

**AWMSG Secretariat Assessment Report – Limited submission****Dolutegravir (Tivicay®) 5 mg dispersible tablets**

Company: ViiV Healthcare UK Ltd.

Licensed indication under consideration: In combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg.

Marketing authorisation date: 11 January 2021

Comparator(s)

- Dolutegravir (Tivicay®) film-coated tablets
- Raltegravir (Isentress®) granules for oral suspension or chewable tablets

Limited submission details

The limited submission criteria were met based on:

- New formulation with a pro-rata or lower cost per treatment.
- Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.
- Estimated small difference in cost compared to comparator(s).

Clinical effectiveness

- Dolutegravir (Tivicay®) is the first integrase inhibitor (INI) available as a dispersible tablet for children weighing at least 3 kg and from four weeks of age.
- The All Wales Medicines Strategy Group (AWMSG) has previously recommended dolutegravir film-coated tablets in combination with other antiretroviral treatments (ART), as an option for use for the treatment of HIV infected adults, adolescents and children aged 6 years or older.
- This submission is for a dispersible tablet formulation of dolutegravir and the indication includes treatment of HIV-1 infection in children ≥ 4 weeks old and weighing at least 3 kg.
- The company's submission includes evidence from two ongoing clinical studies. P1093 (ING112578) is a phase I/II multicentre, open-label, pharmacokinetic, safety and dose-finding study of dolutegravir plus optimised background regimen in HIV-1-infected patients aged ≥ 4 weeks to < 18 years ($n = 161$) who are treatment-naïve or treatment-experienced but INI-naïve. The primary objective was to determine the appropriate dose of dolutegravir for use in paediatric patients with HIV-1 infection; the formulation used in the study varied depending on the age of the patient. Dispersible tablets were given to children aged ≥ 4 weeks to < 12 years.
- ODYSSEY (201296) is a 96-week phase II/III, multicentre, open-label, non-inferiority study designed to assess the efficacy, pharmacokinetics and

Dolutegravir (Tivicay®). Reference number 4611.



Clinical effectiveness

- safety of dolutegravir-based antiretroviral therapy for HIV-1 infection in treatment-naïve and treatment-experienced patients aged ≥ 4 weeks to 18 years ($n = 792$). Patients were randomised (1:1) to receive either dolutegravir (dispersible or film-coated tablets) plus two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) or standard of care. A total of [commercial in confidence figure removed] patients (aged ≥ 4 weeks to < 12 years) received dolutegravir dispersible tablets. The study also included pharmacokinetic sub-studies to evaluate WHO paediatric weight-band dosing.
- The ODYSSEY study met its primary endpoint. Dolutegravir-based HIV-1 treatment combinations were superior compared to standard-of-care regimens in preventing treatment failure by Week 96.
 - Pharmacokinetic modelling and analysis were performed on pooled data from P1093 and ODYSSEY sub-studies across different paediatric age groups. The CHMP considered the modelling supported the proposed dosing regimen of dolutegravir dispersible tablets for all body weights given the plasma levels are similar to those observed in adults.
 - The P1093 study was not powered for efficacy analyses to be performed. The CHMP considered it acceptable to extrapolate efficacy and safety from adults to paediatric patients based on a pharmacokinetic bridge to the adult data. The CHMP concluded that extrapolating efficacy data from adults to children showed exposure is comparable, supporting dolutegravir dispersible tablets for use in patients aged ≥ 4 weeks of age.
 - The safety profile of dolutegravir is well-established. Studies P1093 and ODYSSEY showed that dolutegravir dispersible tablets were generally well tolerated. Most adverse events were mild to moderate and there were no new or unexpected safety concerns. The CHMP concluded that the safety profile of dolutegravir dispersible tablets in paediatric HIV patients aged ≥ 4 weeks is consistent with the known safety profile of dolutegravir film-coated tablets in adults.
 - The bioavailability of dolutegravir film-coated tablets and dispersible tablets is not comparable. The tablets are not interchangeable on a milligram per milligram basis due to differing pharmacokinetic profiles. Dolutegravir dispersible tablets deliver higher plasma exposure than dolutegravir film-coated tablets; therefore, a dose adjustment is necessary when switching between the two dosage forms.
 - The applicant company suggests the dispersible formulation is most likely to be used in children. It may also be used in some adolescents and adults who may have difficulty swallowing tablets.

Budget impact

- The company anticipates dolutegravir dispersible tablets would be used mainly in the paediatric population and estimates 30 patients (aged < 18 years) in Wales would be eligible for treatment each year. This is based on 2019 HIV prevalence and incidence data for Wales reported by Public Health England.
- Assuming a market uptake of [commercial in confidence figure removed], approximately [commercial in confidence figure removed] patients per year would receive dolutegravir dispersible tablets in each of the next five years. The company's rationale for the fixed annual market share was that it expects the number of children treated each year to decrease as children transition into adult care above the age of 18 years and also due to a falling incidence rate of HIV-1 infection diagnosed in children.

- The cost of treatment differs according to a patient's weight. The annual cost per patient for dolutegravir dispersible tablets and each of the comparators was calculated based on the average weight across different age bands.
- Based on the company's market share projections, dolutegravir dispersible tablets are assumed to partly displace dolutegravir film-coated tablets (main comparator) and raltegravir granules for oral suspension and chewable tablets. The net medicine acquisition cost of introducing dolutegravir dispersible tablets is estimated to be [commercial in confidence figure removed] each year from Year 1 to Year 5, based on the approved Wales Patient Access Scheme (WPAS) prices for dolutegravir dispersible and film-coated tablets and the list price for raltegravir formulations.
- The company's scenario analysis suggests the net medicine acquisition cost increases to [commercial in confidence figure removed] each year if dolutegravir dispersible tablets only displace the raltegravir formulations in patients aged < 10 years. The company anticipates this is the likely age group for dispersible tablets usage.
- The company's estimates vary depending on which comparator is displaced. However, overall the budgetary impact is anticipated to be minimal.

Additional information

- AWTTTC is of the opinion that, if recommended, dolutegravir (Tivicay[®]) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.
- The company anticipates that dolutegravir (Tivicay[®]) may be supplied by a home healthcare provider.

Evidence search

Date of evidence search: 7 and 12 April 2021

Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTTC at AWTTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Dolutegravir (Tivicay[®]) 5 mg dispersible tablets. Reference number: 4611. August 2021.