febuxostat	10/11/2016	11/01/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1353/201604.

IB/0042/G	This was an application for a group of variations. 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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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 material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/05/2016	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0041/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 or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling	21/12/2015	08/12/2016	SmPC, Annex II, Labelling and PL	

	down to 10-fold B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms 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.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.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				
PSUSA/1353/201504	Periodic Safety Update EU Single assessment - febuxostat	06/11/2015	n/a		PRAC Recommendation - maintenance
IA/0040/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	28/10/2015	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0038/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.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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	26/05/2015	n/a		
II/0037	Extension of Indication to include the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.	26/02/2015	08/04/2015	SmPC and PL	Please refer to the scientific discussion Adenuric-H-C-777-II-37.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUV/0035	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IB/0036/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.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	04/09/2014	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IA/0034/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 B.II.b.3.a - Change in the manufacturing process of	28/03/2014	n/a		

	the finished or intermediate product - Minor change in the manufacturing process				
II/0032	Update of section 4.5 of the SmPC in accordance with the results of the in vivo drug-drug interaction study with rosiglitazone regarding the effect of multiple oral doses of febuxostat 120 mg on the pharmacokinetics of a single oral dose of rosiglitazone and its metabolite N-desmethylrosiglitazone in healthy subjects. 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	20/02/2014	06/02/2015	SmPC	Febuxostat was shown to be a weak inhibitor of CYP2C8 in vitro. In a study in healthy subjects, coadministration of 120 mg febuxostat QD with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethylrosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor in vivo. Thus, co administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.
II/0031	Update of sections 4.4 and 4.5 of the SmPC in accordance with the results of a phase I drug-drug interaction study with theophylline to evaluate the effect of multiple oral doses of febuxostat on the pharmacokinetics of a single oral dose of theophylline. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template v.9.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	06/02/2015	SmPC, Annex II and PL	A drug-drug interaction in healthy subjects has been performed to evaluate the effect of multiple oral doses of febuxostat on the pharmacokinetics of a single oral dose of theophylline. The results showed that the co-administration of febuxostat 80 mg QD with theophylline 400 mg single dose has no effect on the pharmacokinetics or safety of theophylline. Neither the mean clearance nor the mean half-life values of theophylline were affected by co-administration of febuxostat. Therefore no special caution is advised when febuxostat 80 mg and theophylline are given concomitantly.

PSUV/0033	Periodic Safety Update	21/11/2013	16/01/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0033.
II/0030/G	This was an application for a group of variations. To introduce an alternative manufacturer of the active substance supported by an Active Substance Master File (ASMF) To introduce an alternative control testing site for the active substance. To introduce an alternative manufacturer of an intermediate of the active substance. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is supported by an ASMF B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	19/09/2013	n/a		
IB/0029	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	13/05/2013	n/a		

II/0026/G	This was an application for a group of variations. - To add a new manufacture of the active substance. - To add a new control testing site. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is supported by an ASMF 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	21/02/2013	21/02/2013		
R/0028	Renewal of the marketing authorisation.	18/10/2012	20/12/2012		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 Adenuric continues to be adequately and sufficiently demonstrated and therefore considers that the benefit risk profile of Adenuric continues to be favourable in the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
II/0027	Update of section 4.8 of the SmPC to add "rhabdomyolysis" and "angioedema" as preferred terms following the assessment of data coming from post-marketing experience. Additionally, sections 4.4 and 4.5 of the SmPC were updated with information	20/09/2012	24/10/2012	SmPC and PL	A search in the global safety database of febuxostat for the period 20 April 2008 until 20 April 2012 retrieved 13 cases containing the preferred term rhabdomyolysis and 8 cases containing the preferred term “Angioedema”, all of them collected in the post-marketing experience.

	regarding the interaction with mercaptopurine/azathioprine and the mechanism of action of febuxostat on xanthine oxidase, as requested by the CHMP. Section 4 of the PL was updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				Therefore "rhabdomyolysis" and "angioedema" are included in section 4.8 of the SmPC with frequency "rare" to adequately inform patients and prescribers about these ADRs. Additionally, although interaction studies of febuxostat with drugs that are metabolised by xanthine oxidase (XO) have not been performed, inhibition of XO is known to result in an increase in mercaptopurine or azathioprine levels. On the basis of the mechanism of action of febuxostat on XO inhibition, concomitant use with azathioprine/mercaptopurine is not recommended. This information has been included in sections 4.4 and 4.5 of the SmPC and in section 4 of the PL accordingly.
IB/0025/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	04/07/2012	n/a		
IAIN/0024/G	This was an application for a group of variations. C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a	14/02/2012	n/a		

	DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0023	Update, further to the assessment of PSUR 5, of section 4.4 of the SmPC in order to add a warning and update the safety information in SmPC 4.8 regarding serious hypersensitivity reactions, including Stevens-Johnson syndrome and acute anaphylactic reaction. Inclusion in the table of ADRs in section 4.8 of drug hypersensitivity, rash generalized, tubulointerstitial nephritis, hepatitis, jaundice, blurred vision and thrombocytopenia. The Package Leaflet is updated in accordance. Minor changes to implement short standard terms and minor linguistic changes (in all except English and Estonian). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest	15/12/2011	24/01/2012	SmPC, Annex II, Labelling and PL	Further to assessment of PSUR 5 the product information is updated to address severe hypersensitivity observed with febuxostat in the post-marketing experience. SmPC Section 4.4 is updated with a warning on rare reports of serious hypersensitivity reactions, including Stevens Johnson Syndrome and acute anaphylactic reaction. Section 4.8 of the SmPC was updated accordingly. On the basis of a cumulative review performed on hepatic events, section 4.8 has been updated to include "hepatitis" and "jaundice". Furthermore drug hypersensitivity, rash generalized, tubulointerstitial nephritis, blurred vision and thrombocytopenia were included in the table of ADRs in section 4.8; blurred vision was added in section 4.7 as well. A concise paragraph summarizing safety information derived from both clinical trials and spontaneous reporting, indicating the most serious and/or most frequently occurring adverse reactions, was added as introduction to

	QRD template version 8.0 and with the SmPC guideline. The variation amends the SmPC, Annex II, Labelling and Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				section 4.8; with the frequencies of ADRs in this summary reflecting information from both clinical trials and post marketing data. The information included in section 4.8 concerning the incidence of investigator-reported cardiovascular APTC events is moved to section 4.4 under the heading "Cardiovascular Disorders". Furthermore minor changes (short standard terms and linguistic changes) and changes to bring the product information in line with the current Agency/QRD template, SmPC guideline were also accepted. The variation amends the SmPC, Annex II, Labelling and Package Leaflet. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Czech Republic and Romania.
IA/0022/G	This was an application for a group of variations. B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size 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	14/06/2011	n/a		
II/0020	Update of SPC section 4.8 and PL to include post-marketing experience on skin reactions and hypersensitivity, as requested by CHMP following assessment of PSUR 4. C.I.z - Changes (Safety/Efficacy) of Human and	17/02/2011	28/03/2011	SmPC and PL	SPC section 4.8 was updated as requested by the CHMP following assessment of PSUR 4 to include post-marketing experience on skin reactions and hypersensitivity. There have been post-marketing reports of rare serious rashes, generalised skin rashes and severe hypersensitivity reactions. In most cases, these reactions occurred during

	Veterinary Medicinal Products - Other variation				the first month of therapy with febuxostat.
IA/0021/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	28/03/2011	n/a	Annex II and PL	
II/0018	Update of the SPC as requested by the CHMP further to assessment of FUM 003,004 and 020. The MAH proposed to amend SPC sections 4.4 , 4.8 and 5.1 in order to provide a cumulative safety profile taking into account the results of the CONFIRMS study (FSR (Final Study Report) F-GT06-153) and of 2 long-term studies (FOCUS/FSR TMX-01-005 and EXCEL /FSR C02-021) . The Package Leaflet (section 4) has been updated accordingly; minor change in Annex II. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/12/2010	21/01/2011	SmPC, Annex II and PL	This type II variation concerns an update of sections 4.4 , 4.8 and 5.1 of the SPC with data from the CONFIRMS study and 2 long-term studies (FOCUS and EXCEL). The results from CONFIRMS support the use of febuxostat 80 mg as the maintenance dose for the majority of subjects without a need for dose titration or dose escalation. Persistence of efficacy is supported by final data from the long-term studies (up to 5.5 years). SPC section 5.1 was updated with description and efficacy results from these studies. The list of adverse reactions and the incidence of cardiovascular and hepatic events were updated in SPC sections 4.4 and 4.8 based on the cumulative review of safety data submitted with these studies.
IB/0019/G	This was an application for a group of variations.	19/10/2010	n/a		

	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				

	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.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				
II/0017	Update of the SmPC section 4.5 upon request by the CHMP following assessment of FUM 008.1 (Interaction study warfarin). The Package Leaflet (section 2) has been updated accordingly. In addition, minor linguistic changes to several language versions of the SmPC, Labelling and Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/07/2010	31/08/2010	SmPC and PL	As requested by the CHMP in their conclusion further to assessment of a Follow-Up measure (FUM 008.1), section 4.5 of the SmPC for Adenuric was amended to include data from a finalised study evaluating the effect of febuxostat on the pharmacokinetics (PK) and pharmacodynamics (PD) of warfarin [study F–P107-162]. Section 4.5 of the SmPC has been updated to reflect relevant study results with regard to interaction with warfarin. This study confirmed that febuxostat administration had no effect on the PK and PD of warfarin, and that no dose adjustment is necessary for warfarin when administered with febuxostat.
IB/0016/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished	23/04/2010	23/04/2010	SmPC, Labelling and PL	

	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.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside 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.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes				

IB/0015	Introduction of a new Pharmacovigilance system - which has been assessed by the relevant national competent authority/EMEA for another product of the same MAH C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	08/04/2010	n/a	Annex II	Introduction of a new Pharmacovigilance system which has been assessed by the EMA for another product of the same MAH. Within the framework of the transfer of the marketing authorisation the Detailed Description of the Pharmacovigilance System (DDPS) is replaced with the DDPS of Menarini International Operations Luxembourg (MIOL) version 10.
T/0014	Transfer of Marketing Authorisation	20/11/2009	18/12/2009	SmPC, Annex II, Labelling and PL	
T/0013	Transfer of Marketing Authorisation	17/04/2009	19/05/2009	SmPC, Annex II, Labelling and PL	
IB/0012	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	12/12/2008	n/a		
IB/0011	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	12/12/2008	n/a		
IB/0010	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	12/12/2008	n/a		
IA/0005	IA_13_a_Change in test proc. for active substance - minor change	10/11/2008	n/a		
IA/0004	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	10/11/2008	n/a		

IA/0003	IA_13_a_Change in test proc. for active substance - minor change	10/11/2008	n/a		
IB/0009	IA_13_a_Change in test proc. for active substance - minor change IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	09/11/2008	n/a		
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	09/10/2008	n/a	SmPC	
T/0001	Transfer of Marketing Authorisation	08/08/2008	01/09/2008	SmPC, Labelling and PL	