PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

Part VI contents here reported equally apply to all medicinal products to which this RMP refers: i.e. bilastine 20 mg tablets; bilastine 10 mg orodispersible tablets and bilastine 2.5 mg/ml oral solution.

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns
Important identified risks (confirmed by clinical data) None
Important potential risks 1. Dizziness 2. Somnolence 3. Electrocardiogram QT prolonged 4. Tachycardia 5. Palpitations
Missing information 6. Use in Pregnancy and breastfeeding 7. Use in Children below 6 years of age 8. Use in children aged 6 to 11 years with a body weigth below 20 Kg

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

None.

VI.1.3 Summary of Post authorisation efficacy development plan

Study (type and study number)	**Objectives**	**Efficacy uncertainties addressed**	**Status (planned, started)**	**Date for submission of interim or final reports**
ICPCT-2011-UA-FF: Efficacy of Bilastine in	To assess the efficacy of bilastine 20 mg	Nasal blockage	FPFV (29/02/2012)	-

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (planned, started)	Date for submission of interim or final reports
nasal blockage on a clinical model of nasal allergen provocation in Allergic Rhinitis subjects	on nasal blockage in symptomatic allergic rhinitis patients after nasal provocation with a sensitised allergen			
Pharmacokinetic study of bilastine in Chinese population		Pharmacokinetic in non-Caucasian patients	Planned approval	January 2016
Efficacy and safety of bilastine 20 mg compared to levocetirizine 5 mg in the treatment of CIU in a Chinese population.		Efficacy in non-Caucasian patients	Planned approval	January 2016
Efficacy and safety of bilastine 20 mg compared to desloratadine 5 mg in the treatment of SAR in a Chinese.		Efficacy in non-Caucasian patients	Planned approval	January 2016
Efficacy and safety of bilastine 20 mg compared to cetirizine 10 mg in the treatment of PAR in a Chinese population.		Efficacy in non-Caucasian patients	Planned approval	January 2016
10055030: A phase II/III, comparative study for the efficacy and safety of TAC-202/bilastine versus Fexofenadine and placebo in patients with perennial allergic rhinitis		Efficacy in Japanese patients	Completed	25/08/2015
10055040: A phase III long-term study to evaluate the safety and efficacy of TAC-202/bilastine in patients with perennial allergic rhinitis and seasonal allergic rhinitis		Efficacy in Japanese patients	Completed	09/02/2016
10055050: A double-blind, placebo-control, randomized, dose-finding phase II/III study for the efficacy and safety of TAC-202/bilastine in patients with chronic idiopatic urticaria		Efficacy in Japanese patients	Completed	25/08/2015
10055060: A phase III long-term study to evaluate the safety and efficacy of TAC-202/bilastine in		Efficacy in Japanese patients	Completed	11/1272015

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (planned, started)	Date for submission of interim or final reports
patients with chronic idiopathic urticaria and pruritus accompanied by skin diseases				
10055070: Clinical pharmacology study to evaluate the effect of food on the single dose pharmacokinetics of TAC-202 Primary objective: To evaluate the pharmacokinetics of TAC-202 administered as a single dose under fasting and fed conditions Secondary objective: To evaluate the safety of TAC-202 under fasting and fed conditions		Pharmacokinetics and efficacy in Japanese patients	Completed	24/07/2015
BUCSU: Proof-of-concept (PoC), investigator-initiated trial (IIT), three phase disease activity-controlled dose escalating (updosing) study	To assess the efficacy, and safety of treatment with bilastine 20 mg, 40 mg and 80 mg in chronic spontaneous urticaria	To identify the efficacy and safety of bilastine in difficult-to-treat CSU patients	FP/FV (01/11/2014)	-

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Dizziness	In section 4.8 of bilastine SmPC it has been included dizziness as uncommon (≥0.1% and <1%) undesirable effect both for adults and adolescents as well as for children (2 – 11 years)	None
Somnolence	In Section 4.7 of bilastine SmPC it is stated that a study performed to assess the effects of bilastine on the ability to drive demonstrated that treatment with 20 mg did not affect the driving performance. However, as	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the individual response to the medicinal product may vary, patients should be advised not to drive or use machines until they have established their own response to bilastine. In section 4.8 of bilastine SmPC it has been included somnolence as common (≥1% and <10%) undesirable effect for adults and adolescents only (no case reported in children 2-11 years).	
Electrocardiogram QT prolonged	In section 4.8 of bilastine SmPC for adults and adolescents, it has been included electrocardiogram QT prolonged as uncommon (≥0.1% and <1%) undesirable effect. Electrocardiogram QT prolonged was not observed in clinical trials carried out in children (2 -11 years). In section 5.1 of bilastine SmPC, Pharmacodynamic properties of bilastine is stated that no clinical relevant prolongation of QTc interval or any other cardiovascular effects have been observed in the pre-submission clinical trials performed with bilastine, even at doses of 200 mg daily (10 times the clinical dose) for 7 days, or even co-administered with Pgp inhibitors, such as ketoconazole and erythromycin.	None
Tachycardia	SmPC Section 4.8 Undesirable effects: Frequency not known (cannot be estimated from the available data): tachycardia has been observed during the post-marketing period.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	In section 5.1 of bilastine SmPC Pharmacodynamic properties, it is stated that no clinically relevant cardiovascular effect has been observed in the clinical trials performed with Bilastine, even at doses of 200 mg daily (10 times the clinical dose) for 7 days in 9 subjects, or even when coadministered with P-gp inhibitors, such as ketoconazole (24 subjects) and erythromycin (24 subjects).	
Palpitations	SmPC Section 4.8 Undesirable effects: Frequency not known (cannot be estimated from the available data): palpitations has been observed during the post-marketing period. In section 5.1 of bilastine SmPC Pharmacodynamic properties, it is stated that no clinically relevant cardiovascular effect has been observed in the clinical trials performed with Bilastine, even at doses of 200 mg daily (10 times the clinical dose) for 7 days in 9 subjects, or even when coadministered with P-gp inhibitors, such as ketoconazole (24 subjects) and erythromycin (24 subjects).	None
Use in pregnancy and breastfeeding	In section 4.6 Fertility, pregnancy and breast-feeding women of bilastine SmPC it is stated that: There are no or limited amount of data from the use of bilastine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity,	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	parturition or postnatal development (see section 5.3 of the SmPC). As a precautionary measure, it is preferable to avoid the use of bilastine during pregnancy. Regarding breast feeding women: It is unknown whether bilastine is excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with bilastine should be made taking into account the benefit of breast-feeding to the child and the benefit of bilastine therapy to the mother. Based on the results of the preclinical study PBC-040-105 described in Part II:Module SII, the sentence of the SmPC "The excretion of bilastine in milk has not been studied in animals" has not been included in this section.	
Use in children below 6 years of age	Close monitoring of all AEs related to the use of bilastine in children below 6 years of age.	None
Use in children aged 6 to 11 years with a body weight below 20 Kg	Close monitoring of all AEs related to the use of bilastine in children aged 6 to 11 years with a body weight below 20 Kg	None

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology`

Allergic rhinoconjunctivitis

Seasonal allergic rhinitis is a common problem, affecting 15% of the European population and 20% of the American population. During childhood it is more frequent in boys. However, in adulthood is equal in both sexes. Although allergic rhinitis is more common during childhood, adolescence and early adult years, it may occur at any age.

Both genetic and environmental factors contribute to the development of allergic rhinitis. The most common allergen is the house dust mite, followed by cats and dogs.

People at most risk are:

- •Patients with a history of atopy.
- •Patients with a family history of rhinitis.
- •First-born children.
- •Immigrants.

This condition often improves over the years - particularly seasonal allergic rhinitis, which may spontaneously resolve in up to 20% of patients.

Urticaria

Approximately 20% of people experience urticaria at some time in their lives. Although urticaria can be experienced at any age, the most common age range for chronic urticaria is the fourth and fifth decades. It can occur in any race and is more frequently in women (60%). There are some factors that may lead to develop urticaria, such as stress, heat, cold, pressure, sunlight, some medical conditions, family or personal history of angioedema or drugs.

VI.2.2 Summary of treatment benefits

Allergic rhinoconjunctivitis

Eight studies have involved around 3900 patients worldwide, which received bilastine during two to four weeks. In addition, there was one study involving more than 500 patients who were treated with bilastine for up to one year.

These studies have confirmed the efficacy of bilastine 20 mg once a day for the symptomatic treatment of allergic rhinoconjunctivitis. The available data permit to conclude that bilastine is effective at 24 hours from its administration. Additionally, bilastine has been shown to improve quality of life related to allergic rhinoconjunctivitis.

Urticaria

Two studies have involved around 800 patients worldwide. One of them involved around 500 patients who received bilastine 20 mg, compared to levocetirizine and placebo for the symptomatic treatment of chronic idiopathic urticaria after 4 weeks of treatment.

Bilastine 20 mg has confirmed a statistically better efficacy profile compared to placebo in reducing the symptoms of chronic urticaria during a 28 day treatment period, with an activity very similar to levocetirizine 5 mg. Additionally, bilastine has been shown to improve quality of life related to chronic urticaria.

VI.2.3 Unknowns relating to treatment benefits

In the main and supporting pre-submission studies nearly all patients were white Caucasians over 12 years old. Several studies are currently being performed or scheduled in Asiatic population: 5 ongoing studies in Japan, and 4 planned studies in China. In addition, 1 study was completed in South Korea (including adolescents) and 2 were completed in Japan.

Regarding children from 2 to < 12 years of age, 2 studies are completed. Currently, 449 children below 18 years of age have been exposed to bilastine in clinical trials

No information is available in children less than 2 years of age

There is no evidence to suggest that results are different in non-Caucasian or in younger patients.

VI.2.4 Summary of safety concerns

Important identified risks

None.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Dizziness and drowsiness	Drowsiness is the most frequently reported adverse event (*common (≥1% and <10%))* with the use of bilastine, however not statistically different to placebo in the clinical trial setting. These side effects are considered a potential risk since they have been reported to occur with other similar products (class effect).
Electrocardiogram QT prolonged	Electrocardiogram QT prolonged has been observed in clinical studies with a low frequency. This side effect is considered a potential risk since they have been reported to occur with other similar products (class effect)
Tachycardia and/or awareness of heart rate (Palpitation)	Very few cases of tachycardia and/or awareness of heart rate (palpitation) have been observed in clinical studies (in adult patients) with a frequency not statistically different to placebo. No cases have been observed in the paediatric clinical studies. These side effects are considered a potential risk since they have been reported to occur with other similar products (class effect).

Missing information

Risk	What is known
Use during pregnancy and breastfeeding	There are no data available on the use of bilastine in pregnant women and lactating women. It is unknown whether bilastine is excreted in human milk. Two pre-clinical studies have shown that bilastine can pass the placental barrier and that it can be excreted into the milk in animal models.
Use in children below 6 years of age	There is little clinical experience in children aged 2 to 5 years. Therefore bilastine is not indicated in this age group. Safety and efficacy of bilastine is unknown in children below 2 years of age. The use of bilastine in children under 6 years of age is not recommended.
Use in children aged 6 to 11	There is little clinical experience in children aged 6 to 11 years

Risk	What is known
years with a body weight below 20 Kg	with a body weight below 20 Kg.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
BILA-3009/PED: Multicentre, international, open-label, repeated administration pharmacokinetics study in children	The objective of this study was to assess the pharmacokinetics of bilastine in children (aged 2 to <12 years) with either allergic rhinoconjunctivitis (seasonal allergic rhinitis [SAR] and/or perennial allergic rhinitis [PAR]) or chronic urticaria (CU) in order to ascertain that the systemic exposure attained with a dose of 10 mg/QD or lower is comparable to that achieved in adults and	Use in children	Completed	10 March 2015

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	adolescents administered with a dose of 20 mg/QD.			
ICPCT-2011-UA-FF: Efficacy of Bilastine in nasal blockage on a clinical model of nasal allergen provocation in Allergic Rhinitis subjects	To assess the efficacy of bilastine 20 mg on nasal blockage in symptomatic allergic rhinitis patients after nasal provocation with a sensitised allergen	Nasal blockage	FPFV (29/02/2012)	Planned 27/12/2016
Pharmacokinetic study of bilastine in Chinese population		Pharmacokinetic in non-Caucasian patients	Planned approval	January 2016
Efficacy and safety of bilastine 20 mg compared to levocetirizine 5 mg in the treatment of CIU in a Chinese population.		Efficacy in non-Caucasian patients	Planned approval	January 2016
Efficacy and safety of bilastine 20 mg compared to desloratadine 5 mg in the treatment of SAR in a Chinese.		Efficacy in non-Caucasian patients	Planned approval	January 2016
Efficacy and safety of bilastine 20 mg compared to cetirizine 10 mg in the treatment of PAR in a Chinese population.		Efficacy in non-Caucasian patients	Planned approval	January 2016
10055030: A phase II/III, comparative study for the efficacy and safety of TAC-202/bilastine versus Fexofenadine and placebo in patients with perennial allergic rhinitis		Efficacy in Japanese patients	Completed	25/08/2015
10055040: A phase III long-term study to evaluate the safety and efficacy of TAC-202/bilastine in patients with perennial allergic rhinitis and seasonal allergic rhinitis		Efficacy in Japanese patients	Completed	09/02/2016
10055050: A double-blind, placebo-		Efficacy in	Completed	25/08/2015

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
control, randomized, dose-finding phase II/III study for the efficacy and safety of TAC-202/bilastine in patients with chronic idiopathic urticaria		Japanese patients		
10055060: A phase III long-term study to evaluate the safety and efficacy of TAC-202/bilastine in patients with chronic idiopathic urticaria and pruritus accompanied by skin diseases		Efficacy in Japanese patients	Completed	11/12/2015
10055070: Clinical pharmacology study to evaluate the effect of food on the single dose pharmacokinetics of TAC-202 Primary objective: To evaluate the pharmacokinetics of TAC-202 administered as a single dose under fasting and fed conditions Secondary objective: To evaluate the safety of TAC-202 under fasting and fed conditions		Food interaction in Japanese population	Completed	24/07/2015
BUCSU: Proof-of-concept (PoC), investigator-initiated trial (IIT), three phase disease activity-controlled dose escalating (updosing) study	To assess the efficacy, and safety of treatment with bilastine 20 mg, 40 mg and 80 mg in chronic spontaneous urticaria	To identify the efficacy and safety of bilastine in difficult-to-treat CSU patients	FV/FP (01/11/2014)	Planned 01/05/2016

Studies which are a condition of the marketing authorisation

The studies protocol Nº 10055030, protocol Nº 10055040, protocol Nº 10055050, protocol Nº 10055060 and protocol Nº 10055070 are condition for the marketing authorisation in Japan. Likewise, studies in Chinese population are also a condition for the marketing authorisation in China (no study titles are available).

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 5. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
01.00	February 2009	Important Identified Risks: None Important Potential Risks: • Dizziness • Headache • Somnolence Electrocardiogram QT prolonged Missing Information: • Use in Pregnancy • Use in Children • Use in the elderly	
02.00	July 2010	No changes in relation to safety concerns	The RMP has also been updated with new information from studies. Reassessment of risks based on the new data available.
03.00	May 2012	No changes in relation to safety concerns	The RMP has also been updated with new information from studies. Reassessment of risks based on the new data available.
04.00	May 2013	No changes in relation to safety concerns	The RMP has been adapted to the new template according to guidance EMA/838713/2011 The RMP has also been updated with new information from studies. Reassessment of risks based on the new data available.
05.00	May 2014	No changes in relation to safety concerns	The RMP has also been updated with new information from studies and post-marketing

Version	Date	Safety Concerns	Comment
			information. Reassessment of risks based on the new data available.
06.00	November 2014	Use in the elderly population should no longer be considered missing information.	The RMP has also been updated with new information from studies and post-marketing information. Reassessment of risks based on the new data available.
06.01	April 2015	Headache is no longer considered an important safety concern.	Re-evaluation of the safety concerns after the assessment of the German Agency (BfArM).
06.02	December 2015	Tachycardia and palpitations are considered important potential risks.	Re-evaluation of the safety concerns after the assessment of the German Agency (BfArM)
06.03	March 2016	No changes in relation to safety concerns	The RMP has been updated according to the changes proposed by the BfArM during the evaluation of the version 06.02. "Palpitation and tachicardia" have been added among ""Newly identified safety concerns" (Module SVII); limits of the 95% confidence interval of the reported safety concerns have been specified; the denominator that has been used to calculate the reporting rate of the post marketing adverse events has been specified; the

Version	Date	Safety Concerns	Comment
			statistical method used to compare the data collected in clinical experience has been detailed.
07.00	September 2015	There is no missing information in children between 2 and 12 years of age. Only safety and efficacy information in children less than 2 years of age is missing.	RMP submitted for the authorization of bilastine in children older than 2 years of age.
07.01	August 2016	Tachycardia and palpitations has been added as important potential risks.	The RMP has been updated according to to the changes proposed by the BfArM during the evaluation of the version 07.00 as part of the paediatric dossier
07.02	March 2017	No changes in relation to safety concerns	The RMP has been updated according to to the changes (related to administrative information only) proposed by the BfArM within the RMS Day 120 Draft Assessment Report
07.03	May 2017	The missing information “Use in Children below 2 years of age has been updated to “Use in Children below 4 years of age. The missing information “Limited experience in children aged 4-5 years” has been added	The RMP has been updated according to to the response document submitted in response to the RMS Day 180 Draft Assessment Report (outcome of the clinical evaluation (MO))
7.04	May 2017	The missing information “Use in Children below 4 years of age” has been changed in “Use in Children below 6 years of age”; the missing information ““Limited experience in children aged 4-5 years” has been removed. The missing information “Use in	The RMP has been updated according to the Response to Day180 Draft Assessment Report and Day 195 comments. As the Bilastine indication

Version	Date	Safety Concerns	Comment
		children aged 6 to 11 years with a body weight below 20 Kg" has been added	will include children older than 6 years, with a body weight limit, the RMP text has been revised accordingly