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Avatrombopag (thrombocytopenia and chronic liver disease) –

Addendum to Commission A21-31[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
CLD	chronic liver disease
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial

1 Background

On 10 August 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-31 (Avatrombopag – Benefit assessment according to § 35a Social Code Book V) [1].

For the benefit assessment of avatrombopag in the treatment of adult patients with severe thrombocytopoenia and chronic liver disease (CLD) who are scheduled to undergo an invasive procedure, the pharmaceutical company (hereinafter "company") presented in its dossier [2] a direct comparison of avatrombopag with placebo on the basis of 2 identical randomized controlled trials (RCTs), ADAPT-1 and ADAPT-2. The benefit assessment used the outcome "patients without transfusion" for patients who underwent invasive procedures of moderate or high bleeding risk.

The G-BA requires further analyses to decide on any added benefit. Therefore, the G-BA commissioned IQWiG to assess the results on the outcome "patients without transfusion" for the total population of the ADAPT-1 and ADAPT-2 studies (including an assessment on the outcome's patient relevance), taking into account the information provided in the dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is sent to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Analysis of the results on the outcome "patients without transfusion" for the total population of the ADAPT-1 and ADAPT-2 studies

In the present therapeutic indication, invasive procedures are frequently necessary due to CLD; in patients who also have severe thrombocytopoenia, these procedures are often associated with an elevated bleeding risk [3-5]. Depending on the invasive procedure's bleeding risk as well as other factors, these patients may receive prophylactic platelet transfusion to prevent bleeding [6-8]. However, platelet administration is associated with a risk of subsequent complications. For instance, up to 50% of patients with repeated platelet transfusions developed refractoriness, in part due to antibody production [6,8,9]. In addition, there is a risk of acute transfusion-related events, such as the occurrence of febrile or allergic reactions or of less common, life-threatening complications such as anaphylaxis, transfusion-related bacterial or viral infections, and transfusion-associated acute lung injury [7,9-11]. Consequently, avoiding transfusion prevents the above subsequent complications. The outcome "patients without transfusion" was therefore deemed patient-relevant and included in the benefit assessment.

The CLD patients with severe thrombocytopoenia who were included in the ADAPT-1 and ADAPT-2 studies were scheduled for invasive procedures with a low, moderate, or high bleeding risk. For the outcome "patients without transfusion", the avatrombopag benefit assessment included only patients who underwent an invasive procedure with moderate or high bleeding risk. This delimitation of the patient population was undertaken because it was impossible to determine whether patients undergoing an invasive procedure with a low bleeding risk required prophylactic platelet transfusion. This has been discussed in detail in dossier assessment A21-31 [1]. In the commenting procedure, the company did not submit any further information on the reasons for platelet transfusions [12]. Therefore, the conclusion drawn in dossier assessment A21-31 on the outcome "patients without transfusion" remains unchanged for patients who underwent an invasive procedure with a low bleeding risk.

Appendix A presents the results of the total population of the ADAPT-1 and ADAPT-2 studies regarding the outcome "patients without transfusion".

2.2 Summary

The present addendum does not change the conclusion on the added benefit of avatrombopag drawn in dossier assessment A21-31.

Table 1 below shows the result of the benefit assessment of avatrombopag in consideration of both dossier assessment A21-31 and the present addendum.

Table 1: Avatrombopag – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with severe thrombocytopoenia and CLD who are scheduled to undergo an invasive procedure[c]	Watchful waiting[b]	Invasive procedure with a moderate or high bleeding risk: ▪ proof of considerable added benefit
		Invasive procedure with a low bleeding risk: ▪ added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. It was assumed that platelet transfusions, if indicated, were administered in both study arms. Reasons must be documented. Further, patients in the therapeutic indication were assumed to undergo an invasive medical procedure.
c. No data are available for patients with a MELD score > 24.

ACT: appropriate comparator therapy; CLD: chronic liver disease; G-BA: Federal Joint Committee; MELD: Model for End Stage Liver Disease

The G-BA decides on the added benefit.

3 References

The list of references contains citations by the company which may lack some bibliographic information.

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Appendix A – Results on the outcome "patients without transfusion"

Table 2: Results (morbidity) – RCT, direct comparison: avatrombopag vs. placebo

Outcome category Outcome Study	Avatrombopag N	Avatrombopag Patients with event n (%)[a]	Placebo N	Placebo Patients with event n (%)[a]	Avatrombopag vs. placebo RR [95% CI]; p-value
Morbidity					
Patients without transfusion[b]					
ADAPT-1	149	111 (74.5)	82	24 (29.3)	2.55 [1.79; 3.61]; < 0.001[c]
ADAPT-2	128	101 (78.9)	76	26 (34.2)	2.31 [1.67; 3.19]; < 0.001[c]
Total					2.42 [1.91; 3.07]; < 0.001[d]

a. IQWiG calculations from separate data per cohort with lower/higher baseline platelet count.
b. Percentage of study participants who required neither platelet transfusions nor rescue due to bleeding, from the time of randomization up to 7 days after a scheduled procedure.
c. IQWiG calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [13]).
d. IQWiG calculation from metaanalysis with fixed effect (Mantel-Haenszel).

CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

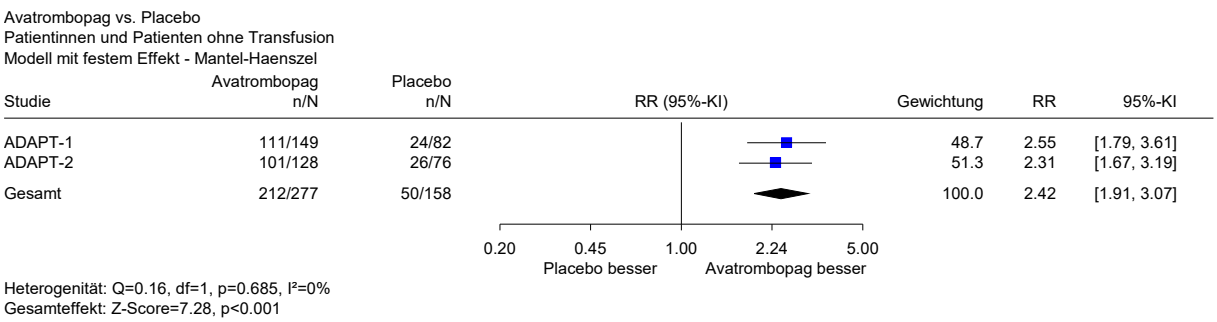

Figure 1: Metaanalysis (fixed-effect model; Mantel-Haenszel method) of the ADAPT-1 and ADAPT-2 studies regarding the outcome "patients without transfusion" for invasive procedures of any bleeding risk