# Dolutegravir in HIV-1 infection: Added benefit in adult patients

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Dolutegravir has been approved since January 2014 in combination with other antiretroviral drugs for the treatment of human immunodeficiency virus (HIV) infected adults and adolescents above 12 years of age. In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) now examined whether the new drug offers an added benefit over the appropriate comparator therapy.

The dossier compiled by the drug manufacturer provided proof of a considerable added benefit in adults without pretreatment and an indication of a minor added benefit in pretreated adults who require integrase inhibitors (INIs) (i. e. whose treatment should include an INI). These patients have fewer side effects with the new drug than with the respective comparator therapy.

No added benefit could be determined for pretreated adults who do not require INIs (i. e. in whom no integrase inhibitor is indicated) and for adolescents above 12 years of age, because there were no study data.

**Comparator therapy depends on pretreatment and age**

Dolutegravir is a so-called integrase inhibitor (INI) and aims to prevent the integration of viral DNA into the nucleus of human cells. The Federal Joint Committee (G-BA) distinguished between adults and adolescents depending on the pretreatment, and specified different appropriate comparator therapies for the different patient groups:

In adults without pretreatment (treatment-naive), dolutegravir was to be compared with efavirenz (NNRTI drug class) in combination with two nucleoside/nucleotide analogues (NRTI drug class), tenofovir plus emtricitabine or abacavir plus lamivudine. In treatment-naive adolescents, the new drug was to be compared with efavirenz in combination with abacavir plus lamivudine.

For adolescents and adults who have already been treated for HIV-1 with other drugs, the G?BA specified an individual antiretroviral treatment depending on their prior therapy and the reason for the treatment switch. Particularly treatment failure because of a lack of antiviral effect (possibly associated with resistance of the virus to some drugs) or side effects were relevant.

In case of resistance to other drug classes in pretreated patients, treatment should include a drug of a further drug class. When resistance to NRTIs or NNRTI has been proven, for example, an INI is a commonly chosen treatment.

**Treatment-naive adults: considerable added benefit**

Two randomized controlled trials (RCTs), SPRING-1 and SINGLE, with a study duration of 96 weeks each and a total of almost 1000 study participants, were included in the assessment. The results of these 2 studies showed no differences between the treatment groups with regard to mortality and morbidity.

Neither HIV symptoms nor the outcome "quality of life" was recorded in the SPRING-1 study, and the SINGLE study produced no evaluable data for these two outcomes. Hence an added benefit of dolutegravir is not proven for these patient-relevant outcome criteria.

Untreated adults had noticeably fewer side effects under dolutegravir, however: Study discontinuations due to side effects and skin rash occurred less frequently in both sexes, and in men, nervous system disorders were less common under treatment with dolutegravir.

As no indication of considerably worse results can

be inferred from the data on morbidity in treatment-naive adults, proof of a considerable added benefit can be derived for dolutegravir in the overall assessment of the results on side effects.

**Different comparator therapies depending on individual pretreatment**

In the only study (SAILING) that investigated pretreated adults, dolutegravir was compared with another INI (raltegravir). The study participants were not pretreated with INIs and all of them had resistance to various drugs. They received dolutegravir or raltegravir in addition to an individual antiretroviral treatment, which depended on the respective resistance and which was already individually specified before randomization.

**Pretreated adults requiring INI: minor added benefit**

In pretreated adults with HIV-1 infection with mandatory INI treatment, the study groups in the SAILING study did not differ with regard to mortality and symptoms (morbidity). HIV symptoms were not recorded in the study, which also produced no evaluable data on quality of life. Hence no added benefit of dolutegravir can be determined for these patient-relevant outcomes.

However, dolutegravir had advantages with respect to side effects for patients who require INIs: Severe side effects like infection were less common, and nervous system disorders were also less frequent in patients over the age of 50 years. Overall, there is an indication of a minor added benefit of dolutegravir because there were fewer side effects than under the comparator therapy.

In contrast, no conclusions can be derived from the results of the SAILING study for pretreated patients in whom INI was possible but not mandatory.

**No data on adolescents**

As no study could be identified that investigated HIV-1 infected adolescents aged 12 years or older – neither treatment-naive nor pretreated – there were no data on the comparison of dolutegravir with the appropriate comparator therapy. Hence an added benefit of dolutegravir is not proven for adolescent patients.

**G-BA decides on the extent of added benefit**

The dossier assessment is part of the overall procedure for early benefit assessments supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and result in a change to the benefit assessment. The G-BA decides on the extent of the added benefit, thus completing the early benefit assessment.

Provided by Institute for Quality and Efficiency in Health Care

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