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Health Technology Briefing
January 2025

Doravirine-islatravir for previously untreated HIV-1 infection

Company/Developer	Merck, Sharp and Dohme

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 37518	NICE ID: Not Available	UKPS ID: 671491

Licensing and Market Availability Plans

In phase III clinical development.

Summary

Doravirine-islatravir is in development for the treatment of human immunodeficiency virus 1 (HIV-1) in people who have not received previous treatment (treatment naïve). 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. Current treatment regimens for patients with HIV-1 who are treatment naïve typically consist of multiple oral tablets, which can be complex and associated with poor treatment adherence.

Doravirine and islatravir inhibit reverse transcriptase (RT), an enzyme that allows HIV-1 to replicate. These technologies inhibit RT with 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. Doravirine-islatravir (100 mg/0.25 mg) is given as a single oral tablet once daily, which may improve treatment adherence compared with taking multiple oral tablets. If licensed, doravirine-islatravir would offer an additional treatment option to patients with HIV-1 who are treatment naïve.

Proposed Indication

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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For the treatment of human immunodeficiency virus-1 (HIV-1) in people who are treatment-naïve.[1]

Technology

Description

Doravirine-islatravir (MK-8591A) is a fixed-dose combination tablet for the management of HIV-1.[2] Doravirine is a pyridinone non-nucleoside reverse transcriptase inhibitor (NNRTI) and acts as a non-competitive inhibitor of HIV-1 reverse transcriptase (RT).[3] HIV-1 RT is a virally encoded enzyme that transcribes the viral RNA genome into a proviral DNA precursor prior to integration into the host genome.[4] Reverse transcription is an essential step in retroviral replication.[5] RT is an important target for anti-HIV drugs.[4] By inhibiting RT, doravirine 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).[6] Doravirine does not inhibit the human cellular DNA polymerases α and ß, or mitochondrial DNA polymerase γ.[3] Islatravir is a nucleoside analogue which inhibits RT by multiple mechanisms. Intracellularly, islatravir is converted to its active triphosphate form (ISL-TP).[7] Primarily, ISL-TP 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. Islatravir can be misincorporated by RT, resulting in mismatched primers that cannot be extended or excised.[7] The multiple mechanisms of action of islatravir, coupled with the high binding affinity to RT, translates to robust antiviral efficacy.[8]

Doravirine-islatravir is in development for the first-line treatment of HIV-1 in treatment-naïve patients.[1] In the phase III trial (NCT05705349), participants receive 100 mg/0.25 mg oral tablets once daily.[1]

Key Innovation

Current treatment regimens for patients with HIV-1 who are treatment naïve typically consist of multiple oral tablets, which can be complex and associated with poorer treatment adherence.[9,10] Doravirine-islatravir requires taking only one tablet daily, which may improve treatment adherence due to the lower pill burden.[11] Doravirine-islatravir has high antiretroviral potency and a low propensity for resistance.[12] 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.[12] The chemical structure of islatravir means it has a very high binding affinity for RT, and it can block primer translocation and cause immediate chain termination, minimising the risk of developing resistance.[8,12] In the phase IIb trial (NCT03272347), the combination of doravirine and islatravir for HIV-1 patients who were treatment naïve was well tolerated and showed good antiviral efficacy.[13] If licensed, doravirine-islatravir will offer a new treatment option for patients with HIV-1 who are treatment naïve.

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 therapy (ART) drugs for treating HIV-1.[3]

Doravirine-islatravir is in phase II and III clinical trials for maintenance treatment of HIV-1 infection in:[14]

- heavily treatment experienced participants
- treatment of participants who have previously received doravirine-islatravir treatment
- antiretroviral treatment naïve participants
- paediatric participants under 18 years old who weigh 35kg or more

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- participants 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.[15,16] 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.[16,17] 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.[18] Other risk factors for contracting HIV include sharing needles, contact with infected blood or mother to child during pregnancy, childbirth or breast-feeding.[15,19]

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.[20] 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.[21]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends treatment with a combination of two nucleoside RT inhibitors as a backbone regimen plus one of the following as a third drug: an integrase inhibitor, a NNRTI or a boosted protease inhibitor for treatment naïve HIV-1 patients.[22]

Clinical Trial Information

Trial	NCT05705349: A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate the Antiretroviral Activity, Safety, and Tolerability of Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in HIV-1 Infected Treatment-Naïve Participants **Phase III –** Active, not recruiting **Locations:** 3 EU countries, UK, US and other countries **Primary Completion Date:** October 2025
Trial Design	Randomised, parallel assignment, double-blinded.
Population	N (estimated) = 500. HIV-1 positive with plasma HIV-1 RNA ≥500 copies/mL at screening, aged 18 years and older, is treatment naïve to antiretroviral therapy.
Intervention(s)	Oral doravirine-islatravir (100mg/0.25mg) once daily. Oral placebo for bictegravir/emtricitabine/tenofovir alafenamide once daily.
Comparator(s)	Oral bictegravir-emtricitabine-tenofovir alafenamide (50mg/200mg/25mg) plus placebo to doravirine-islatravir once daily.

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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

No recommended NICE guidance.

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.[23]
- British HIV Association (BHIVA). BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022 (2023 interim update). 2023.[9]
- 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.[24]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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