Doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®) for the treatment of adults infected with HIV-1

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 27 June 2019.

Zorginstituut Nederland carried out an assessment of the medicinal product doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®) and came to the following conclusion.

In a letter dated 12 February 2019 (CIBG-19-07666), the Minister of Health, Welfare and Sport (VWS) asked *Zorginstituut Nederland* to carry out a substantive assessment of whether the product Delstrigo® 100 mg/300 mg/245 mg film-coated tablet can be included in the Medicine Reimbursement System (GVS). In the letter, the Minister also asked for an assessment of Pifeltro® 100 mg film-coated tablets. Although both medicines contain doravirine, they do not have the same composition, which is why these two products are dealt with separately. This advice relates only to the assessment of Delstrigo®.

The HIV-inhibiting medicinal products have held a special place within the GVS since 2000. On 30 March 2000, a predecessor of the Minister indicated that all antiretroviral medicinal products for the treatment of HIV infection were, in principle, eligible for inclusion on List 1B of the Health Insurance Regulation. No pharmacoeconomic analysis is required for these medicinal products. This means no assessment of their interchangeability is needed.
As long as the Ministry's individual policy for HIV-inhibiting medicinal products remains in place, in these cases the *Zorginstituut* draws up an abbreviated report when assessing an HIV inhibitor for inclusion in the GVS (i.e. for placement on List 1B of the Health Insurance Regulation).

Starting point of the assessment
Delstrigo® is a combination product comprised of three active ingredients: doravirine 100 mg, lamivudine 300 mg and 300 mg, equivalent to 245 mg tenofovir disoproxil.
Delstrigo® is registered for the treatment of adults infected with human immunodeficiency virus 1 (HIV-1) without past or present evidence of resistance to the NNRTI-class, lamivudine or tenofovir.[1] [2] The dosage is 1 tablet once daily.

The manufacturer claims that for the treatment of HIV-1-infected adults without past or present evidence of resistance to the NNRTI-class, lamivudine or tenofovir, the therapeutic value of the fixed combination doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF; Delstrigo®) is equal to that of the fixed combination efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF; Atripla®). This applies both to treatment-naive patients and virologically suppressed patients.

Treatment guidelines on HIV-infections
The Dutch guidelines of the NVHB (Dutch Association of HIV Specialists) refers to the American guidelines of the DHHS (US Department of Health and Human Services) for the medicinal treatment of HIV infections.[3] [4] The NVHB does have one addition: if characteristics of the HIV-infected person permit the use of various first-choice treatment regimens, then costs should also be taken into

account.

The DHHS recommends the following for antiretroviral therapy in adult patients:

- The optimum antiretroviral treatment of therapy-naive patients is generally comprised of two NRTIs in combination with a third active antiviral medicinal product from one of these 3 classes: an integrase inhibitor (INSTI), and NNRTI, or a protease inhibitor (PI) with a pharmacokinetic booster.[‡] The following specific combinations are recommended, all involving an integrase inhibitor. These are, listed alphabetically:
  - bictegravir/tenofovir alafenamide/emtricitabine;
  - dolutegravir/abacavir/lamivudine(only for HLA-B*5701-negative patients);
  - dolutegravir plus tenofovir/emtricitabine;
  - raltegravir plus tenofovir/emtricitabine.

  Treatment takes place according to the resistance profile and ultimately the choice of a combination is determined based on patient characteristics and regimen-specific considerations. In specific situations, when opting for one of the first-choice combinations is inappropriate, an alternative combination can be considered. This could even be a combination with doravirine.
- According to the guidelines, antiretroviral therapy for therapy-experienced HIV-infected patients is highly individual. The basic principle of a switch to a different combination treatment is to recover or maintain virological suppression without endangering (excessively) future treatment options. No specific treatment is preferred.

Substantive assessment

Appendix 3 provided the Minister with background information about the intended and unintended effects of doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®) in comparison with comparable treatments. Appendix 4 reflects the costs (pharmacy purchase prices) of these comparisons.

Important outcomes of the assessment

- For the treatment of therapy-naive HIV-1 infected patients, doravirine was examined in 2 clinical studies.[6] [7] In the one study DOR/3TC/TDF (Delstrigo®) was directly compared with EFV/FTC/TDF (Atripla®) and in the second supportive study doravirine (Pifeltro®) was directly compared with darunavir, boosted with ritonavir, both in the presence of a background treatment. These 2 RCTs revealed that the efficacy of doravirine is not inferior to that of efavirenz or darunavir: more than 80% of the patients treated had a plasma HIV-1 RNA <50 copies/ml after 48 weeks of treatment. In general, the safety profile of doravirine (with or without 3TC/TDF) seems favourable. Tolerance of doravirine is better in comparison with efavirenz, and its tolerance is equal to – or possibly slightly better than – that of darunavir boosted with ritonavir.
- Doravirine was not directly compared with a first-choice treatment for the initial therapy of a HIV infection. The guidelines recommend specific combinations, all of which involve an integrase inhibitor. In previous assessments of integrase inhibitors (bictegravir and dolutegravir), the *Zorginstituut* concluded that a combination treatment with bictegravir or with dolutegravir has a therapeutic added value in comparison with efavirenz-emtricitabine-tenofovir (Atripla®).[9] [10] [11] According to the manufacturer, the

[‡] A summary of the abbreviations used can be found Appendix 1. The classification of HIV-inhibiting medicinal products per class can be found in appendix 2.

expected position of doravirine/tenofovir disoproxil fumarate/lamivudine for treatment-naive patients is limited.[5]

- In virologically suppressed patients, switching from the current antiretroviral treatment to DOR/3TC/TDF (Delstrigo®) leads to a similar response in comparison with continuing on the existing treatment. However, unclear is what effect doravirine has on patients who could not be virologically suppressed with the existing combination treatment.[8]
- Delstrigo® is cheaper than the first-choice treatment with an integrase inhibitor (€5,920 per patient per year for Delstrigo® versus €10,938 per patient per year for Biktarvy® [bictegravir/emtricitabine/tenofoviralafenamide] or Triumeq® [dolutegravir/abacavir/lamivudine]). As doravirine is not first-choice treatment, Delstrigo® is not expected to replace a combination treatment with bictegravir or with dolutegravir. For this reason, economies on the costs of an integrase inhibitor if Delstrigo® is included in the package are therefore not to be expected.
- In comparison with the combination containing efavirenz, Delstrigo® is not always more expensive: Delstrigo® will cost €5,920 per patient per year and the combination with emtricitabine/tenofovirdisoproxil/efavirenz costs €5,682 (generic) to €6,474 (Atripla®) per patient per year. Depending on the use of a generic, treatment with Delstrigo® is between €238 per patient per year more expensive and €554 per patient per year cheaper. In practice, both branded products and generics are used. In view of the limited use of doravirine, the additional costs are estimated to be minimal.

Summarising
For the initial treatment of HIV-1-infected adults, specific combinations are recommended, all including an integrase inhibitor.

Doravirine is an NNRTI and it is not regarded as first-choice treatment.
In comparison with the fixed combination EFV/FTC/TDF (Atripla® or generic) that is not regarded as first-choice treatment either, DOR/3TC/TDF (Delstrigo®) has the same therapeutic value. This applies both to treatment-naive patients and virologically suppressed (treatment-experienced) patients .

The costs of these combination treatments based on NNRTI are comparable. The *Zorginstituut* expects the effect of including Delstrigo® in the package to be cost-neutral.

***Zorginstituut Nederland*'s advice**
Delstrigo®, the fixed combination with doravirine/lamivudine/tenofovir disoproxil fumarate, can be included in the GVS on List 1B of the Health Insurance Decree.

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The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this

report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.

Appendix 1. **List of abbreviations**

Abbreviation	Name
3TC	lamivudine
aip	pharmacy purchase price
ABC	abacavir
BIC	bictegravir
cART	combination antiretroviral treatment (combination antiretroviral treatment)
CI	Confidence interval
DOR	doravirine
DRV/r	darunavir, boosted with ritonavir
DTG	dolutegravir
EFV	efavirenz
FTC	emtricitabine
GVS	Medicine Reimbursement System
hiv-1	human immunodeficiency virus-1
INSTI	integrase inhibitor
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
PI	protease inhibitor
RCT	Randomised Controlled Trial
STR	single tablet regimen
TDF	tenofovir disoproxil fumarate

Appendix 2. **Groups of medicines for the treatment of HIV infection**. Taxe February 2019.

Group of medicines	Substance name (proprietary name)
Integrase inhibitors (INSTIs)	dolutegravir (Tivicay®) elvitegravir* raltegravir (Isentress®)
NNRTIs	efavirenz (Efavirenz®, Stocrin®) etravirine (Intelence®) nevirapine (Nevirapine®, Viramune®) rilpivirine (Edurant®) [doravirine#]
NRTIs	abacavir (Ziagen®) didanosine (Videx®) emtricitabine (Emtriva®) lamivudine (Epivir®, Zeffix®, generics) stavudine (Zerit®) tenofovir (Viread®) zidovudine (Retrovir®)
Protease inhibitors	atazanavir (Reyataz®) darunavir (Prezista®) fosamprenavir (Telzir®) inidinavir (Crixivan®) ritonavir (Norvir®, generics) saquinavir (Invirase®)
Fusion inhibitors	enfuvirtide (Fuzeon®)
CCR5-antagonists	maraviroc (Celsentri®)
Fixed combination preparations	
- abacavir/lamivudine (Kivexa®, generics) - abacavir/lamivudine/zidovudine (Trizivir®) - bictegravir/emtricitabine/tenofoviralafenamide (Biktarvy®) - barunavir/cobicistat (Rezolsta®) - darunavir/cobicistat/emtricitabine/tenofoviralafenamide (Symtuza®) - dolutegravir/abacavir/lamivudine (Triumeq®) - dolutegravir/rilpivirine (Juluca®) - emtricitabine/tenofoviralafenamide (Descovy®) - emtricitabine/tenofoviralafenamide/elvitegravir/cobicistat (Genvoya®) - emtricitabine/tenofoviralafenamide/rilpivirine (Odefsey®) - emtricitabine/tenofovirdisoproxil (Truvada®, generics) - emtricitabine/tenofovirdisoproxil/efavirenz (Atripla®, generics) - emtricitabine/tenofovirdisoproxil/elvitegravir/cobicistat (Stribild®) - emtricitabine/tenofovirdisoproxil/rilpivirine (Eviplera®) - lamivudine/zidovudine (Combivir®, generics) - lopinavir/ritonavir (Kaletra®)	
NNRTI: non-nucleoside reverse transcriptase inhibitors NRTI: nucleoside reverse transcriptase inhibitors * elvitegravir is not available as a single preparation, only in the fixed combination preparations Stribild® and Genvoya®. # doravirine (Pifeltro®) and doravirin/tenofovirdisoproxil/lamivudine (Delstrigo®) are currently not available in the Netherlands (current assessment).	

Appendix 3. **Assessment of intended and unintended effects**

Doravirine is a new antiretroviral medicinal product belonging to the group of non-nucleoside reverse-transcriptase inhibitors (NNRTIs). The other active ingredients of Delstrigo®, i.e. lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), both belong to the group of nucleoside reverse-transcriptase inhibitors (NRTIs) and are known substances that have been used for some time as part of a combination treatment for HIV-infection.

Intended effects

The manufacturer has supplied 2 clinical studies to substantiate the intended effects of the substance doravirine on therapy-naive HIV-1 infected adults. Both randomised controlled trials (RCTs) had a non-inferiority (margin: 10%) set-up. Alongside the primary phase of 48 weeks of treatment, both studies will continue with the extension phase, up to a total duration of about 4 years.

One RCT (study P021) was carried out with Delstrigo® (DOR/3TC/TDF), in which Delstrigo® was directly compared with Atripla® (EFV/FTC/TDF).[6]
In the second RCT, Pifeltro® (DOR; study P018) was directly compared with darunavir boosted with ritonavir (DAR/r).[7] As part of their antiretroviral treatment, all patients also received 2 NRTIs as background treatment, the choice was Truvada® (FTC/TDF) or Kivexa® (ABC/3TC). This study was not carried out with the product Delstrigo® which is currently being assessed, but it did study the effects of the substance doravirine in therapy-naive HIV-1-infected adults. The results of this study are used as secondary evidence for substantiating its effiectiveness.

- The most important study for the registration of Delstrigo® is the DRIVE-AHEAD trial (P021) of Orkin et al.[6] In this RCT, adult HIV-1-infected patients, who were being treated for the first time with an antiretroviral treatment (therapy-naive patients), were randomised into 2 treatment groups. The intervention group (n =364) received Delstrigo® (DOR/3TC/TDF) and the control group received Atripla® (EFV/FTC/TDF). After 48 weeks of treatment, 84.3% (307/364) of the Delstrigo® users versus 80.8% (294/364) of the Atripla® users reached the primary outcome parameter (plasma HIV-1 RNA <50 copies/ml). The difference between these 2 groups (3.5%; 95% CI: -2.0 to 9.0) is statistically not significant. This study showed that for the treatment of therapy-naive HIV-1 patients, the fixed combination of DOR/3TC/TDF (Delstrigo®) is not inferior to the fixed combination of EFV/FTC/TDF (Atripla®).
- The supporting study (DRIVE-FORWARD study; Molina et al.; study P018) directly compared doravirine (DOR) with darunavir boosted with ritonavir (DRV/r; darunavir is a protease inhibitor).[7] All patients received FTC/TDF (Truvada®) or ABC/3TC (Kivexa®) as background treatment. After 48 weeks, 84% (321/385) of the intervention group with doravirine reached a plasma HIV-1 RNA <50 copies/ml, in the control group with DRV/r this was the case in 80% (306/384). The difference of 3.9% (95% CI: -1.6 to 9.4) is not statistically significant. Non-inferiority was also demonstrated in this study: for the treatment of therapy-naive HIV-1 patients, as addition to a background treatment, doravirine is not inferior to the protease inhibitor darunavir boosted with ritonavir.

A summary of the intended effects of doravirine in the clinical study is provided below.

Patients who were not previously treated (therapy-naive HIV-1 patients)			
Study [ref]	Intervention vs. control	Response (HIV-1 RNA <50 copies per ml) after 48 weeks	Difference (95% CI)
DRIVE-AHEAD, NCT02403674, P021, [Orkin 2018][6]	DOR/3TC/TDF (Delstrigo®) vs. EFV/FTC/TDF (Atripla®)	84.3% (307/364) 80.8% (294/364)	3.5% (-2.0 to 9.0) n.s.
DRIVE-FORWARD, NCT02275780, P018, [Molina 2018][7]	DOR (Pifeltro®) vs. DAR/r Background treatment in both arms: FTC/TDF (Truvada®) or ABC/3TC (Kivexa®)	84% (321/385) 80% (306/384)	3.9% (-1.6 to 9.4) n.s.

- According to the EPAR for Delstrigo®, the efficacy of doravirine at week 96 is consistent with that at week 48.[2] The effect on *viral load* (plasma HIV-1 RNA <50 copies/ml) persists.
- Number of patients who failed on the therapy due to developing resistance was very low in the doravirine group (P018 study; 1/383) and not reported in the group with DRV/v (0/383). In the P021 study, 6/364 of the doravirine (Delstrigo®) users and 12/364 in the efavirenz (Atripla®) group developed resistance. It is not clear whether this slightly higher number of documented resistance can be explained in part by the difference in the cytidine-analogues (lamivudine versus emtricitabine).
- The effect of doravirine on virologically suppressed HIV-patients was not described in more detail in the file. A new study about this was published during the assessment (April 2019).[8] This was an open-label non-inferiority study (margin: 8%) with 670 patients who were virologically suppressed for ≥6 months with a combination treatment comprised of 2 NRTIs supplemented with a boosted PI (atazanavir, darunavir or lopinavir), boosted elvitegravir, or an NNRTI (efavirenz, nevirapine, or rilpivirine). After randomisation, the patients were assigned to a group that was switched immediately to DOR/3TC/TDF (Delstrigo®; n=447; direct switch group) or the group that continued on the existing combination treatment (n=223) and after 24 weeks did switch to DOR/3TC/TDF (late switch group).
  After 24 weeks of treatment with DOR/3TC/TDF, the patients were still virologically suppressed. The effect is not inferior to continuing the current combination therapy. The measured response in the study (93.4% and 94.6% respectively) can be described as high. After 48 weeks of treatment with DOR/3TC/TDF (Delstrigo®), the response percentage was 90.8% (406/447). It should be commented that at t=48 weeks 9.1% (61/670) of the participants had left the study prematurely.

Therapy-experienced HIV-1 patients (≥6 months virologically suppressed)			
Study [ref]	Intervention vs. control	Response (HIV-1 RNA <50 copies per ml) at t=24 weeks	Difference (95% CI)
DRIVE-SHIFT trial; NCT02397096; [Johnson 2019][8]	switch to DOR/3TC/TDF (Delstrigo®) vs continuing current combination treatment	93.7% (419/447) 94.6% (211/223)	-0.9 [-4.7 to 3.0] n.s.

Unintended effects

For the assessment of safety, the CHMP studied the EMA data on 667 patients who had been exposed to 100 mg per day during at least 48 weeks. The most frequent side effects that may be, or probably are, linked to doravirine were nausea (6%) and headache (5%).[1] [2]

In general, the safety profile of doravirine (with or without 3TC/TDF) seems favourable. Tolerance of doravirine is better in comparison with efavirenz, and its tolerance is equal to – or possibly slightly better than – that of darunavir boosted with ritonavir.
In comparison with efavirenz, patients who were treated with doravirine had fewer neuropsychiatric side effects, a lower risk of skin rashes and a more favourable lipid profile. In comparison with DRV/r, patients treated with doravirine had a more favourable lipid profile and fewer gastro-intestinal adverse effects. Respiratory symptoms, such as coughing, occur more frequently in the doravirine-groups, but these could be random effects.[2]

Discussion of the intended and unintended effects

- For optimum antiretroviral treatment of therapy-naive patients, the guidelines recommend a combination treatment with two NRTIs and an integrase inhibitor (bictegravir, dolutegravir or raltegravir). The group with NNRTIs is no longer recommended as first-choice treatment for therapy-naive HIV-infected adults. This group has not been reverted to an alternative option (not a first-choice).
- Doravirine was not studied in a direct comparison with a first-choice integrase inhibitor. The effect of doravirine in comparison with the first-choice treatment was therefore determined indirectly.
- In previous assessments of HIV-inhibiting medicinal products from the group of integrase inhibitors, the *Zorginstituut* concluded that a combination treatment with bictegravir or with dolutegravir has a therapeutic added value in comparison with efavirenz-emtricitabine-tenofovir (Atripla®). For further information, see our assessment reports on Biktarvy® and Tivicay®.[9] [10] [11]
- In comparison with other NNRTIs (efavirenz and darunavir), the efficacy of doravirine did not prove inferior in 2 RCTs: more than 80% of the patients treated had a plasma HIV-1 RNA <50 copies/ml after 48 weeks.
- The (international) guidelines show that combination therapies with an integrase inhibitor are recommended. The integrase inhibitors bictegravir and dolutegravir are generally well tolerated, and they do not have the adverse effects (such as neuropsychiatric adverse effects) reported with efavirenz.
- In virologically suppressed patientt, switching from the current antiretroviral treatment to a treatment with DOR/3TC/TDF (Delstrigo®) leads to a similar response in comparison with continuing on the existing treatment. Non-

inferiority was demonstrated between both groups in the open-label study.[8]

- Doravirine can only be used on patients infected with HIV-1, without past or present evidence of resistance to the NNRTI-class. This means that doravirine cannot be a replacement within the group of NNRTI. It is not clear what effect doravirine has on patients who could not be virologically suppressed with the existing treatment.

Appendix 4. **Costs**

The marketing authorisation holder of Delstrigo® proposes registering this product in the G-standard of the Z-index at a maximum pharmacy purchase price (aip) of €660.00 for a package of 30 tablets (Source: MSD file, January 2019). In the addendum to the file (MSD, 2 May 2019), the marketing authorisation holder states that the aip will be amended to €486.60 for a package of 30 tablets.[5] At a dose of 1 tablet once daily, the costs amount to €16.22 per patient per day, excluding 9% VAT and delivery charge. This amounts to €5,920.30 per patient per year (365 days).

Combination antiretroviral treatment (cART), in the form of a single tablet regimen	Proprietary name	Price per patient per year
doravirine/lamivudine/tenofovir disoproxil fumarate	Delstrigo®	€5,920.30

For the comparison, below are the aip (Source: G-standard, Taxe May 2019) of a number of combinations of antiretroviral treatments. These are examples with a single tablet regimen (STR), i.e. fixed combinations with a dose of 1 tablet once daily. Other costs, other than the costs of the medicines, remain the same.

Combination antiretroviral treatment (cART), in the form of a single tablet regimen	Proprietary name	Price per patient per year
bictegravir/emtricitabine/tenofoviralafenamide*	Biktarvy®	€10,937.78
dolutegravir/abacavir/lamivudine*	Triumeq	€10,937.78
emtricitabine/tenofovirdisoproxil/efavirenz	Atripla	€6,474.01
emtricitabine/tenofovirdisoproxil/efavirenz	generic	€5,681.83
** a first-choice treatment, recommended by the guidelines.*		

Delstrigo® is cheaper than the first-choice treatment with an integrase inhibitor (€5,920 per patient per year for Delstrigo® versus €10,938 per patient per year for Biktarvy® or Triumeq®). As doravirine is not first-choice treatment, Delstrigo® is not expected to replace a combination treatment with bictegravir or with dolutegravir. For this reason, economies on the costs of an integrase inhibitor if Delstrigo® is included in the package are therefore not to be expected.

In comparison with the combination containing efavirenz (not a first-choice treatment), the costs of Delstrigo®, after the proposed price reduction, are within range of one another. Delstrigo® will cost €5,920 per patient per year and the combination with emtricitabine/tenofovirdisoproxil/efavirenz agreement costs €5,682 (generic) to €6,474 (Atripla®) per patient per year. Depending on the use of a generic, treatment with Delstrigo® is between €238 per patient per year more expensive and €554 per patient per year cheaper.

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