Annex II

Scientific conclusions

Scientific conclusions

This procedure concerns an application submitted according to Article 10b of Directive 2001/83/EC (fixed combination).

Rambis and associated names is a hard capsule containing ramipril and bisoprolol fumarate in the strengths of 2.5 mg + 1.25 mg; 2.5 mg + 2.5 mg; 5 mg + 2.5 mg; 5 mg + 5 mg; 10 mg + 5 mg and 10 mg + 10 mg, respectively.

Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation. Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion.

Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

At the start of the CHMP referral, Rambis and associated names was proposed to be indicated for:

- 2.5 mg + 1.25 mg:

Substitution therapy in chronic coronary syndrome (in patients with a history of myocardial infarction and/or revascularisation) and/or chronic heart failure with reduced systolic left ventricular function in adult patients adequately controlled with ramipril and bisoprolol given concurrently at the same dose level.

- 2.5 mg + 2.5 mg; 5 mg + 2.5 mg; 5 mg + 5 mg; 10 mg + 5 mg; 10 mg + 10 mg:

Substitution therapy for treatment of hypertension, hypertension with coexisting chronic coronary syndrome (in patients with a history of myocardial infarction and/or revascularisation) and/or chronic heart failure with reduced systolic left ventricular function in adult patients adequately controlled with ramipril and bisoprolol given concurrently at the same dose level.

However, as discussed further down, these indications are not fully in accordance with the authorised mono-component products Tritace and Concor, as 'chronic coronary syndrome' is not reflected in the indication wording for mono component products.

The Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017, hereinafter 'FDC Guideline') provides that for a substitution scenario (where the fixed combination medicinal product is intended to be used in patients who are already stabilised on optimal doses of the combination of the same, but separately administered, active substances, taken at the same dose interval and time), the following requirements apply:

1. Justification of the pharmacological and medical rationale for the combination (including documentation of clinical use of relevant medicinal products in combination, either through clinical studies or published literature, or a combination of both).

2. Establishment of the evidence base for the:

    a. relevant contribution of all active substances to the desired therapeutic effect (efficacy and/or safety);

b. positive benefit-risk across all dose and strength combinations available in the targeted indication.

Therapeutic guidelines should be considered in identifying the population in need of the fixed combination medicinal product. The evidence base available and the indications of the monotherapies will determine the therapeutic indication targeted.

3. Demonstration that the evidence presented is relevant to the fixed combination medicinal product for which the application is made (including demonstration of similar pharmacokinetic (PK) behaviour, usually through demonstrating bioequivalence, in order to bridge the data obtained with combined use of individual active substance products to the use of the fixed combination medicinal product).

The applicant presented the following data, based on which criteria 1 and 3 of the FDC Guideline above were considered met:

- Demonstration of absence of drug-drug interactions (DDI).

- Recommendations of combined use from the current therapeutic guidelines.

- Co-prescription data documenting concomitant use from Poland, Italy and Germany.

- Demonstration of similar PK (bioequivalence (BE) study) of the fixed combination medicinal product versus its individual active substances taken simultaneously.

The applicant also presented the following literature and clinical data in support of criterion 2, which was considered sufficient by the RMS (PL) but not by the CMS (CZ):

- Published studies demonstrating the efficacy/safety of both mono-components in monotherapy or on efficacy/safety of other combinations of the active substances from the same classes i.e., beta-blockers and angiotensin-converting enzyme (ACE) inhibitors.

- Observational non-interventional study (NT-RAM-BIS-01-19/02) performed by the applicant.

- Meta-analysis (DUS RAMBIS V1 26/04/2021) of six observational non-interventional studies performed by the applicant.

Overall summary of the scientific evaluation by the CHMP

This referral procedure under Article 29(4) concerns a fixed dose combination (FDC) application for Rambis (ramipril/bisoprolol 2.5mg/1.25mg; 2.5mg/2.5mg; 5mg/2.5mg; 5 mg/5mg; 10mg/5mg; 10mg/10mg) hard capsule and associated names, applied according to Article 10b of Directive 2001/83/EC under the decentralised procedure.

Ramipril/bisoprolol 2.5mg/1.25mg; 2.5mg/2.5mg; 5mg/2.5mg; 5 mg/5mg; 10mg/5mg; 10mg/10mg has been approved based on the same dossier in parallel applications.

According to the FDC guideline, documentation of clinical use of relevant medicinal products in combination should be provided either through clinical studies or published literature, or a combination of both. These data should support the rationale for combined use of the active substances however evidence of combined use only would not suffice to establish the positive benefit/risk of the combination.

The proposed FDC is intended for substitution therapy. In this scenario, the fixed combination medicinal product is intended to be used in patients who are already stabilised on optimal doses of the combination of the same, but separately administered, active substances, taken at the same dose interval and time. Patients will discontinue taking the single active substance products and initiate therapy with the fixed combination medicinal product. For that, the issues raised in the referral procedure, which pertain to 1) further substantiate that each substance makes a relevant contribution

to the desired therapeutic effect (efficacy/safety) and 2) that the benefit-risk balance for the combination is positive for the combination in the targeted indication in line with the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017), should be justified.

Overall, concomitant use of ramipril and bisoprolol in the proposed indications is considered well justified from the pharmacological and medical perspective. The selection of strengths of the proposed FDC product is in line with the approved strengths of both monocomponents.

Moreover, evidence of safety (in addition to justification of the pharmacological and medical rationale for the combination) is further supported by the available co-prescription data obtained from Italy, Poland and Germany, and in line with the European Society of Cardiology (ESC) Guidelines, where combination of angiotensin-converting enzyme (ACE)-inhibitors and beta-adrenergic receptor antagonists is recommended in the treatment of hypertension and hypertension with comorbidities, including heart failure and coronary artery disease.

BE between the proposed fixed combination product and authorised mono-components taken simultaneously was considered demonstrated and the DDI study conducted by the applicant concluded that no PK interactions should be expected between ramipril and bisoprolol. These conclusions are considered to support the clinical safety profile on the FDC.

Additionally, the CHMP noted the preliminary results of a Real-World Evidence (RWE) study which was conducted to evaluate efficacy of ramipril/bisoprolol combined therapy in comparison to ramipril or bisoprolol monotherapy in patients with hypertension and other cardiovascular diseases. However, as only a brief report from the study was submitted and conclusion could not be drawn, therefore the preliminary results are seen as supportive only.

Own observational non-interventional study (NT-RAM-BIS-01-19/0) presented various limitations: no separate treatment arms for each strength, patients in bisoprolol arm were co-administered with hydrochlorothiazide or amlodipine, thus the additional effect cannot be excluded and bias can be included into study outcomes. The number of subjects in bisoprolol group was low. Moreover, NT-RAM-BIS study was a non-inferiority study.

Own meta-analysis (DUS RAMBIS V1 26/04/2021) of six observational non-interventional studies also presented various limitations: Studies BENT/2010, BKAR/2013, KARPOZ/2014 didn't recorded doses of ramipril and bisoprolol. In studies with recorded doses of antihypertensive drugs (BONT/2013, BNT/2016, BNT/2019), there were not separate treatment arms for each strength. Numerous patients were using other antihypertensive drugs. However, information regarding the type of products concomitantly used is not available, thus the additional effect cannot be excluded and bias can be included into study outcomes. The efficacy (defined as the values of BP lower than 140 mmHg/90 mmHg) of ramipril/bisoprolol was 29.5% (95%CI: 27.8 – 31.2) in the studies BENT/2010, BKAR/2013, KARPOZ/2014. Controlled hypertension was not achieved in these studies, as average SBP in patients treated with ramipril/bisoprolol was 145.4±18.2 mmHg. The efficacy of ramipril/bisoprolol was 57.5% (95%CI: 55.1 – 59.8) in the studies BONT/2013, BNT/2016, BNT/2019. The overall efficacy of the ramipril/bisoprolol for observational studies included in the meta-analysis was 39.7% (95%CI: 38.3 – 41.2). A comparison with the efficacy of mono-components ramipril and bisoprolol administered alone is missing in this study.

Furthermore, the applicant provided information from published studies that demonstrated the efficacy/safety of both mono-components in monotherapy or efficacy/safety of other combinations of the active substances from the same classes i.e. β-blockers and ACE-inhibitors.

In conclusion, the CHMP considered the submitted meta-analysis, the non-interventional study and preliminary results of a real word evidence study, in the context of the published studies

demonstrating the efficacy/safety of both monotherapies and the efficacy/safety of other combinations of the active substances from the same class. It was acknowledged that the studies performed suffered from limitations (e.g., doses not specified, or not separated by treatment arms, possible confounding effect by other treatments, low sample size, results insufficiently detailed), and that results were inconsistent. However, the additive effect of ACE-inhibitors and beta-blockers is well established, and demonstrated in the literature, as well as reflected in clinical practice as exemplified in the therapeutic guidelines. Therefore, although literature data regarding combined use of ramipril/bisoprolol were not provided, taken in combination with the data on the FDC from the studies performed, including a BE study and a drug-drug interaction study, the CHMP considers that the data allows to sufficiently establish the relevant contribution of each active substance to the desired therapeutic effect (efficacy/safety) and the efficacy and safety of the combination in the targeted substitution indication, across all dose and strengths combinations of the application.

Grounds for the CHMP opinion

Whereas,

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC.
- The Committee considered the totality of the data submitted and presented in an oral explanation by the applicant in relation to the objections raised as potential serious risk to public health.
- The Committee was of the view that an evidence base demonstrating the relevant contribution of all active substances to the desired therapeutic effect and the efficacy and safety of the combination in the targeted indications, was sufficiently established.

The Committee, as a consequence, considers that the benefit-risk balance of Rambis and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion subject to the agreed amendments to the product information as set out in Annex III of the CHMP opinion.