Raltegravir 600 mg once-daily

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Background

Raltegravir is an integrase strand transfer inhibitor (InSTI) which interferes with the human immunodeficiency virus (HIV) integrase enzyme responsible for transfer of virally encoded DNA into the host genome, thus limiting the ability of the virus to replicate and infect new cells.\(^1\)\(^,\)\(^4\) In 2007, raltegravir 400 mg film-coated tablets (Isentress®, MSD Ltd) were approved for twice-daily use in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infection in adults, adolescents, children, toddlers and infants from the age of four weeks weighing at least 25 kg.\(^3\) In September 2017, a 600 mg once-daily tablet formulation of raltegravir (Isentress®, MSD Ltd) was launched in the UK in order to reduce the pill burden and offer a more convenient treatment option.\(^2\) The 600 mg film-coated tablets are indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infection in adults, and paediatric patients weighing at least 40 kg. The recommended dosage is 1200 mg (two 600 mg tablets) once-daily for treatment-naïve patients or patients who are virologically suppressed on an initial regimen of raltegravir 400 mg twice daily.

This bulletin reviews the new once-daily raltegravir 1200 mg regimen (two 600 mg tablets taken once-daily) and compares this to the existing 400 mg twice-daily regimen.

Product comparison

The 600 mg once-daily film coated tablets contain the active substance raltegravir as potassium salt, which is identical to that used in the original 400 mg tablets.\(^2\)\(^,\)\(^3\) However, the 400 mg tablets should not be used to administer the 1200 mg once daily regimen.

In terms of appearance, the 600 mg tablets are yellow, oval-shaped, film-coated tablets with Merck logo and “242” on one side and plain on the other side. The 400 mg tablets are pink, oval-shaped, film-coated tablets with “227” on one side. Both products are currently available in packs of 60 tablets. Storage and handling requirements are identical.

Pharmacokinetics

Two open-label phase 1 studies in healthy male and female subjects were conducted to examine the relative single-dose and steady-state pharmacokinetic properties of the 1200 mg dose using the two tablet strengths in fasted and fed states.\(^1\)\(^,\)\(^5\) The new 600 mg tablet had a higher relative bioavailability compared with the 400 mg tablets, which is likely due, at least in part to improvements in tablet disintegration/dissolution. However, once absorbed, both dosage forms of raltegravir exhibited similar systemic pharmacokinetics with steady-state generally reached in around two days, and little to no accumulation with multiple-dose administration. Food had no clinically relevant effect on raltegravir exposure.

Clinical efficacy

The efficacy of the new strength and dosing regimen was evaluated in a single, randomised, double-blind, parallel-group, phase 3, non-inferiority study (ONCEMRK).\(^1\)\(^,\)\(^6\) Subjects eligible for this 96-week multicentre study were adults (aged ≥18 years) with a HIV-1 RNA of ≥1,000 copies per mL within 60 days of study treatment, and no prior use of ART antiretroviral therapy for treatment of HIV-1 infection. Subjects with acute hepatitis, symptoms of other active infection, or
resistance to any of the study regimen components were excluded. Participants received either raltegravir 1200 mg (two 600 mg tablets) once-daily or raltegravir 400 mg (one tablet) twice-daily, in addition to a fixed combination of tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) taken orally with food once daily. Randomisation was stratified by screening HIV-1 viral load, and by hepatitis B or C co-infection status. The primary efficacy endpoint was the proportion of subjects achieving HIV-1 RNA <40 copies per mL at week 48. Non-inferiority was concluded if the lower bound of the two-sided 95% confidence interval was greater than -10%. The secondary efficacy endpoint was the mean change from baseline in CD4 cell count at week 48.

During double-blind treatment, the total follow-up for subjects with raltegravir 1200 mg once-daily (n=531) was 516 patient-years and for raltegravir 400 mg twice-daily (n=266) was 258 patient-years. At week 48, the proportion of subjects in the full analysis set (all randomized and treated) achieving HIV-1 RNA <40 copies per mL were 88.9% and 88.3%, respectively (treatment difference 0.51% [95% CI: -4.2 to 5.2]). Since the lower bound of the 95% CI falls within the pre-specified -10% non-inferiority margin the once-daily regimen was shown to be non-inferior to the twice-daily regimen. In the retrospectively defined per protocol population, the proportion of subjects achieving HIV-1 RNA <40 copies per mL were 93.2% and 91.3%, respectively (treatment difference 1.89% [95% CI: -2.25 to 6.03]). Reductions in viral load were rapid in both treatment groups, with a similar time to virological response. The mean change from baseline in CD4 cell counts at week 48 was around 230 cells/µL in both treatment groups. The improvements in CD4 cell counts were generally consistent across demographic groups and baseline prognostic factors. Protocol-defined virological failure occurred in 7% of subjects in both treatment groups before week 48, and was equally divided between non-response and virological rebound after initial response.

Analysis of treatment compliance was self-reported by subjects by means of an electronic study medication diary (eDiary). The average days of treatment duration were similar between groups at approximately 390 days. However, the double-dummy design of ONCEMRK, in which all subjects received the same number of tablets, meant this trial was unable to compare or assess overall treatment compliance in relation to the once-daily versus twice-daily regimen.

Safety
The once-daily raltegravir 1200 mg regimen was generally well tolerated and displayed a similar safety profile to that of the 400 mg twice-daily regimen when each was used in combination with tenofovir disoproxil fumarate and emtricitabine. Up to week 48, adverse events (AEs) occurred in 83% of subjects in the once-daily group, and 87% of subjects in the twice-daily group. Adverse events occurring in ≥2 percent of subjects in either treatment group included abdominal pain, diarrhoea, vomiting, and decreased appetite. Adverse events considered to be associated with immune reconstitution syndrome occurred in 2% of once-daily recipients, and 1% of twice-daily recipients. Serious AEs occurred at lower rate in the in once-daily group (6% vs 9%, respectively). Discontinuation due to AEs was low in both treatment groups at 1% and 2%, respectively.

The once-daily and twice-daily regimens were associated with comparable rates of drug-related AEs (25% vs. 26%, respectively). Serious drug-related AEs (0.2% vs. 0.8%) and discontinuations due to any drug-related AE (0% vs 0.8%) were marginally lower in once-daily recipients. The most common drug-related AEs in either treatment group were nausea, headache and dizziness. Decreased appetite and abdominal pain occurred at least 2% more frequently in the once-daily group than in the twice-daily group, but these events were generally mild, self-limiting and did not lead to treatment discontinuation. There were three fatal AEs in the
study, two in the once-daily group, and one in the twice-daily group. However, none of these events were considered to be drug related. Drug-related laboratory anomalies occurred in 1.5% of subjects in both treatment groups, and none were serious. Overall, the safety profile of once-daily raltegravir was not affected by the presence of hepatitis B or C co-infection, and the incidence of AEs were generally similar in patient sub-groups based on gender, age, ethnicity and race.

Interchangeability, substitution and switching of products

The raltegravir 1200 mg (two 600 mg tablets) once-daily regimen demonstrated comparable efficacy and safety to that of the 400 mg twice-daily regimen when used in combination with tenofovir disoproxil fumarate and emtricitabine across a variety of patient populations. At the time of publication, the 600 mg tablet allows once-daily dosing (1200 mg once-daily) at no additional cost compared with raltegravir 400 mg tablets administered twice-daily.

The raltegravir 600 mg and 400 mg tablets are not interchangeable as the two formulations have different pharmacokinetic profiles, and there are some important differences in the drug interaction profiles. Co-administration of raltegravir 600 mg with calcium carbonate antacids, rifampin, tipranavir/ritonavir, or etravirine is not recommended. These recommendations are contrary to the current recommendations for raltegravir 400 mg which may be co-administered with each of these medications, with or without dosage adjustment. The 400 mg tablets should not be used to create a 1200 mg once-daily dose. Similarly, the chewable tablets used in paediatric patients should not be substituted for by either the 600 mg or 400 mg tablets.

The ONCEMRK trial did not include HIV-1 infected subjects who were virologically suppressed at baseline. Therefore, there are no clinical data from this study to support the use of the once-daily regimen as a switch regimen. However, in accordance with the licensed indication, there is no reason to exclude treatment-experienced patients from raltegravir 600 mg, as the efficacy and safety of the 400 mg tablets is well established in these patients. 7,9

The comparative efficacy and safety of the once-daily and twice-daily regimens has not been evaluated in combination with background therapies other than tenofovir disoproxil fumarate and emtricitabine. However, the efficacy profile of the raltegravir 400 mg tablets is established with alternative backbone therapy in clinical practice, and there is no reason to assume the new strength and dosing regimen would have a different effect. 1,3,6,9

The efficacy and safety of once-daily raltegravir has not been evaluated in paediatric patients. However, pharmacokinetic modelling and simulation support the use of once-daily raltegravir 1200 mg (2 x 600 mg) in paediatric patients weighing at least 40 kg. 1,2
References


https://www.medicines.org.uk/emc/medicine/20484/SPC/.


Search strategy
In order to ensure sufficient coverage of the relevant literature, all searches were undertaken using Medline, Embase and PubMed from 1946 to present. Key words included raltegravir, Isentress, L900612, and MK-0518. Records were limited to those in English language.

In addition to the primary literature searches, the websites of the European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA), and the Food and Drug Administration (FDA) were searched for relevant assessment reports, Summary of Product Characteristics and safety reviews.

Google search terms: raltegravir, Isentress, Isentress HD.

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