EMA/621814/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adempas

International non-proprietary name: riociguat

Procedure No. EMEA/H/C/002737/II/0032/G

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	19 Jul 2021	19 Jul 2021	☐
☐	CHMP Rapporteur Assessment Report	23 Aug 2021	23 Aug 2021	☐
☐	CHMP members comments	06 Sep 2021	06 Sep 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	09 Sep 2021	n/a	☐
☒	Opinion	16 Sep 2021	16 Sep 2021	☐

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Table of contents

Table of contents 3

Abbreviations 4

1. Background information on the procedure 5

2. Overall conclusion and impact on the benefit/risk balance 5

3. Recommendations 5

4. Introduction 8

4.1. Product development rationale 8

5. Clinical pharmacology aspects 8

5.1. Pharmacokinetics 8

6. Clinical safety aspects 9

6.1. Drugs interacting by mode of action 9

7. Changes to the product information 10

7.1. Section 4.3 10

7.1.1. MAH proposal 10

7.1.2. Assessor's comment 10

7.2. Section 4.4 11

7.2.1. MAH proposal 11

7.2.2. Assessor's comment 11

7.3. Section 4.5 (1) 11

7.3.1. MAH proposal 11

4.5 Interaction with other medicinal products and other forms of interaction 11

7.3.2. Assessor's comment 11

7.4. Section 4.5 (2) 12

7.4.1. MAH proposal 12

7.4.2. Assessor's comment 12

8. Request for supplementary information 12

8.1. Major objections 12

8.2. Other concerns 13

9. Assessment of the responses to the request for supplementary information 13

Abbreviations

AUC	Area under the plasma concentration vs time curve from zero to infinity after single (first) dose
CCDS	Company Core Data Sheet
Cmax	Maximum observed drug concentration in plasma after single dose administration
CTEPH	Chronic thromboembolic pulmonary hypertension
CV	Cardiovascular
EU	European Union
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
MAH	Marketing authorization holder
MoA	Mode of action
NO	Nitric oxide
PAH	Pulmonary artery hypertension
PDE5	Phospho-diesterase 5
sGC	Soluble guanylate-cyclase
SmPC	Summary of product characteristics

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 17 June 2021 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Group of variations:
Type II C.I.4. update to SmPC section 4.3 and section 4.5 to contraindicate coadministration of riociguat (adempas) with other sGC stimulators.
Type II C.I.4. update to SmPC section 4.5 to rectify the Cmax value related to concommitant use with HAART treatment.
The package leaflet is updated accordingly.
In addition the MAH takes to opportunity to implement editorial changes and updates to QRD Template version 10.2.
The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

The changes to the product information are acceptable. The benefit-risk balance of Adempas, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Group of variations:
Type II C.I.4. update to SmPC section 4.3 and section 4.5 to contraindicate coadministration of riociguat (adempas) with other sGC stimulators.
Type II C.I.4. update to SmPC section 4.5 to rectify the Cmax value related to concomitant use with HAART treatment.

The package leaflet is updated accordingly.

In addition the MAH takes to opportunity to implement editorial changes and updates to QRD Template version 10.2.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I and IIIB are recommended.

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

Riociguat belongs to the class of soluble guanylate-cyclase (sGC) stimulators and is approved in the EU under the tradename "Adempas" for the treatment of pulmonary artery hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). Riociguat has a dual mode of action: it sensitizes sGC to the body's own nitric oxide (NO) and can also increase sGC activity in the absence of NO. With its dual mode of action, riociguat is restoring the NO-sGC-cGMP pathway causing vasorelaxation.

Vericiguat is another member of the class of sGC stimulators. The vericiguat company core data sheet (CCDS) states that concomitant use of other sGC stimulators, such as riociguat is contraindicated. To ensure a consistent safety instruction for this pharmacological class of sGC stimulators, the MAH has amended the CCDS of riociguat (current version CCDS #07) and proposes to update SmPC sections 4.3 and 4.5 by adding a contraindication for coadministration with other sGC stimulators (e.g. vericiguat).

Following CCDS #06, Type II variation EMEA/H/C/002737/II/0028 was submitted to include the results from the drug-drug interaction study between riociguat and HAART medications. In this update the change in the pharmacokinetic properties of riociguat (AUC and C_{max}) in HIV patients in comparison to healthy subjects was presented. Afterwards an incorrect value for the increase in C_{max} in HIV patients was erroneously depicted. Hence, the CCDS and SmPC section 4.5 are updated to rectify the riociguat peak plasma concentration (C_{max}) increase in combination with HAART treatment. This error occurred only in the SmPC and not in the source document.

4.1. Product development rationale

Riociguat belongs to a class of sGC stimulators for the treatment of PAH and CTEPH.

Compounds using similar pathway(s)/MoAs like sGC stimulators, nitrates, and PDE5 inhibitors are contraindicated for use in combination with riociguat because of an increased risk of hypotension as demonstrated in preclinical investigations and clinical studies.

5. Clinical pharmacology aspects

5.1. Pharmacokinetics

The SmPC for riociguat provides information regarding drug-drug interaction of riociguat with HAART medication used for treatment of HIV patients. The increase of riociguat peak plasma concentration in combination with HAART treatment should be corrected reflecting a maximum increase of 30%.

Table 1: Summary of historical comparison - fasted (PKS, N=64, excluding 16 subjects from study 11261) provides the corrected outcome of the statistical analysis showing AUC and Cmax ratio for riociguat on top of antiretroviral therapies versus a historical control (riociguat alone).

Table 1: Summary of historical comparison - fasted (PKS, N=64, excluding 16 subjects from study 11261)

Parameter	Geom. CV	Comparison	LS means ratio [a]	90% confidence interval
Riociguat AUC (µg*h/L)	96.68	Atripla / Riociguat alone	0.9703	(0.5414 , 1.7390)
		Complera / Riociguat alone	1.8803	(1.0799 , 3.2738)
		HIV combined therapy / Riociguat alone	1.1765	(0.6757 , 2.0485)
		Stribild / Riociguat alone	1.8831	(1.0816 , 3.2786)
		Triumeq / Riociguat alone	2.5903	(1.4877 , 4.5099)
Riociguat C_{max} (µg/L)	43.81	Atripla / Riociguat alone	0.8955	(0.6728 , 1.1919)
		Complera / Riociguat alone	1.0299	(0.7738 , 1.3708)
		HIV combined therapy / Riociguat alone	1.0006	(0.7517 , 1.3318)
		Stribild / Riociguat alone	1.2859	(0.9661 , 1.7116)
		Triumeq / Riociguat alone	1.2657	(0.9509 , 1.6847)

Note: LS mean for each comparison as well as the 90% confidence interval limits are obtained from an ANOVA including factor treatment and study nested within treatment
Calculated by re-transformation of the logarithmic data
PKS = pharmacokinetics set, CV = coefficient of variation, AUC = area under the plasma concentration vs time curve from zero to infinity after single (first) dose, C_{max} = maximum observed drug concentration in plasma after single dose administration
Subjects of study 11261 were excluded as they received breakfast prior to study drug administration

Concomitant administration of HAART combinations led to an increase in riociguat mean AUC of up to about 160% and to an approximate 30% increase in mean Cmax.

The update of Cmax value does not change the overall positive benefit-risk balance for riociguat.

6. Clinical safety aspects

6.1. Drugs interacting by mode of action

Riociguat belongs to a novel class of sGC stimulators and is approved in the EU for the treatment of PAH and CTEPH. With its dual mode of action, riociguat is restoring the NO-sGC-cGMP pathway, causing vasorelaxation.

Compounds using similar pathway(s)/MoAs such as PDE5 inhibitors and nitrates are already contraindicated in riociguat because of an increased risk of hypotension. Therefore, like for PDE5 inhibitors and nitrates, the MAH proposes to include a contraindication for co-administration with other sGC stimulators as an additive effect on the systemic circulation is to be expected.

The current riociguat SmPC contains the following contraindications for co-administration with other drugs:

- Co-administration with PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil) (Sections 4.2 and 4.5).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs called 'poppers' (Section 4.5).

There are no data for co-administration of riociguat with other sGC stimulators, nevertheless it can be argued that compounds using similar pathway(s)/MoAs are already contraindicated in riociguat because

of an increased risk of hypotension and therefore, from a theoretical perspective, this can be expected from co-administration with other sGC stimulators like vericiguat (BAY 1021189 / MK1242).

Vericiguat CCDS v 01.1 (**Error! Reference source not found.**) states that concomitant use of other sGC stimulators, such as riociguat is contraindicated. The rationale for the contraindication with other sGC stimulators is further explained as follows (**Error! Reference source not found.**): Coadministration of vericiguat and other sGC stimulators was not permitted in the Phase 3 VICTORIA clinical study.

To ensure a consistent safety message for the pharmacological class of sGC stimulators, the MAH proposes for riociguat SmPC to contraindicate the coadministration with other sGC stimulators (e.g. vericiguat).

7. Changes to the product information

7.1. Section 4.3

7.1.1. MAH proposal

The MAH proposes addition of the underlined text.

- Co-administration with PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil) (see sections 4.2 and 4.5).
- Severe hepatic impairment (Child Pugh C).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see sections 4.4; 4.5 and 4.6).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs called 'poppers' (see section 4.5).
- Co-administration of Adempas with other soluble guanylate cyclase stimulators is contraindicated (*see section* 4.5).
- Patients with systolic blood pressure < 95 mm Hg at treatment initiation.
- Patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) (see section 5.1)

7.1.2. Assessor's comment

The addition of the contra-indication is acceptable as it is consistent with the reciprocal contra-indication in the SmPC of vericiguat (the only other authorised sGC stimulator). However, the wording needs to be amended:

- The contra-indication should refer to concomitant use rather than co-administration (suggesting use at the same timepoint)
- Use of the tradename is redundant.
- No complete sentence is required in 4.3
- The cross reference to 4.5 retrieves no additional information and is therefore also redundant.

The following changes result:

- Concomitant use ~~administration of Adempas~~ with other soluble guanylate cyclase stimulators ~~is contraindicated (*see section* 4.5)~~.

The following would therefore be acceptable:

- Concomitant use with other soluble guanylate cyclase stimulators.

7.2. Section 4.4

7.2.1. MAH proposal

The MAH proposes deletion of the ~~text in strikethrough~~

Concomitant use with other medicinal products

- The concomitant use of riociguat with strong multi pathway ~~cytochrome P450 (~~CYP~~)~~ and ~~P-glycoprotein (~~P-gp~~)~~ / ~~breast cancer resistance protein (~~BCRP~~)~~ inhibitors such as azole antimycotics (e.g. ketoconazole, posaconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) results in a pronounced increase in riociguat exposure (see sections 4.5 and 5.2).

7.2.2. Assessor's comment

This editorial change is accepted. The abbreviations are spelled out in section 4.2.

Of note: there is some text in 4.2 near "BCRP" in 12 point font.

7.3. Section 4.5 (1)

7.3.1. MAH proposal

The MAH proposes addition of the underlined text

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacodynamic interactions

(…)

Soluble Guanylate Cyclase Stimulators
Co-administration of Adempas with other soluble guanylate cyclase stimulators is contraindicated (*see section* 4.3).

7.3.2. Assessor's comment

The addition of the contra-indication is acceptable (see above). However, the wording needs to be amended:

- The contra-indication should refer to concomitant use rather than co-administration (suggesting use at the same timepoint)
- Use of the tradename is redundant.
- The cross reference can be set in normal font.

The following would be acceptable:

Soluble Guanylate Cyclase Stimulators
Concomitant use of riociguat with other soluble guanylate cyclase stimulators is contraindicated (see section 4.3).

7.4. Section 4.5 (2)

7.4.1. MAH proposal

The MAH proposes deletion of the ~~text in strikethrough~~ and addition of the underlined text

Effects of other substances on riociguat

Riociguat is cleared mainly via cytochrome P450-mediated (CYP1A1, CYP3A4, CYP3A5, CYP2J2) oxidative metabolism, direct biliary/faecal excretion of unchanged riociguat and renal excretion of unchanged riociguat via glomerular filtration.

Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors

Highly active antiretroviral therapy (HAART)

In *vitro,* abacavir, rilpivirine, efavirenz, ritonavir, cobicistat and elvitegravir inhibited CYP1A1 and the metabolism of riociguat in the order listed with abacavir as the strongest inhibitor. Cobicistat, ritonavir, atazanavir and darunavir are additionally classified as CYP3A inhibitors. In addition, ritonavir showed inhibition of P-gp.

The impact of HAART (including different combinations of abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir) on riociguat exposure was investigated in a dedicated study in HIV patients. Concomitant administration of HAART combinations led to an increase in riociguat mean AUC of up to about 160% and to an approximate ~~20~~30% increase in mean C_{max}. The safety profile observed in HIV patients taking a single dose of 0.5 mg riociguat together with different combinations of HIV drugs used in HAART was generally comparable to other patient populations.

To mitigate the risk of hypotension when Adempas is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, e.g. as contained in HAART, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and 4.4).

7.4.2. Assessor's comment

The correction of the error is accepted.

Of note: In at least 15 instances (such as here), the use of the tradename in the current Adempas SmPC is redundant.

8. Request for supplementary information

8.1. Major objections

None

8.2. Other concerns

Clinical aspects

See SmPC comments in section 8, and Appendix 1.

9. Assessment of the responses to the request for supplementary information

Clinical aspects

The MAH accepts the PI proposals of the assessor. The changes in SmPC section 4.4 and PIL section 2 are supported.