Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolution on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V - Doravirine

of 4 July 2019

At its session on 4 July 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient doravirine as follows:

Doravirine

Resolution of: 4 July 2019
Entry into force on: 4 July 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 22 November 2018):

Pifeltro® is indicated, in combination with other anti-retroviral medicinal products, for the treatment of adults infected with the human immunodeficiency virus (HIV-1). The HI viruses must not have mutations known to be associated with resistance to the NNRTI (non-nucleosidic reverse transcriptase inhibitor) class of substances.

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

a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances

Appropriate comparator therapy:

Rilpivirine in combination with tenofovir disoproxil/alafenamide plus emtricitabine or in combination with abacavir plus lamivudine

or

Dolutegravir in combination with tenofovir disoproxil/alafenamide plus emtricitabine or in combination with abacavir plus lamivudine

Extent and probability of the additional benefit of doravirine compared with dolutegravir:

An additional benefit is not proven.

b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances

Appropriate comparator therapy:

Individual anti-retroviral therapy depending on the previous therapy(ies) and taking into account the reason for the change of therapy, in particular therapy failure because of virological failure and possible associated development of resistance or because of side effects

Extent and probability of the additional benefit of doravirine compared with the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances

Indirect comparisons: Doravirine (DOR) + 2 NRTI (RCTs 007, 018, 021) vs dolutegravir (DTG) + 2 NRTI (RCTs SINGLE, SPRING-1, FLAMINGO) via bridge comparators (EFV) and darunavir boosted with ritonavir (DRV/r):

Endpoint category Endpoint Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N	 Patients with event n (%)	EFV + 2 NRTI or DRV/r + 2 NRTI N	 Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
Mortality					
Overall mortality					
DOR + 2 NRTI vs EFV + 2 NRTI					
007	108	0 (0)	108	0 (0)	–
021	364	0 (0)	364	2 (0.5)	0.20 [0.01; 4.15]; 0.298
DTG + 2 NRTI vs EFV + 2 NRTI					
SINGLE	414	0 (0)	419	2 (0.5)	0.20 [0.01; 4.20]; no data available
SPRING-1	51	1 (2.0)	50	0 (0)	2.94 [0.12; 70.53]; no data available
Total[b)]					0.67 [0.11; 3.99]; 0.655
Indirect comparison via bridge comparator EFV[c)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					0.30 [0.01; 10.18]; 0.504
DOR + 2 NRTI vs DRV/r + 2 NRTI					
018	383	3 (0.8)	383	1 (0.3)	3.00 [0.31; 28.71][d)]; 0.378[e)]
DTG + 2 NRTI vs DRV/r + 2 NRTI					
FLAMINGO	242	1 (0.4)	242	0 (0)	3.00 [0.12; 73.28][d)]; 0.410[e)]
Indirect comparison via bridge comparator DRV/r[f)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					1.00 [0.02; 50.07]; > 0.999
Indirect comparison (overall)[g)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					0.51 [0.04; 6.81]; 0.610

[1] Data from the dossier evaluation of the IQWiG (A19-07) unless otherwise indicated.

Endpoint category Endpoint Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N	 Patients with event n (%)	EFV + 2 NRTI or DRV/r + 2 NRTI N	 Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
Morbidity					
AIDS-defining events (CDC class C)					
DOR + 2 NRTI vs EFV + 2 NRTI					
007	Endpoint not recorded				
021	364	0 (0)	364	2 (0.6)	0.20 [0.01; 4.15][d)]; 0.170[e)]
DTG + 2 NRTI vs EFV + 2 NRTI					
SINGLE	414	5 (1.2)	419	5 (1.2)	1.01 [0.30; 3.47][d)]; no data available
SPRING-1	51	1 (2.0)	50	0 (0)	2.94 [0.12; 70.56][d)]; no data available
Total[h)]					1.19 [0.38; 3.68]; 0.763
Indirect comparison via bridge comparator EFV[f)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					0.17 [0.01; 4.28]; 0.280
DOR + 2 NRTI vs DRV/r + 2 NRTI					
018	383	0 (0)	383	6 (1.6)	0.08 [0.00; 1.36][d)]; 0.015[e)]
DTG + 2 NRTI vs DRV/r + 2 NRTI					
FLAMINGO		no data available[i)]		no data available[i)]	no data available

Endpoint category Endpoint Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N	 Patients with event n (%)	EFV + 2 NRTI or DRV/r + 2 NRTI N	 Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
Morbidity					
Virological response (HIV-1 RNA < 50 copies/ml)[j)]					
DOR + 2 NRTI vs EFV + 2 NRTI					
007	108	82 (75.9)	108	82 (75.9)	1.00 [0.86; 1.16]; no data available
021	364	282 (77.5)	364	268 (73.6)	1.05 [0.97; 1.14]; 0.228
Total[b)]					1.04 [0.97; 1.12]; 0.289
DTG + 2 NRTI vs EFV + 2 NRTI					
SINGLE	414	319 (77.1)	419	293 (69.9)	1.10 [1.02; 1.20]; no data available
SPRING-1	51	45 (88.2)	50	36 (72.0)	1.23 [1.00; 1.50]; no data available
Total[b)]					1.12 [1.03; 1.20]; 0.005
Indirect comparison via bridge comparator EFV[c)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					0.93 [0.84; 1.04]; 0.190
DOR + 2 NRTI vs DRV/r + 2 NRTI					
018	379	277 (73.1)	376	248 (66.0)	1.11 [1.01; 1.22]; 0.034
DTG + 2 NRTI vs DRV/r + 2 NRTI					
FLAMINGO	242	194 (80.2)	242	164 (67.8)	1.18 [1.06; 1.32]; 0.002
Indirect comparison via bridge comparator DRV/r[c)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					0.94 [0.81; 1.08]; 0.371
Indirect comparison (overall)[g)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					0.93 [0.86; 1.02]; 0.116

Endpoint category Endpoint Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N[k)]	Baseline MV (SD)	Change at week 96 MV [95% CI][l)]	EFV + 2 NRTI or DRV/r + 2 NRTI N[k)]	Baseline MV (SD)	Change at week 96 MV [95% CI][l)]	Group difference MD [95% CI]; p value
Morbidity							
CD4 cell count (cells/µl)							
DOR + 2 NRTI vs EFV + 2 NRTI							
007	95	435.6 (no data available)	259.2 [220.0; 298.3]	93	455.9 (no data available)	263.6 [218.1; 309.1]	−4.4 [−64.0; 55.1]; no data available
021	337	435.9 (no data available)	237.7 [214.9; 260.6]	311	413.5 (no data available)	223.0 [198.4; 247.6]	14.7 [−18.7; 48.2]; no data available
Total[m)]							10.1 [−19.0; 39.3]; 0.497
DTG + 2 NRTI vs EFV + 2 NRTI							
SINGLE	414	349 (158.2)	324 (205.7)	419	351 (157.5)	286 (196.0)	43.95 [14.34; 73.55][n)]; no data available
SPRING-1	51	327 (122.3)	338 (162.6)	50	328 (106.5)	321 (218.9)	17.0 [−65.5; 99.5]; no data available
Total[o)]							40.79 [12.98; 68.61]; 0.004
Indirect comparison via bridge comparator EFV[c)]:							
DOR + 2 NRTI vs DTG + 2 NRTI							−30.67 [−70.97; 9.63]; 0.136
DOR + 2 NRTI vs DRV/r							
018	342	429.6 (no data available)	224.1 [200.8; 247.4]	327	405.0 (no data available)	206.7 [184.9; 228.5]	17.4 [−14.5; 49.3]; no data available
DTG + 2 NRTI vs DRV/r							
FLAMINGO	242	390 [290; 500][p)]	260 [185; 400][p)]	242	400 [300; 530][p)]	250 [130; 400][p)]	no data available

Endpoint category Endpoint Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N	 Patients with event n (%)	EFV + 2 NRTI or DRV/r + 2 NRTI N	 Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
Health-related quality of life					
007	Not collected				
018	Not collected				
021	Not collected				
Side effects					
AEs (additionally shown)					
DOR + 2 NRTI vs EFV + 2 NRTI					
007	108	97 (89.8)	108	104 (96.3)	–
021	364	321 (88.2)	364	339 (93.1)	–
DTG + 2 NRTI vs EFV + 2 NRTI					
SINGLE	414	376 (90.8)	419	394 (94.0)	–
SPRING-1	51	46 (90.2)	50	46 (92.0)	–
DOR + 2 NRTI vs DRV/r + 2 NRTI					
018	383	324 (84.6)	383	317 (82.8)	–
DTG + 2 NRTI vs DRV/r + 2 NRTI					
FLAMINGO	242	222 (91.7)	242	217 (89.7)	–
SAEs					
DOR + 2 NRTI vs EFV + 2 NRTI					
007	108	11 (10.2)	108	13 (12.0)	0.85 [0.40; 1.80]; no data available
021	364	21 (5.8)	364	30 (8.2)	0.70 [0.41; 1.20]; 0.194
Total[b)]					0.74 [0.48; 1.15]; 0.187
DTG + 2 NRTI vs EFV + 2 NRTI					
SINGLE	414	44 (10.6)	419	50[q)] (11.9)	0.89 [0.61; 1.30]; no data available
SPRING-1	51	7 (13.7)	50	7 (14.0)	0.98 [0.37; 2.59]; no data available
Total[b)]					0.90 [0.63; 1.29]; 0.569
Indirect comparison via bridge comparator EFV[c)]: **DOR + 2 NRTI vs DTG + 2 NRTI**					0.83 [0.47; 1.45]; 0.505
DOR + 2 NRTI vs DRV/r + 2 NRTI					
018	383	27 (7.0)	383	33 (8.6)	0.82 [0.50; 1.33]; 0.421
DTG + 2 NRTI vs DRV/r + 2 NRTI					
FLAMINGO	242	36 (14.9)	242	21 (8.7)	1.71 [1.03; 2.85]; 0.038
Indirect comparison via bridge comparator DRV/r[c)]:					

Endpoint category Endpoint Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N	 Patients with event n (%)	EFV + 2 NRTI or DRV/r + 2 NRTI N	 Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
DOR + 2 NRTI vs DTG + 2 NRTI					0.48 [0.24; 0.97]; 0.040
Indirect comparison (overall)[g)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					0.67 [0.43; 1.04]; 0.072
Withdrawal because of AEs					
DOR + 2 NRTI vs EFV + 2 NRTI					
007	108	5 (4.6)	108	11 (10.2)	0.45 [0.16; 1.26]; no data available
021	364	11 (3.0)	364	27 (7.4)	0.41 [0.21; 0.81]; 0.010
Total[b)]					0.42 [0.24; 0.74]; 0.003
DTG + 2 NRTI vs EFV + 2 NRTI					
SINGLE	414	14 (3.4)	419	52 (12.4)	0.27 [0.15; 0.48]; no data available
SPRING-1	51	2 (3.9)	50	5 (10.0)	0.39 [0.08; 1.93]; no data available
Total[b)]					0.28 [0.17; 0.49]; < 0.001
Indirect comparison via bridge comparator EFV[c)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					1.49 [0.68; 3.26]; 0.322
DOR + 2 NRTI vs DRV/r + 2 NRTI					
018	383	6 (1.6)	383	13 (3.4)	0.46 [0.18; 1.20]; 0.113
DTG + 2 NRTI vs DRV/r + 2 NRTI					
FLAMINGO	242	7 (2.9)	242	15 (6.2)	0.47 [0.19; 1.12]; 0.089
Indirect comparison via bridge comparator DRV/r[c)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					0.99 [0.27; 3.63]; 0.987
Indirect comparison (overall)[g)]:					
DOR + 2 NRTI vs DTG + 2 NRTI					1.34 [0.68; 2.61]; 0.397

Endpoint category Endpoint Comparison Study	DOR + 2 NRTI or DTG + 2 NRTI N	 Patients with event n (%)	EFV + 2 NRTI or DRV/r + 2 NRTI N	 Patients with event n (%)	Group difference RR [95% CI]; p value[a)]

a) Unless otherwise stated: two-sided p value (Wald test)
b) Meta analysis from model with fixed effect (Mantel-Haenszel)
c) Indirect comparison according to Bucher
d) Calculation of the IQWiG, asymptotic
e) Calculation by the IQWiG, unconditional exact test (CSZ method)
f) Calculation of the IQWiG, indirect comparison according to Bucher
g) Calculation of IQWiG, pools of indirect comparisons, model with fixed effect (inverse variance)
h) Calculation by the IQWiG, model with fixed effect (Mantel-Haenszel)
i) up to week 48, no patient with HIV-1-associated progression (change of symptoms to CDC-class C event, new event corresponding to CDC-class C, or death)
j) Evaluation in accordance with the Snapshot algorithm (007, 018, 021, SINGLE, and FLAMINGO studies) or TLOVR (SPRING-1 study)
k) Number of patients evaluated at 96 weeks; values at start of study may be based on other patient numbers.
l) Missing values were replaced using the observed failure approach (baseline transferred for patients who discontinued treatment because of lack of efficacy and excluded from other patients with missing values).
m) Model with fixed effect
n) Difference of adjusted mean values [95 % CI] from MMRM model
o) Model with random effects according to DerSimonian-Laird (essentially corresponds to a model with fixed effect [inverse variance] in the case of a homogeneous data basis [$I^2 = 0$])
p) Median [25% quantile; 75% quantile]
q) Data from module 4 A; there is a discrepancy with data in dossier evaluation A14-08 dolutegravir. However, this has no effect on the overall result.

Abbreviations:
/r: boosted ritonavir; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centres for Disease Control and Prevention; DOR: doravirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; HIV: immunodeficiency virus; CI: confidence interval; MMRM: Mixed Model with Repeated Measurements; MD: mean value difference; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NRTI: nucleosidic/nucleotic reverse transcriptase inhibitor; RCT: randomised controlled trial; RNA: ribonucleic acid; RR: relative risk, SD: standard deviation; SAE: serious adverse event; TLOVR: time to loss of virologic response; AE: adverse event; vs: versus

b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances

No data were submitted.

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

a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances

approx. 5,300–10,900 patients

b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances

approx. 52,500–62,800 patients

3. Requirements for a quality-assured application

The requirements of 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 Pifeltro® (active ingredient: doravirine) at the following publicly accessible link (last access: 24 May 2019):
https://www.ema.europa.eu/documents/product-information/pifeltro-epar-product-information_de.pdf

Treatment with doravirine should only be initiated and monitored by specialists who are experienced in the treatment of patients with HIV-1.

4. Treatment costs

Annual treatment costs:

a) Therapy-naïve adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Doravirine	€7,818.26
Appropriate comparator therapy:	
Dolutegravir	€8,650.95
Rilpivirine	€4,531.48

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2019)

Costs for additionally required SHI services: not applicable

b) Therapy experienced adult HIV-1 patients in whom the HI viruses have no mutations known to be associated with resistance to the NNRTI class of substances

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Doravirine	€7,818.26
Appropriate comparator therapy:	

Designation of the therapy	Annual treatment costs/patient
Individual anti-retroviral therapy[2]	€1,536.16–12,317.90

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2019)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 4 July 2019.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 4 July 2019

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The chair

Prof Hecken

[2] Because of the different combination possibilities in individual therapy, not all possible variants of combination therapies are presented and considered but rather the cost range from a cost-effective (nevirapine) to a cost-intensive therapy (maraviroc) is given as an example. The base therapy is not considered because it does not normally differ from that of doravirine.