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.

Urticaria

One study 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.

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: 4 ongoing studies and 1 planned 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, 1 study is currently pending final report and 1 is completed.

There is no evidence to suggest that results would be any 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 not statistically significant from placebo. This side effect is considered a potential risk since they have been reported to occur with other similar products (class effect).

Risk	What is known (Including reason why it is considered a potential risk)
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 with a frequency not statistically different to placebo. 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.
Use in children (paediatric exposure)	Safety and efficacy of bilastine is currently being studied in children under 12 years of age. The use of bilastine in children under this age is not recommended until further information is available.

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	Use in children	Ongoing (pending final report)	First interim report: 20 September 2011 Second interim report: 5 June 2012

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	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 adolescents administered with a dose of 20 mg/QD.			Planned final report: March 2015
BILA-3312/PED (Paediatric Safety/Tol AR/CU Peds): A multicenter, double-blind, randomized, placebo-controlled, parallel group study. Category 3	To evaluate the safety and tolerability of 10 mg once daily bilastine in children from 2 to 11 years of age with either allergic rhinoconjunctivitis or chronic urticaria	Use in children	Completed	October 2014
FAE-BIL-2012-01: Post-Authorization Safety Study to assess the safety profile of 20 mg bilastine in elderly patients	Observational study to assess safety and tolerability in elderly patients	Use in elderly patients.	Completed	November 2014

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
(>64 yoa) Category 3				
YCD159: Randomized, double-blind, placebo/active-controlled, multi-center clinical trial to investigate the safety/ tolerability and efficacy of bilastine 20 mg after 14-day oral administration in patients with seasonal allergic rhinitis.	To evaluate the efficacy and safety of bilastine 20 mg compared with placebo in Asian patients (including adolescents) with seasonal allergic rhinitis.	Efficacy in non-Caucasian patients, including adolescents	Completed	28/05/2014
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 (23/01/2012)	Pending
Pharmacokinetic study of bilastine in Chinese population		Pharmacokinetic in non-Caucasian patients	Planned	-
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	Planned end date: November 2015
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	Planned end date: November 2015

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
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	Planned end date: November 2015
10055010: A two part, phase I, randomized, single-blind, placebo-controlled, dose-escalation study		Safety, pharmacokinetics, and pharmacodynamics in Japanese patients	Completed	27/12/2013
10055020: A randomized, double-blind, 4-way crossover, placebo-controlled, phase II study to evaluate the efficacy and safety of TAC-202/bilastine in Japanese cedar pollinosis exposure to antigen in an environmental exposure chamber (EEC).		Efficacy in Japanese patients	Completed	26/08/2014
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	Started	-
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	Started	-
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 idiopathic urticaria		Efficacy in Japanese patients	Started	-
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	Started	-

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
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	Protocol submission planned to start in December 2014	**-**
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	Screening	-
BCRU/11/Bil-AR/001: An open, randomised, phase III, comparative study	To evaluate the efficacy and safety of bilastine 20 mg compared to desloratadine 5 mg in the treatment of AR	Efficacy vs. desloratadine	Completed	28/06/2013

Studies which are a condition of the marketing authorisation

The studies YCD159, protocol Nº 10055010, protocol Nº 10055020, protocol Nº 10055030, protocol Nº 10055040, protocol Nº 10055050, protocol Nº 10055060 and BRCU/11/Bil-AR/001 are condition for the marketing authorisation in South Korea, Japan, Russia and Ukraine. 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 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

Version	Date	Safety Concerns	Comment
06.01	April 2015	Headache is no longer considered a 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 statistical method used to compare the data collected in clinical experience has been detailed.