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15 December 2022
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Rambis and associated names

INN: ramipril/bisoprolol

Procedure number: EMEA/H/A-29(4)/1519

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

An application was submitted under the decentralised procedure for Rambis (ramipril/bisoprolol fumarate) and associated names, (2.5mg/1.25mg; 2.5mg/2.5mg; 5mg/2.5mg; 5 mg/5mg; 10mg/5mg; 10mg/10mg, capsule, hard) on 15 December 2020.

The legal basis under which the application was submitted is: Article 10b fixed combination application of Directive 2001/83/EC.

The application was submitted to the reference Member State (RMS): Poland (PL) and the concerned Member States (CMSs): Czechia (CZ) and Slovakia (SK).

The decentralised procedure PL/H/0758/001-006/DC started on 22 April 2021.

On day 210, major issues on efficacy raised by CZ, remained unsolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by PL on 18 March 2022. The CMDh 60-day procedure was initiated on 27 March 2022.

Day 60 of the CMDh procedure was on 25 May 2022 and as no agreement could be reached, the procedure was referred to the CHMP.

On 22 June 2022, PL triggered a referral procedure under Article 29(4) of Directive 2001/83/EC.

CZ raised objections on the establishment of the evidence for the relevant contribution of both substances ramipril and bisoprolol to the desired therapeutic effect (efficacy/safety) of the proposed fixed dose combination (FDC) product according to Article 10b of Directive 2001/83/EC and on the benefit-risk balance for the combination in the targeted indications that were considered to constitute a potential serious risk to public health[1].

2. Scientific discussion

2.1. Introduction

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.

[1] The definition of the 'potential serious risk to public health' can be found in Guideline on the definition of a potential serious risk to public health

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.

2.2. Assessment of the issues raised as a potential serious risk to public health

The applicant was requested in the context of the present referral procedure to justify/further substantiate the relevant contribution of each active substance to the desired therapeutic effect (efficacy/safety) and the positive benefit-risk balance in the proposed indications across all dose and strengths combinations of the application.

The applicant provided the data package mentioned above as well as: a justified alternative proposal of indications, further justification for the lower strength, recommendation letter from key opinion leaders and preliminary results of a Real-World Evidence (RWE) study.

Indication structure of the Fixed Dose Combination

For substitution indication, the final indication of the product is based on the indication in the SmPC of particular mono products in accordance to FDC Guideline EMA/CHMP/158268/2017 and should not include any additional indication which is not authorised for the mono products.

Ramipril as a mono-component is approved for *the treatment of hypertension and cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with: manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or diabetes with at least one cardiovascular risk factor, treatment of symptomatic heart failure, secondary prevention after acute myocardial infarction and treatment of renal disease*.

Bisoprolol, as a mono-component is approved for *the treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides*. Bisoprolol (strengths: 2.5 mg, 5 mg and 10 mg) is indicated for the *treatment of hypertension and ischemic heart disease (angina pectoris)*.

The product information of the mono-component products did not clearly reflect 'chronic coronary syndrome' in the indication wording, as opposed to the indication of the combination proposed at the start of the CHMP referral. The proposed indication was amended accordingly using consistent terminology to avoid any confusion as follows for the strengths 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 and/or hypertension with coexisting chronic coronary syndrome:

- in patient with manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or

- diabetes with at least one cardiovascular risk factor, and/or chronic heart failure with reduced systolic left ventricular function (secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction).

In adult patients adequately controlled with ramipril and bisoprolol given concurrently at the same dose level.

The CHMP considered that the latest proposed indication is in line with the currently approved indications for ramipril and bisoprolol.

Strengths justification

Available strengths of respective reference mono products, Tritace (ramipril) and Concor (bisoprolol fumarate) were considered by the applicant when choosing the most appropriate strengths combinations for the developing FDC product.

Tritace is available in strengths 1.25, 2.5, 5 and 10 mg and Concor is available in strengths 1.25, 2.5, 3.75, 5, 7.5 and 10 mg. The free combination therapy is considered as already established.

The FDC proposed strengths (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) reflect respective recommendations in hypertension, coronary artery disease, and heart failure guidelines. The developed FDC product is indicated for substitution therapy, and therefore intends to cover all clinically relevant combinations of strengths of the single substances used in clinical practice, and no additional indication or strength, which is not authorised for the respective mono-component products. This approach is in line with the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017), thus acceptable.

However, the lowest 2.5+1.25 mg dose strengths do not seem to be used in clinical practice and was argued that a gradual up-titration to maximal tolerated dose or achievement of the expected clinical effect is envisaged. Ramipril in the strength 2.5 mg was shown to have a significant impact on haemodynamic parameters. Bisoprolol in the strength 1.25 mg is only for initial therapy, however, based on the applicant's argumentation the strength 1.25 mg can be combined with other strengths to obtain another desired dose (e.g. FDC 2.5/1.25 mg can be combined with 2.5/2.5 mg to obtain a final dose of 5/3.75 mg), and therefore cover all clinically relevant combinations used in a clinical practice without developing all possible FDC combinations with respect to the available strengths of mono-products.

It is acknowledged by the CHMP that availability of different dose strengths combinations will allow individual dose adjustment, including situations when intermediate dose is required. This can be achieved by administration of combination of different strengths of the proposed FDC product. Simplification of the treatment regimen improves compliance and adherence to the treatment. Based on the FDC Guideline, this can serve as a part of the rationale for fixed combination medicinal products. Therefore, the CHMP considers the justification of strength 2.5/1.5 mg acceptable.

Clinical efficacy/safety data

DUS-RAMBIS study (V1 26/04/2021)

The applicant performed a meta-analysis of six observational non-interventional studies (BENT/2010, BKAR/2013, KARPOZ/2014, BONT/2013, BNT/2016, BNT/2019) on the use of the polytherapy consisting of ramipril and bisoprolol in 76841 patients with arterial hypertension and/or ischemic heart disease and/or stable chronic heart failure in the Polish population. The analysis included data from 5695 elderly subjects (PolSenior 1 Study). The efficacy data were calculated separately for the observational studies with and without recorded drug doses and for the epidemiological study

(PolSenior1) for subjects treated with ramipril and bisoprolol (N = 1,664; N = 2,872, and N = 170 respectively).

The assessment of effectiveness of blood pressure (BP) lowering therapy was based on average BP values from two measurements during visits. The values lower than 140 mmHg (systolic BP) and 90 mmHg (diastolic BP) in patients taking at least one hypotensive drug were scored as effective BP control.

The efficacy of antihypertensive therapy in subgroups of hypertensive subjects treated with ramipril and bisoprolol was 29.5% (95%CI: 27.8 – 31.2) in observational studies BENT/2010, BKAR/2013, KARPOZ/2014 without any recorded doses of antihypertensive drugs performed in years 2010 – 2014, and 57.5% (95%CI: 55.1 – 59.8) in studies BONT/2013, BNT/2016, BNT/2019 with recorded doses of antihypertensive drugs performed in years 2013 – 2019. Overall efficacy of the antihypertensive therapy with ramipril and bisoprolol from observational studies included in the meta-analysis was 39.7% (95%CI: 38.3 – 41.2). The efficacy of antihypertensive therapy in subgroups of hypertensive subjects treated with ramipril and bisoprolol was 42.4% (95%CI: 34.9 – 49.8) in older adults, participants of PolSenior study (2007 – 2011). Also, overall, sufficient control of hypertension was reported in 36.3%, 33.8% and 42.4% of patients treated with bisoprolol, ramipril and ramipril and bisoprolol in combination, respectively. However, it was not clear from the presented final report if differences between groups (patients treated with ramipril/bisoprolol vs patients treated only with ramipril vs patients treated only with bisoprolol) were statistically significant.

Additionally in the observational study meta-analysis, safety data were calculated in the whole group of patients participating in observational studies treated with ramipril or bisoprolol (31,412) and ramipril and bisoprolol (4,536). There were 250 adverse reactions (ADRs) reported in observational studies in patients treated with ramipril and/or bisoprolol. Thirty-nine ADRs (0.86%) in the subgroups treated with ramipril or bisoprolol and 211 ADRs (0.67%) in the subgroups treated with ramipril and bisoprolol concomitantly. No serious ADRs were reported.

Those results should be interpreted with caution as several limitations of source studies were noted: Studies BENT/2010, BKAR/2013, KARPOZ/2014 were without recorded doses of ramipril and bisoprolol. In studies with recorded doses of antihypertensive drugs (BONT/2013, BNT/2016, BNT/2019), there were no separate treatment arms for each strength. Numerous patients were using other antihypertensive drugs, however, information about concomitant use of other antihypertensive drugs was not available, thus the additional effect could not be excluded and bias could be included into study outcomes. Controlled hypertension was not achieved in studies BENT/2010, BKAR/2013, KARPOZ/2014, as average systolic blood pressure (SBP) in patients treated with ramipril/bisoprolol was 145.4±18.2 mmHg. The comparison with efficacy of mono-components ramipril and bisoprolol administered alone is missing in the study.

NT-RAM-BIS study (01-19/02)

The applicant additionally performed a non-interventional, observational, open-label, with no control arm study with a partially retrospective medical history assessment of 1 to 6 months before enrolment and prospective data assessment for up to 3 months of follow-up of ramipril monotherapy or bisoprolol in different combination therapies versus combined administration of ramipril with bisoprolol as a mono-components in patients with hypertension, stable coronary artery disease and stable chronic heart failure.

The primary objectives of the study were to assess efficacy of ramipril monotherapy compared to ramipril and bisoprolol combination therapy and to evaluate efficacy of bisoprolol in combination

therapy (with hydrochlorothiazide, amlodipine, etc.) compared to combination therapy of bisoprolol with ramipril.

In total, 267 patients were screened, 263 were enrolled (8 in bisoprolol, 125 in ramipril alone and 130 in RAM-BIS group) and 229 completed the observation period.

Primary endpoints were defined as follows: (1) efficacy of ramipril monotherapy compared to ramipril and bisoprolol combination therapy in patients with hypertension and / or stable coronary artery disease and / or stable chronic heart failure in daily practice and (2) efficacy of bisoprolol in combination therapy (with hydrochlorothiazide, amlodipine, etc.) compared to combination therapy of bisoprolol with ramipril in patients with hypertension, stable coronary artery disease or stable chronic heart failure in daily practice, where efficacy was defined as time to achieve and maintain target SBP and difference in SBP between ramipril monotherapy, bisoprolol in combination therapy (with hydrochlorothiazide, amlodipine, etc.) and combination of ramipril and bisoprolol.

Secondary endpoints included efficacy, defined as the time to achieve and maintain target diastolic blood pressure (DBP) for (1) ramipril monotherapy compared with ramipril / bisoprolol combination therapy in patients with hypertension, stable coronary artery disease and / or stable chronic heart failure in daily practice and (2) bisoprolol in combination therapy (with hydrochlorothiazide, amlodipine, etc.) compared to combination of bisoprolol and ramipril in patients with hypertension, stable coronary artery disease and / or stable chronic heart failure as well as safety evaluation (adverse events (AEs), serious (AEs)) in terms of frequency, severity and causal relationship with drug therapy.

It was shown that no significant difference in proportions of patients achieving sustained control of SBP based on baseline ambulatory measurements and average of the last three measurements in patients' diaries was noted between ramipril/bisoprolol and ramipril or ramipril/bisoprolol and bisoprolol groups. The SBP decrease was noted in all treatment arms, numerically lowest in the ramipril/bisoprolol arm.

Overall, 9.5% of patients experienced treatment emergent adverse events (TEAEs) (25 subjects). Three cases were considered serious (one in bisoprolol and two in ramipril group, all three not related to study drugs). No significant difference in the number of subjects experiencing AEs was observed between groups. However, 72 AEs in 13 subjects were reported in RAM-BIS group compared with ramipril group (13 AEs in 8 subjects) or bisoprolol (one AE). There were six TEAEs with a definite relationship to the study medication. Two of them were reported in ramipril arm (two subjects with cough) and four in RAM-BIS arm: asthenia, cough, headache and vertigo (one subject in each case). Two AEs in two subjects led to permanent treatment discontinuation.

It is noticed that fundamental differences in median time from diagnosis of hypertension was observed between the study groups (1,127 days in ramipril-bisoprolol group, 16.5 days in bisoprolol group and 7 days in ramipril group).

Comparable lowering of SBP and DBP was observed with bisoprolol or ramipril used as monotherapy compared with the concomitant administration of bisoprolol and ramipril. Additionally, there were no serious ADRs reported. The incidence of ADRs was generally very low and can be considered comparable between groups treated with ramipril or bisoprolol and combination of both monocomponents. However, those results should be interpreted with caution as several limitations were noted: there were no separate treatment arms for each strength, patients in bisoprolol arm were co-administrated 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, the study was non-inferiority study.

Additional studies submitted in support of the efficacy/safety

Demonstration of absence of drug-drug interactions (DDI study):

The DDI study conducted showed that no PK interactions is expected between ramipril and bisoprolol, as no effect of bisoprolol on the extent and rate of ramipril absorption and no effect of ramipril on the extent and rate of bisoprolol absorption was observed.

BE study (RAM-BIS-BIO-01-19):

The applicant conducted one pivotal BE study comparing PK data between the FDC and the authorised mono-components taken simultaneously. Based on the results of the BE study, equivalence between the FDC under consideration and the authorised mono-component products was considered demonstrated.

In order to demostrate the safety of the FDC, the applicant further explained that the comparison of the safety and tolerability of the investigational medicinal products were also the objective of this BE study. AEs were monitored and reported, clinical signs and symptoms assessed, laboratory measurements prior to and following administration of a single dose of test and reference products. The BE study demonstrated that ramipril/bisoprolol 10 mg/10 mg, hard capsules was tolerated in the same way as the authorised mono-component products (Concor 10 mg film-coated tablets and Tritace 10 mg tablets).

Real-World Evidence (RWE) study

Moreover, the applicant submitted new preliminary results of a RWE study aimed to evaluate efficacy of ramipril/bisoprolol combined therapy in comparison to ramipril or bisoprolol monotherapy in patients with hypertension and other cardiovascular diseases. Medical records from two databases were analysed: France LPD (17.7 M total patient count) and Germany DA (39.6 M total patient count) with study period starting 01 January 2016 with a duration of 12 months. Adult patients diagnosed with hypertension grade 1 or 2, chronic heart syndrome or chronic heart failure with reduced systolic left ventricular function and treated with ramipril, bisoprolol or combination of ramipril and bisoprolol were included in the analysis. Moreover, patients had to have at least two valid measurements of SBP and DBP within a year to be included in the analysis. The primary outcome of the study was estimated change from baseline in the office BP measurement through SBP with ramipril/bisoprolol dual agent combined therapy in comparison to patients on monotherapy either with ramipril or bisoprolol.

In total, 26,194, 23,554 and 6,700 patients treated with ramipril, bisoprolol and combination of ramipril and bisoprolol were included in the analysis. At month 12, only a very limited numerical difference in SBP and DBP values was observed in patients treated with ramipril/bisoprolol combination compared to patients treated with ramipril or bisoprolol monotherapy. In France data set the ramipril/bisoprolol achieved numerically lowest BP, while in German dataset the lowest DBP was noted in bisoprolol treated group. However, the applicant only provided a very short description of the analysis and data are very difficult to interpret. Therefore, no conclusion could be drawn from this data and the CHMP considered the preliminary results of the RWE study as supportive only.

Literature data on efficacy/safety

The applicant presented an extensive summary of the available literature data supporting use of ramipril and bisoprolol as monocomponents in the treatment of hypertension:

- Published studies demonstrating the efficacy/safety of both mono-components in monotherapy (de Leeuw, 1987, Aire, 1993, Cibis II 1999, Baxter 2002, Yusuf 2000, Anderson 2006, de Grote 2007).
- Published studies demonstrating the efficacy/safety of other combinations of the active substances from the same classes i.e. beta-blockers and ACE inhibitors (Spargias 1999; Remme 2004 Willenheimer 2005; CIBIS II; Ivanova 2004; Califf 2009 and Konishi 2011) and demonstrating

interchangeability of products within ACE-Inhibitor Class (Garg 1995; Dagenais 2006 and Heran 2008).

Published studies mentioned above showed:

- In patients with hypertension, with consistent results showing a clinically significant additional decrease in BP when adding ACE inhibitor to beta-blocker.

- In patients with stable coronary artery disease, with a demonstration of their benefit on the reduction of morbidity and/or mortality.

- In patients with chronic heart failure, with a demonstration of their benefit on the reduction of total mortality.

Moreover, in order to further justify that a population exist for which the proposed FDC would be useful, the applicant also referred to the current European Society of Cardiology (ESC) and European Society of Hypertension (ESH) therapeutic Guidelines. According to the Guidelines, combination of 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. The applicant also presented treatment algorithms placed in ESC guidelines and described as first-class recommendation as well as further detailed analysis and results of the studies used in the ESC guideline recommendations to justify the extrapolation of the results to ramipril/bisoprolol combination at the intended indication.

Other data

The CHMP noted the recommendation letters from the key opinion leaders from Spain and Poland, supporting concomitant use of bisoprolol and ramipril in the proposed indications. Concomitant use of these mono products is common in clinical practice and this is acknowledged by the CHMP as well as potential advantages for combinations of medicinal products compared to treatment with monotherapy are widely known.

Additionally, to further justify the safety of the mono-components when these are combined, the applicant collected data related to the number of prescriptions of ramipril and bisoprolol for monotherapy as well as the number of co-prescriptions where both substances were prescribed simultaneously for the same patient. The collected data for all strengths were made in two representative European countries: Italy and Poland, from the last two and half years.

According to the data obtained from IQVIA database, approximately 3 and 4 million co-prescriptions of ramipril and bisoprolol are reported annually in Italy and Poland, respectively.

Moreover, information regarding co-prescription of ramipril and bisoprolol in Germany has been provided (Sus et al, 2021), reporting that 20% of patients treated with bisoprolol are also treated with ramipril and approximately 14% of patients treated with ramipril are also treated with bisoprolol.

The CHMP acknowledged the co-prescription data provided as sufficient documentation of use of combination in real-world.

Discussion and conclusion

The CHMP agreed to the revised proposed indication, which is in line with the approved indications for ramipril and bisoprolol. It was noted that the SmPC of the mono-component products do not specifically mention use in combination as part of the indication. However, for this class of products where use in combination is very frequent not all are listed in the indication section of the summary of product characteristics.

The CHMP noted that the equivalence between the FDC under consideration and the authorised mono-component products had been demonstrated, and that in that study the FDC was tolerated in the same way as the authorised mono-component products, whilst it had also been shown that no PK interactions is expected between ramipril and bisoprolol based on the DDI study.

The CHMP considered the submitted meta-analysis of 6 observational studies, a 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-I 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, 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.

3. Benefit-risk balance

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 ESC Guidelines, where combination of 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.

4. Grounds for 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.

References

AIRE. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet. 1993 Oct 2;342(8875):821-8. PMID: 8104270 6.

Anderson VR, Perry CM, Robinson DM. Ramipril: a review of its use in preventing cardiovascular outcomes in high-risk patients. Am J Cardiovasc Drugs. 2006;6(6):41732.

Baxter AJ, Spensley A, Hildreth A, Karimova G, O'Connell JE, Gray CS. Beta blockers in older persons with heart failure: tolerability and impact on quality of life. Heart. 2002;88(6):611-4.

Califf RM, Lokhnygina Y, Velazquez EJ, et al. Usefulness of beta blockers in high-risk patients after myocardial infarction in conjunction with captopril and/or valsartan (from the VALsartan In Acute Myocardial Infarction [VALIANT] trial). Am J Cardiol. 2009;104(2):151-157.

CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomized trial. Lancet 1999;353: 9-13.

Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. Eur Heart J. 1997;18(1):41-51.

Dagenais GR, Yusuf S, Bourassa MG, et al. Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study. Circulation. 2001;104(5):522-526.

Garg R, Yusuf S, 'Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials', 273(18):1450-6, May 1995.

Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy. Lancet. 1997;349(9064):1493-1497.

Heran BS, Wong M, Heran IK, Wright JM, 'Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension', Oct 8;2008(4).

Ivanova LA, Kanorskii SG, Rostovtseva ON, Halil Sufian B, Galenko-Yaroshevskii PA. Treatment of acute coronary syndromes in patients with type 2 diabetes mellitus with beta-adrenoblockers and angiotensin-converting enzyme inhibitors: cardiohemodynamic effects and impact for prognosis. Bull Exp Biol Med. 2004;138(3):301-304.

Konishi M, Haraguchi G, Yoshikawa S, Kimura S, Inagaki H, Isobe M, 'Additive effects of β-blockers on renin-angiotensin system inhibitors for patients after acute myocardial infarction treated with primary coronary revascularization', 75(8):1982-91, 2011.

de Leeuw PW and Birkenhager WH. Short- and long-term effects of ramipril in hypertension. Am J Cardiol. 1987; 59(10): 79D-82D.

Remme WJ, Riegger G, Hildebrandt P, et al. The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction. The carvedilol and ACE-inhibitor remodelling mild heart failure evaluation trial (CARMEN). Cardiovasc Drugs Ther. 2004;18(1):57-66.

Spargias KS, Hall AS, Greenwood DC, Ball SG. beta blocker treatment and other prognostic variables in patients with clinical evidence of heart failure after acute myocardial infarction: evidence from the AIRE study. Heart. 1999;81(1):25-32.

Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005;112(16):2426-2435.

Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in highrisk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000 Jan 20;342(3):145-53.

Appendix

Divergent positions

Article 29(4) of Directive 2001/83/EC

Procedure No: EMEA/H/A-29(4)/1519

Rambis and associated names (INN: ramipril/bisoprolol fumarate)

Divergent statement

The following CHMP Members consider that the Benefit/Risk ratio of Rambis and associated names is not favourable based on the following grounds:

- A relevant contribution of each active substance to the desired therapeutic effect of the combination has not been demonstrated. No bibliographic data have been submitted to indicate superiority of the ramipril/bisoprolol combination over the monocomponents. The applicant provided inconclusive results of 3 studies, i.e. a non-interventional non-inferiority study (NT-RAM-BIS-01-19/02), a meta-analysis (DUS RAMBIS V1 26/04/2021) of six observational non-interventional studies and preliminary results of an ongoing study using real-world data. However, these data do not indicate superiority of the blood pressure lowering effect of the combination over ramipril alone and do not allow to estimate the contribution of the monocomponents to the therapeutic effects.
- Although the ramipril/bisoprolol comedication belongs to the class-I recommended combinations in clinical practice guidelines, the extrapolation of the relative contribution of both monocomponents from other members of this class to ramipril and bisoprolol have not been sufficiently justified, considering the known differences in pharmacokinetic and/or pharmacodynamic properties of the compounds within both product classes.
- Furthermore, bisoprolol in the strength 1.25 mg is currently only used and recommended for treatment initiation as part of an uptitration regimen. Therefore, this bisoprolol strength of the FDC will not be used in the frame of the substitution indication, which the applicant applies for. Instead, the ramipril /bisoprolol 2.5mg/1.25mg is likely to be used for titration of add-on therapy or initial combination therapy, both of which are not part of the indication. No patient population stabilized on an optimal dose of the free combination of the monocomponents, as required for a substitution indication, exists that would be switched to this low-dose FDC.

When considering the level of clinical evidence in their totality, the benefit risk ratio of the FDC product is negative.

CHMP Members expressing a divergent opinion:

- Alexandre Moreau (France)
- Armando Genazzani (Italy)
- Frantisek Drafi (Slovakia)
- Martina Weise (Germany)
- Ondřej Slanař (Czechia)
- Blanka Hirschlerova (Co-opted Member)
- Jan Mueller-Berghaus (Co-opted Member)
- Ingrid Wang (Norway)