Pharmacotherapeutic report, summary

Dolutegravir (Tivicay®) for the indication 'infection with HIV-1'

Approved on 28-7-2014 by Zorginstituut Nederland, based on an evaluation by the WAR (Scientific Advisory Committee)

The WAR has approved a pharmacotherapeutic report for the medicine dolutegravir (Tivicay®). In determining its therapeutic value, dolutegravir was compared with the standard treatments or usual treatments for HIV-1 infection in adults. They reached the following conclusion.

- for the treatment of HIV-1 infected adults and adolescents aged 12-18 years, who are previously untreated with antiretroviral drugs, a dolutegravir-containing combination treatment has an **added therapeutic value** in comparison to efavirenz-emtricitabine-tenofovir (Atripla®) and an **equal therapeutic value** in comparison to darunavir-ritonavir-emtricitabine-tenofovir.
- for the treatment of HIV-1 infected adults and adolescents from the age of 12 years, who were previously treated with antiretroviral drugs but not with an integrase inhibitor, dolutegravir as part of a combination treatment has a **therapeutic added value** in comparison to a combination treatment containing raltegravir.
- for the treatment of HIV-1 infected adults with resistance to raltegravir and/or elvitegravir, dolutegravir has an **added therapeutic value** in comparison to the usual treatment.

Medicine. Dolutegravir tablet (Tivicay®). Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir.

Registered indication. Dolutegravir, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus (HIV infection) infected adults and adolescents above 12 years of age.

Posology. Once daily, 50 mg (1 tablet) orally in HIV-1 infected patients without resistance to the class of integrase inhibitors. For HIV-1 infected patients who are resistant to the integrase class (documented or clinically suspected), and for patients treated simultaneously with some drugs (e.g., efavirenz, nevirapin, tipranavir/ritonavir, rifampicin): twice daily, 1 50-mg tablet.

Mechanism of action. Dolutegravir is an *integrase strand transfer inhibitor* (INSTI) of HIV-1. Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of DNA integration which is essential for the HIV replication cycle. Its combination with other antiretroviral agents inhibits the virus in a number of ways. The combination has a synergistic effect.

Specific details.

- the registered indication of dolutegravir is not limited to a specific type of HIV-virus; in principle it comprises treatment of an infection with both HIV-1 and HIV-2. As no clinical research data are available on dolutegravir in HIV-2 infected patients, the registration-holder's claim for this application is limited to the use of dolutegravir for HIV-1 infection.
- on 26 June, the CHMP issued a positive opinion on the product Triumeq®, a combination product with dolutegravir, abacavir and lamivudine.

Summary of the therapeutic value

Intended effects. A combination treatment with dolutegravir is no less effective than the standard treatment for a therapy-naive HIV-1 infected adult. For the assessment a direct comparison was made with emtricitabine-tenofovir-efavirenz (FTC-TDF-EFV; Atripla®) and with emtricitabine-tenofovir, darunavir and ritonavir (FTC-TDF-DRV/r). The percentage of patients with a virological response (i.e., in whom a plasma HIV-1 RNA <50 copies/ml was achieved) after 48 weeks treatment with dolutegravir was almost 90%; this effect is not inferior to that of the standard treatments.
A dolutegravir-containing regime was more effective than a raltegravir-containing regime in the treatment of therapy-experienced, but integrase inhibitor-naive patients aged 12 years or older. A virological response was measured in 71% of the patients treated with dolutegravir and in 64% of those using raltegravir, a significant difference of 7.4% (P=0.03).
Dolutegravir proved efficacious in the treatment of HIV-1 infected patients aged 18 years or older with resistance to raltegravir and/or elvitegravir. Replacing raltegravir/elvitegravir by dolutegravir, in combination with optimised background regimen, leads to a plasma HIV-1 <50 copies/ml (virological response) in 64% of the patients after 24 weeks treatment.

Unintended effects. The most frequently reported unintended effects during treatment with dolutegravir were nausea, diarrhoea and headache. The most severe unintended effect seen in an individual patient was a hypersensitivity reaction with skin rash and severe liver effects. The unintended effects of a dolutegravir-containing combination treatment do not essentially differ from those of the treatments with which it was compared. There was a different in therapy discontinuation due to unintended effects. More patients ceased treatment with emtricitabine-tenofovir-efavirenz (Atripla®) due to neuropsychiatric adverse effects than those in the group using dolutegravir. No resistance to dolutegravir was established in the clinical studies with therapy-naive patients; the number of reported cases of *de novo* resistance was not larger among therapy-experienced patients in the dolutegravir-group than in the control group. Data on the safety of dolutegravir among adolescents aged 12-18 years is limited.

Experience. Experience with dolutegravir and elvitegravir is limited. Sufficient experience has been obtained with efavirenz, emtricitabine, tenofovir, darunavir, abacavir, lamivudine and raltegravir, and ample experience has been gained with ritonavir.

Applicability. Dolutegravir is generally well tolerated and can be put to broad use.
No dose adjustment was considered necessary for patients with mild, moderate or severe renal impairment (creatinine clearance <30 ml/min, not on dialysis) or for patients with a moderately severe hepatic impairment (Child-Pugh class B). Dolutegravir is registered for people aged 12 years or older who are infected with a human immunodeficiency virus. Dolutegravir can be used

on therapy-naive patients, therapy-experienced patients and on patients who have developed resistance to raltegravir or elvitegravir. The activity of dolutegravir is considerably compromised by viral strains with Q148-mutation, if these are accompanied by >2 secondary mutations of G140A/C/S, E138A/K/T, L741.

Ease of use. There are no major differences between dolutegravir and other antiretroviral drugs with which it was compared. All these drugs are taken orally with a frequency of 1 to 2 times daily.

Final conclusion on therapeutic value.
For the treatment of HIV-1 infected adults and adolescents aged 12-18 years who have not been treated previously with antiretroviral drugs, treatment with a dolutegravir-containing combination has a therapeutic added value compared to efavirenz-emtricitabine-tenofovir (Atripla®) and its therapeutic value is comparable to that of darunavir-ritonavir-emtricitabine-tenofovir. The results show that dolutegravir is not inferior to the standard treatments with which it was compared in respect of virological response (i.e. plasma HIV-1 RNA <50 copies/ml) after treatment lasting 48 weeks. The adverse effects of treatment with efavirenz-emtricitabine-tenofovir are greater than those of the combination with dolutegravir; the adverse effects of treatment with darunavir-ritonavir-emtricitabine-tenofovir are comparable to those of a combination treatment with dolutegravir. There are no significant differences in applicability and ease of use between a regime containing dolutegravir and the treatments with which it was compared. Experience with dolutegravir is more limited than with the drugs with which it was compared.

The therapeutic value of using dolutegravir to treat therapy-experienced, but integrase inhibitor-naive, HIV-1 infected patients aged 12 years and older with a combination treatment is greater than that of the usual treatment. The dolutegravir-containing regime is more effective in achieving a virological response.

Treating HIV-1 infected adult patients aged 18 years and older who are resistant to raltegravir and/or elvitegravir with dolutegravir in combination with an optimised background regimen has an added therapeutic value. The efficacy of the combination treatment has been demonstrated in this group who have no further treatment options.

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