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 according to Section 35a SGB V - Doravirine/Lamivudine/Tenofovir Disoproxil

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 combination doravirine/lamivudine/tenofovir disoproxil as follows:

Doravirine/Lamivudine/Tenofovir Disoproxil

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):

Delstrigo® is indicated 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, lamivudine, or tenofovir.

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, lamivudine, or tenofovir

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/lamivudine/tenofovir disoproxilcompared 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, lamivudine, or tenofovir

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/lamivudine/tenofovir disoproxilcompared 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, lamivudine, or tenofovir

Indirect comparison: doravirine/lamivudine/tenofovir disoproxil (DOR/3TC/TDF) + 2 NRTI (RCT 021) vs dolutegravir (DTG) + 2 NRTI (RCTs SINGLE, SPRING-1) via the bridge comparator efavirenz (EFV):

Endpoint category Endpoint Comparison Study	DOR or DTG N	DOR or DTG Patients with event n (%)	EFV N	EFV Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
Mortality					
Overall mortality					
DOR/3TC/TDF vs EFV + 2 NRTI					
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 comparators[c)]:					
DOR/3TC/TDF vs DTG + 2 NRTI					0.30 [0.01; 10.18]; 0.504
Morbidity					
AIDS-defining events (CDC class C)					
DOR/3TC/TDF vs EFV + 2 NRTI					
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[f)]					1.19 [0.38; 3.68]; 0.763
Indirect comparison via bridge comparators[g)]:					
DOR/3TC/TDF vs DTG + 2 NRTI					0.17 [0.01; 4.28]; 0.280
Virological response (HIV-1 RNA < 50 copies/ml)[h)]					
DOR/3TC/TDF vs EFV + 2 NRTI					
021	364	282 (77.5)	364	268 (73.6)	1.05 [0.97; 1.14]; 0.228
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

[1] Data from the dossier evaluation of the IQWiG (A19-05) unless otherwise indicated.

Endpoint category Endpoint Comparison Study	DOR or DTG N	DOR or DTG Patients with event n (%)	EFV N	EFV Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
Indirect comparison via bridge comparators[c)]:					
DOR/3TC/TDF vs DTG + 2 NRTI					0.94 [0.84; 1.06]; 0.308

Endpoint category Endpoint Comparison Study	DOR/3TC/TDF or DTG + 2 NRTI N[i)]	DOR/3TC/TDF or DTG + 2 NRTI Values at the start of study MV (SD)	DOR/3TC/TDF or DTG + 2 NRTI Change at the end of study MV (SD)	EFV+ 2 NRTI N[i)]	EFV+ 2 NRTI Values at the start of study MV (SD)	EFV+ 2 NRTI Change at the end of study MV (SD)	Group difference MD [95% CI]; p value
Morbidity							
CD4 cell count (cells/µl)							
DOR/3TC/TDF vs EFV + 2 NRTI							
021	337	435.9 (no data available)	237.7 [214.9; 260.6][j)]	311	413.5 (no data available)	223.0 [198.4; 247.6][j)]	14.7 [−18.7; 48.2]; no data available
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][k)] 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[l)]							40.79 [12.98; 68.61]; 0.004
Indirect comparison via bridge comparators[m)]:							
DOR/3TC/TDF vs DTG + 2 NRTI							-[n)]

Endpoint category Endpoint Comparison Study	DOR or DTG N	 Patients with event n (%)	EFV N	 Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
Health-related quality of life					
021	Not collected				
Side effects					
AEs (additionally shown)					
DOR/3TC/TDF vs EFV + 2 NRTI					
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)	–
SAEs					
DOR/3TC/TDF vs EFV + 2 NRTI					
021	364	21 (5.8)	364	30 (8.2)	0.70 [0.41; 1.20]; 0.194
DTG + 2 NRTI vs EFV + 2 NRTI					
SINGLE	414	44 (10.6)	419	50[o)] (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 comparators[c)]:					
DOR/3TC/TDF vs DTG + 2 NRTI					0.78 [0.41; 1.48]; 0.441
Withdrawal because of AEs					
DOR/3TC/TDF vs EFV + 2 NRTI					
021	364	11 (3.0)	364	27 (7.4)	0.41 [0.21; 0.81]; 0.010
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 comparators[c)]:					
DOR/3TC/TDF vs DTG + 2 NRTI					1.44 [0.60; 3.44]; 0.414

a) Unless otherwise stated: two-sided p value (Wald test)
b) Model with fixed effect (Mantel-Haenszel)
c) Indirect comparison according to Bucher
d) Own calculation, asymptotic
e) Own calculation, unconditional exact test (CSZ method)
f) Own calculation, model with fixed effect (Mantel-Haenszel)
g) Own calculation, indirect comparison according to Bucher
h) Evaluation according to Snapshot algorithm (Study 021, SINGLE study) or TLOVR (SPRING-1 study)

Endpoint category Endpoint Comparison Study	DOR or DTG N	DOR or DTG Patients with event n (%)	EFV N	EFV Patients with event n (%)	Group difference RR [95% CI]; p value[a)]
i) Number of patients evaluated at 96 weeks; values at start of study may be based on other patient numbers. j) [95% CI] k) Difference of adjusted mean values [95% CI] from MMRM model l) 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 [$I^2 = 0$]) m) Indirect comparison according to Bucher, for Study 021, the standard errors of the changes at the end of study were calculated from the respective confidence intervals n) No representation of the effect estimator because in the adjusted indirect comparison for DOR/3TC/TDF, there is only one study with a high endpoint-specific risk of bias o) 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: 3TC: lamivudine; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centres for Disease Control and Prevention; DOR: doravirine; DTG: dolutegravir; EFV: efavirenz; HIV: human 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; PT: preferred term; RCT: randomised controlled trial; RNA: ribonucleic acid; RR: relative risk, SD: Standard deviation; SOC: system organ class; SAE: serious adverse event; TDF: tenofovir disoproxil fumarate; 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, lamivudine, or tenofovir

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, lamivudine, or tenofovir

approx. 4,900–10,000 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, lamivudine, or tenofovir

approx. 43,900–58,000 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 Delstrigo® (active ingredient combination:doravirine/lamivudine/tenofovir disoproxil) at the following publicly accessible link (last access: 27 May 2019):

https://www.ema.europa.eu/documents/product-information/delstrigo-epar-product-information_de.pdf

Treatment with doravirine/lamivudine/tenofovir disoproxil 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, lamivudine, or tenofovir

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Doravirine/lamivudine/tenofovir disoproxil	€9,505.57
Appropriate comparator therapy:	
Dolutegravir/abacavir/lamivudine	€11,857.19
Dolutegravir + emtricitabine/tenofovir alafenamide	€14,628.02
Dolutegravir + emtricitabine/tenofovir disoproxil	€9,194.17
Rilpivirine + abacavir/lamivudine	€10,058.31
Rilpivirine + emtricitabine/tenofovir alafenamide	€10,508.55
Rilpivirine + emtricitabine/tenofovir disoproxil	€5,074.70

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, lamivudine, or tenofovir

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Doravirine/lamivudine/tenofovir disoproxil	€9,505.57
Appropriate comparator therapy:	
Individual anti-retroviral therapy[2]	€2.079.39–19,773.27

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 + emtricitabine/tenofovir disoproxil) to a cost-intensive therapy (maraviroc + abacavir + emtricitabine) is given as an example.