Avatrombopag (thrombocytopenia with chronic liver disease)

Resolution of:　　　16 September 2021　　　　　　Valid until: unlimited
Entry into force on:　16 September 2021
BAnz AT 14 10 2021 B4

Therapeutic indication (according to the marketing authorisation of 20 June 2019):

Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

Therapeutic indication (according to the marketing authorisation of 18 January 2021):

Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Therapeutic indication of the resolution (resolution of 16 September 2021):

Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

1. **Additional benefit of the medicinal product in relation to the appropriate comparator therapy**

Adults with severe thrombocytopenia with chronic liver disease who are scheduled to undergo an invasive procedure

Appropriate comparator therapy:

Monitoring wait-and-see approach

Extent and probability of the additional benefit of avatrombopag compared to a monitoring wait-and-see approach:

An additional benefit is not proven.

Study results according to endpoints[1]:

Adults with severe thrombocytopenia with chronic liver disease who are scheduled to undergo an invasive procedure

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	∅	No data is available.
Side effects	↔	No relevant difference for the benefit assessment.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔ : no relevant difference ∅: no data available n.a.: not assessable		

- Randomised, double-blind phase III study ADAPT-1: Avatrombopag versus placebo
- Randomised, double-blind phase III study ADAPT-2: Avatrombopag versus placebo

Mortality

Endpoint	Avatrombopag		Placebo		Avatrombopag vs placebo
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	Relative risk [95% CI] p-value
Overall survival					
ADAPT-1	147	2 (1.4)	80	0 (0)	2.74 [0.13; 56.31] 0.407[b]
ADAPT-2	127	0 (0)	76	1 (1.3)	0.20 [0.01; 4.86] 0.235[b]
Meta-analysis					0.85 [0.14; 5.18] 0.861[c]

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[1] Data from the dossier assessment of the IQWiG (A21-31) and from the addendum (A21-103), unless otherwise indicated.

Morbidity

Endpoint	Avatrombopag		Placebo		Avatrombopag vs placebo
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	Relative risk [95% CI] p-value
Patients without transfusion[d]					
ADAPT-1	149	111 (74.5)	82	24 (29.3)	2.55 [1.79; 3.61] < 0.001[b]
ADAPT-2	128	101 (78.9)	76	26 (34.2)	2.31 [1.67; 3.19] < 0.001[b]
Meta-analysis					2.42 [1.91; 3.07] <0.001[c]
Bleeding WHO grade ≥ 2[e]					
ADAPT-1	149	9 (6.0)	82	4 (4.9)	1.24 [0.39; 3.90] 0.797[b]
ADAPT-2	128	2 (1.6)	76	2 (2.6)	0.59 [0.09; 4.13] 0.616[b]
Meta-analysis					1.03 [0.39; 2.72] 0.957[c]

Health-related quality of life

Not collected in the ADAPT-1 and ADAPT-2 studies.

Side effects

Endpoint	Avatrombopag		Placebo		Avatrombopag vs placebo
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	Relative risk [95% CI] p-value
Adverse events (AEs; presented additionally)[f]					
ADAPT-1	147	81 (55.1)	80	47 (58.8)	-
ADAPT-2	127	59 (46.5)	76	34 (44.7)	-

(continuation)

Side effects

Endpoint	Avatrombopag		Placebo		Avatrombopag vs placebo
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	Relative risk [95% CI] p-value
Serious adverse events (SAE)[f]					
ADAPT-1	147	16 (10.9)	80	9 (11.3)	0.97 [0.45; 2.09] 0.966[b]
ADAPT-2	127	1 (0.8)	76	2 (2.6)	0.30 [0.03; 3.24] 0.421[b]
Meta-analysis					0.85 [0.41; 1.75] 0.657[c]
Therapy discontinuation due to adverse events					
ADAPT-1	147	2 (1.4)	80	0 (0)	2.74 [0.13; 56.31] 0.407[b]
ADAPT-2	127	0 (0)	76	0 (0)	-
Meta-analysis					_[g]
Thromboembolic events (SMQ[h], AEs)					
ADAPT-1	147	0 (0)	80	0 (0)	-
ADAPT-2	127	1 (0.8)	76	2 (2.6)	0.30 [0.03; 3.24]; 0.421[b]
					_[g]

a   IQWiG calculation from separate data per cohort with lower or higher baseline platelet count.
b   IQWiG calculation of RR, 95% CI and p-value
c   IQWiG calculation from meta-analysis with fixed effect
d   Primary endpoint of the ADAPT-1 and ADAPT-2 studies. Percentage of study participants who did not require platelet transfusions or rescue procedures due to bleeding after randomisation and up to 7 days after a planned procedure. Based on the results of the endpoint "patients without transfusion", no additional benefit is derived.
e   Grade 2: mild bleeding (clinically significant), Grade 3: major bleeding requiring transfusion (severe). Only 2 major bleeding events (grade 3) occurred overall, each in the avatrombopag arm of the ADAPT-1 study.
f   With the exclusion of blood-specific PTs
g   A meta-analysis was not performed because no event occurred in one of two studies.
h   SMQ "Embolism and thrombosis events"

Abbreviations used:
CI = confidence interval; n = number of patients with (at least 1) event; N = number of patients evaluated; PT = preferred term; RR = relative risk; SMQ = Standardised MedDRA Query; SAE = serious adverse event; AE = adverse event; vs = versus; WHO = World Health Organization

2. Number of patients or demarcation of patient groups eligible for treatment

Adults with severe thrombocytopenia with chronic liver disease who are scheduled to undergo an invasive procedure

approx. 1,790 – 24,130 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Doptelet (active ingredient: avatrombopag) at the following publicly accessible link (last access: 11 June 2021):

https://www.ema.europa.eu/en/documents/product-information/doptelet-epar-product-information_en.pdf

Treatment with avatrombopag should be started and continuously monitored by doctors experienced in the treatment of haematological diseases.

4. Treatment costs

Annual treatment costs:

Adults with severe thrombocytopenia with chronic liver disease who are scheduled to undergo an invasive procedure

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Avatrombopag	€ 1,189.38 - € 5,305.59[2]
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Patient-individual[3]

(Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2021)

Costs for additionally required SHI services: not applicable

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[2] Platelet transfusions may be indicated in addition to avatrombopag.
[3] Platelet transfusions may be indicated patient-individual as part of the appropriate comparator therapy.