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Health Technology Briefing
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Doravirine-islatravir for managing HIV-1 infection in people who are virally suppressed on antiretroviral therapy

Company/Developer	Merck, Sharp and Dohme

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 37510	NICE ID: Not Available	UKPS ID: 671490

Licensing and Market Availability Plans

In phase III clinical development.

Summary

Doravirine-islatravir is in development for the management of patients with human immunodeficiency virus 1 (HIV-1) who have a low level of HIV in their body, due to treatment with medications called antiretroviral therapy. HIV-1 is a virus that attacks the cells of the immune system. Damage to the immune system caused by HIV-1 can cause acquired immunodeficiency syndrome (AIDS), which is a chronic and potentially life-threatening condition. Symptoms of AIDS can include weight loss, chronic diarrhoea, night sweats, fever, persistent cough, mouth and skin problems, regular infections and serious illness or disease. Current treatment for HIV-1 includes antiretroviral therapies that may require taking multiple tablets daily, which can lead to problems with treatment adherence. Some people may also develop resistance to certain antiretroviral therapies, leading to disease progression.

Doravirine and islatravir, which is given as a single oral tablet once daily, inhibits reverse transcriptase (RT), an enzyme that allows HIV-1 to replicate. These technologies inhibit RT using different mechanisms, which reduces the chance of HIV-1 becoming resistant to the combination. Previous trials have found that doravirine-islatravir is as effective as other combinations of drugs used to manage HIV. If licensed, doravirine-islatravir would offer an additional treatment option to patients with HIV-1 who are virologically supressed on antiretroviral therapy.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

For the management of people with Human Immunodeficiency Virus 1 (HIV-1) who are virologically supressed on antiretroviral therapy (ART).[1]

Technology

Description

Doravirine-islatravir (MK-8591A) is a tablet for treatment of patients with HIV-1.[1,2] Doravirine is a pyridinone non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV, and inhibits HIV replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). This reduces the amount of HIV in the blood, which reduces damage to the immune system and the risk of infections and diseases associated with acquired immunodeficiency syndrome (AIDS).[3] Doravirine does not inhibit the human cellular DNA polymerases α and ß, or mitochondrial DNA polymerase γ.[4] Islatravir is a nucleoside analogue which inhibits RT by multiple mechanisms. Intracellularly, islatravir is converted to its active triphosphate form (ISL-TP),[5] which primarily functions as an immediate chain terminator. After it is incorporated into viral DNA, it blocks RT translocation and prevents nucleotide attachment onto the viral DNA chain. When RT translocation does occur and additional nucleotides are incorporated onto the viral DNA chain, ISL-TP can act as a delayed chain terminator by causing structural changes to the viral chain. Furthermore, islatravir can be misincorporated by RT, resulting in mismatched primers that cannot be extended or excised.[5] The multiple mechanisms of action of islatravir, coupled with the high binding affinity to RT, translates to robust antiviral efficacy.[6]

Doravirine-islatravir is in clinical development for management of patients with HIV-1 who are virologically supressed on antiretroviral therapy (ART).[1] In the phase III clinical trial (NCT05631093), participants receive 100 mg/0.25 mg oral tablets once daily.[1]

Key Innovation

Current ART maintenance therapies for HIV-1 can require two or three daily tablets to achieve virological suppression.[7] Doravirine-islatravir requires only one tablet daily, and the reduced pill burden may improve treatment adherence.[8] Doravirine-islatravir has high antiretroviral potency and a low propensity for resistance.[9] Doravirine has an improved drug profile compared with other NNRTIs, with in-vitro evidence of activity against clinically relevant NNRTI-resistant variants, a lower risk for drug-drug interactions and no food restrictions.[9] The chemical structure of islatravir means it has a very high binding affinity for RT, and it can block primer translocation and cause delayed chain termination, minimising the risk of developing resistance.[6,9] In the phase III trial NCT04223778, switching to single-tablet doravirine (100 mg) and islatravir (0.75 mg) maintained viral suppression up to week 48 and was non-inferior to antiretroviral combinations used in clinical practice for adults with HIV-1.[9] If licensed, doravirine-islatravir will offer an additional treatment option for patients who are virologically supressed on ART.

Regulatory & Development Status

Doravirine-islatravir does not currently have marketing authorisation in the UK/EU for any indication.

Doravirine is licensed in combination with other antiretroviral drugs for treatment of HIV-1.[4]

Doravirine-islatravir is in phase II and III clinical trials for maintenance treatment of HIV-1 infection in:[10]

- heavily treatment experienced participants
- treatment of participants who have previously received doravirine-islatravir treatment

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- antiretroviral treatment naïve participants
- paediatric participants under 18 years old who weigh 35kg or more
- participants previously treated with bictegravir, emtricitabine and tenofovir alafenamide and who are virologically supressed

Patient Group

Disease Area and Clinical Need

HIV is a virus that attacks the cells of the immune system. Damage to the immune system caused by HIV can lead to AIDS, which is a chronic and potentially life-threatening condition.[11] Upon initial infection, symptoms of HIV include fever, rash, sore throat, swollen glands, headache, upset stomach or diarrhoea, and joint and muscle pain. After initial symptoms have dissipated, an asymptomatic phase occurs, and further symptoms may not present for many years. Later stage symptoms include weight loss, chronic diarrhoea, night sweats, fever, persistent cough, mouth and skin problems, regular infections and serious illness or disease.[12,13] There are two main types of HIV. The most common is HIV-1, while HIV-2 is relatively uncommon and less infectious. The most common method of HIV transmission is sexual, through unprotected vaginal or anal sex. Additionally, HIV infections can occur from unprotected oral sex and sharing sex toys with someone infected with HIV.[14] Other risk factors for contracting HIV include sharing needles, contact with infected blood or mother to child during pregnancy, childbirth or breast-feeding.[11,15]

In England in 2023, there were 6,008 HIV diagnoses (including people previously diagnosed abroad), this was a 51% rise from 3,975 in 2022 and a 56% rise from 3,859 in 2019. In 2023, nearly half (49%) of all new diagnoses first made in England were among people exposed through sex between men and women.[16] In England, in 2023-2024 there were 3,000 finished consult episodes (FCE) for HIV (ICD10 code: B20-B24), resulting in 558 day cases and 20,171 FCE bed days.[17]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends cabotegravir with rilpivirine for the treatment of HIV-1 in patients who are virologically suppressed on ART.[18]

Clinical Trial Information

Trial	NCT05631093; EU CTIS 2022-502127-22 A Phase 3, Randomized, Active-Controlled, Open-Label Clinical Study to Evaluate a Switch to Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Who Are Virologically Suppressed on Antiretroviral Therapy **Phase III –** Active, not recruiting **Locations:** UK, US and other countries **Primary completion date:** October 2024
Trial Design	Randomised, parallel assignment, open-label.
Population	N (actual) = 553. HIV-1 positive with plasma HIV-1 RNA <50 copies/mL, aged 18 years or older, receiving continuous, stable oral 2-drug or 3-drug combination (± PK booster) ART for ≥3 consecutive months; no history of prior virologic treatment failure on any past or current regimen.
Intervention(s)	Oral doravirine-islatravir 100 mg/0.25 mg tablets once daily.

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Comparator(s)	Standard of care ART with oral doravirine-islatravir 100mg/0.25mg tablets once daily.
Outcome(s)	Primary outcome measures: • Percentage of participants with HIV-1 RNA ≥50 copies/mL at week 48 [time frame: week 48] • Percentage of participants who experience adverse events (AEs) up to week 48 [time frame: up to week 48] • Percentage of participants who discontinue study intervention due to AEs up to week 48 [time frame: up to week 48] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of doravirine-islatravir is not yet known.

Relevant Guidance

NICE Guidance

NICE technology appraisal guidance. Cabotegravir with rilpivirine for treating HIV-1. (TA757). January 2022.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Treatment as Prevention (TasP) in HIV infected adults. F03/P/c. July 2015.
- NHS England. 2013/2014 NHS Standard Contract for Specialised Immunology (all ages). B09/S/a
- NHS England. 2013/2014 NHS Standard Contract for Specialised Human Immunodeficiency Virus services (Adults). B06/S/a

Other Guidance

- European AIDS Clinical Society. EACS Guidelines 2023. 2023.[19]
- British HIV Association (BHIVA). BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022 (2023 interim update). 2023.[7]
- Ryom L, Cotter A, de Miguel R, Beguelin C, Podlekareva D, Arribas JR et al. 2019 update of the European Aids Clinical Society guidelines for treatment of people living with HIV version 10.0. 2019.[20]

Additional Information

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