



## **Doravirine/Lamivudine/Tenofovir Disoproxil**

Resolution of: 4 July 2019 / 26 May 2020

Valid until: unlimited

Entry into force on: 4 July 2019 / 26 May 2020

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### **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 disoproxil compared with dolutegravir in combination with 2 NRTI (abacavir/lamivudine or tenofovir disoproxil/emtricitabine):**

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 disoproxil compared with the appropriate comparator therapy:**

An additional benefit is not proven.

## Study results according to endpoints:<sup>1</sup>

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<br>Endpoint<br>Comparison<br>Study            | DOR or DTG |                                 | EFV |                                 | Group difference<br>RR [95% CI];<br>p value <sup>a)</sup> |
|---|------------|---------------------------------|-----|---------------------------------|---|
|   | N          | Patients<br>with event<br>n (%) | N   | Patients<br>with event<br>n (%) |   |
| <b>Mortality</b>  |            |                                 |     |                                 |   |
| 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 <sup>b)</sup>   |            |                                 |     |                                 | 0.67 [0.11; 3.99]; 0.655                                  |
| <b>Indirect comparison via bridge comparators<sup>c)</sup>:</b> |            |                                 |     |                                 |   |
| <b>DOR/3TC/TDF vs DTG + 2 NRTI</b>                              |            |                                 |     |                                 |   |
|   |            |                                 |     |                                 | 0.30 [0.01; 10.18]; 0.504                                 |
| <b>Morbidity</b>  |            |                                 |     |                                 |   |
| 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] <sup>d)</sup> ; 0.170 <sup>e)</sup>     |
| DTG + 2 NRTI vs EFV + 2 NRTI                                    |            |                                 |     |                                 |   |
| SINGLE  | 414        | 5 (1.2)                         | 419 | 5 (1.2)                         | 1.01 [0.30; 3.47] <sup>d)</sup> no data available         |
| SPRING-1  | 51         | 1 (2.0)                         | 50  | 0 (0)                           | 2.94 [0.12; 70.56] <sup>d)</sup> no data available        |
| Total <sup>f)</sup>   |            |                                 |     |                                 | 1.19 [0.38; 3.68]; 0.763                                  |
| <b>Indirect comparison via bridge comparators<sup>g)</sup>:</b> |            |                                 |     |                                 |   |
| <b>DOR/3TC/TDF vs DTG + 2 NRTI</b>                              |            |                                 |     |                                 |   |
|   |            |                                 |     |                                 | 0.17 [0.01; 4.28]; 0.280                                  |
| Virological response (HIV-1 RNA < 50 copies/ml) <sup>h)</sup>   |            |                                 |     |                                 |   |
| 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                       |

<sup>1</sup> Data from the dossier evaluation of the IQWiG (A19-05) unless otherwise indicated.

| Endpoint category<br>Endpoint<br>Comparison<br>Study            | DOR or DTG |                                 | EFV |                                 | Group difference<br>RR [95% CI];<br>p value <sup>a)</sup> |                          |
|---|------------|---------------------------------|-----|---------------------------------|---|--------------------------|
|   | N          | Patients<br>with event<br>n (%) | N   | Patients<br>with event<br>n (%) |   |                          |
| SPRING-1  | 51         | 45 (88.2)                       | 50  | 36 (72.0)                       | 1.23 [1.00; 1.50] no<br>data available                    |                          |
| Total <sup>b)</sup>   |            |                                 |     |                                 | 1.12 [1.03; 1.20]; 0.005                                  |                          |
| <b>Indirect comparison via bridge comparators<sup>c)</sup>:</b> |            |                                 |     |                                 |   |                          |
| <b>DOR/3TC/TDF vs DTG + 2 NRTI</b>                              |            |                                 |     |                                 |   | 0.94 [0.84; 1.06]; 0.308 |

| Endpoint category<br>Endpoint<br>Comparison<br>Study            | DOR/3TC/TDF or<br>DTG + 2 NRTI |  |   | EFV+ 2 NRTI     |   |   | Group difference<br>MD [95% CI];<br>p value                |                 |
|---|--------------------------------|--|---|-----------------|---|---|--|-----------------|
|   | N <sup>i)</sup>                | Values<br>at the<br>start of<br>study<br>MV (SD) | Change at<br>the end of<br>study<br>MV (SD) | N <sup>i)</sup> | Values at<br>the start<br>of study<br>MV (SD) | Change at<br>the end of<br>study<br>MV (SD) |  |                 |
| <b>Morbidity</b>  |                                |  |   |                 |   |   |  |                 |
| CD4 cell count (cells/μl)                                       |                                |  |   |                 |   |   |  |                 |
| DOR/3TC/TDF vs EFV + 2 NRTI                                     |                                |  |   |                 |   |   |  |                 |
| 021   | 337                            | 435.9<br>(no data<br>available<br>)              | 237.7<br>[214.9;<br>260.6] <sup>j)</sup>    | 311             | 413.5 (no<br>data<br>available)               | 223.0<br>[198.4; 247.6] <sup>j)</sup>       | 14.7 [-18.7; 48.2];<br>no data available                   |                 |
| DTG + 2 NRTI vs EFV + 2 NRTI                                    |                                |  |   |                 |   |   |  |                 |
| SINGLE  | 414                            | 349<br>(158.2)                                   | 324<br>(205.7)                              | 419             | 351<br>(157.5)                                | 286<br>(196.0)                              | 43.95 [14.34;<br>73.55] <sup>k)</sup> no data<br>available |                 |
| SPRING-1  | 51                             | 327<br>(122.3)                                   | 338<br>(162.6)                              | 50              | 328<br>(106.5)                                | 321<br>(218.9)                              | 17.0 [-65.5; 99.5]<br>no data available                    |                 |
| Total <sup>l)</sup>   |                                |  |   |                 |   |   | 40.79 [12.98;<br>68.61];<br>0.004                          |                 |
| <b>Indirect comparison via bridge comparators<sup>m)</sup>:</b> |                                |  |   |                 |   |   |  |                 |
| <b>DOR/3TC/TDF vs DTG + 2 NRTI</b>                              |                                |  |   |                 |   |   |  | - <sup>n)</sup> |

| Endpoint category<br>Endpoint<br>Comparison<br>Study  | DOR or DTG    |                              | EFV |                              | Group difference<br>RR [95% CI];<br>p value <sup>a)</sup> |
|---|---------------|------------------------------|-----|------------------------------|---|
|   | N             | Patients with event<br>n (%) | N   | Patients with event<br>n (%) |   |
| <b>Health-related quality of life</b>   |               |                              |     |                              |   |
| 021   | Not collected |                              |     |                              |   |
| <b>Side effects</b>   |               |                              |     |                              |   |
| 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)                    | –   |
| <b>SAEs</b>   |               |                              |     |                              |   |
| DOR/3TC/TDF vs EFV + 2 NRTI   |               |                              |     |                              |   |
| 021   | 364           | 21 (5.8)                     | 364 | 30 (8.2)                     | 0.70 [0.41; 1.20];<br>0.194                               |
| DTG + 2 NRTI vs EFV + 2 NRTI  |               |                              |     |                              |   |
| SINGLE  | 414           | 44 (10.6)                    | 419 | 50 <sup>d)</sup> (11.9)      | 0.89 [0.61; 1.30]<br>no data available                    |
| SPRING-1  | 51            | 7 (13.7)                     | 50  | 7 (14.0)                     | 0.98 [0.37; 2.59]<br>no data available                    |
| Total <sup>b)</sup>   |               |                              |     |                              | 0.90 [0.63; 1.29];<br>0.569                               |
| <b>Indirect comparison via bridge comparators<sup>e)</sup>:</b>   |               |                              |     |                              |   |
| <b>DOR/3TC/TDF vs DTG + 2 NRTI</b>  |               |                              |     |                              |   |
|   |               |                              |     |                              | 0.78 [0.41; 1.48];<br>0.441                               |
| <b>Withdrawal because of AEs</b>  |               |                              |     |                              |   |
| DOR/3TC/TDF vs EFV + 2 NRTI   |               |                              |     |                              |   |
| 021   | 364           | 11 (3.0)                     | 364 | 27 (7.4)                     | 0.41 [0.21; 0.81];<br>0.010                               |
| DTG + 2 NRTI vs EFV + 2 NRTI  |               |                              |     |                              |   |
| SINGLE  | 414           | 14 (3.4)                     | 419 | 52 (12.4)                    | 0.27 [0.15; 0.48]<br>no data available                    |
| SPRING-1  | 51            | 2 (3.9)                      | 50  | 5 (10.0)                     | 0.39 [0.08; 1.93]<br>no data available                    |
| Total <sup>b)</sup>   |               |                              |     |                              | 0.28 [0.17; 0.49];<br>< 0.001                             |
| <b>Indirect comparison via bridge comparators<sup>e)</sup>:</b>   |               |                              |     |                              |   |
| <b>DOR/3TC/TDF vs DTG + 2 NRTI</b>  |               |                              |     |                              |   |
|   |               |                              |     |                              | 1.44 [0.60; 3.44];<br>0.414                               |
| a) Unless otherwise stated: two-sided p value (Wald test)<br>b) Model with fixed effect (Mantel-Haenszel)<br>c) Indirect comparison according to Bucher<br>d) Own calculation, asymptotic<br>e) Own calculation, unconditional exact test (CSZ method)<br>f) Own calculation, model with fixed effect (Mantel-Haenszel)<br>g) Own calculation, indirect comparison according to Bucher<br>h) Evaluation according to Snapshot algorithm (Study 021, SINGLE study) or TLOVR (SPRING-1 study) |               |                              |     |                              |   |

| Endpoint category<br>Endpoint<br>Comparison<br>Study  | DOR or DTG |                              | EFV |                              | Group difference<br>RR [95% CI];<br>p value <sup>a)</sup> |
|---|------------|------------------------------|-----|------------------------------|---|
|   | N          | Patients with event<br>n (%) | N   | Patients with event<br>n (%) |   |
| i) Number of patients evaluated at 96 weeks; values at start of study may be based on other patient numbers.<br>j) [95% CI]<br>k) Difference of adjusted mean values [95% CI] from MMRM model<br>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 [ $I^2 = 0$ ])<br>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<br>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<br>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:<br>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](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 <sup>2</sup> | €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

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<sup>2</sup> 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.