Health Technology Briefing
December 2023

Olorofim for invasive fungal infections

Company/Developer	Shionogi Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 24164	NICE ID: Not available	UKPS ID: 671265

Licensing and Market Availability Plans

Currently in phase IIb clinical trial

Summary

Olorofim is currently in development for the treatment of invasive fungal infections caused by rare moulds. Scedosporiosis (including lomentosporiosis) is an infection caused by a group of fungi called *Scedosporium* species (a rare mould). These moulds are often spread by spores in the environment, which can be inhaled or get inside the skin and spread locally, invading the blood vessels, which causes infection. They are usually seen in patients with a weakened immune system, and it is often resistant to many antifungal medicines. They are life-threatening infections that can be fatal due to damage to the lungs and other organs. The symptoms can include shortness of breath, cough, fever, and chest pain. Resistance to existing treatments is a growing challenge in the management of these rare moulds and invasive fungal infections.

Olorofim is the first medicine developed for a new class of antifungals called orotomides. It is an oral tablet, that is expected to interfere with the production of pyrimidine, a compound needed by the fungus to make DNA. It does this by blocking an enzyme called dihydroorotate dehydrogenase, which produces pyrimidine. The resulting lack of pyrimidine is expected to prevent the rare moulds and invasive fungi from multiplying and spreading. If licensed, olorofim may provide an alternative treatment option for patients with invasive fungal infections caused by rare moulds.

Proposed Indication

Treatment of patients aged 16 – 17 years weighing at least 40 kg, or patients aged 18 years and above, with invasive fungal disease, due to *Lomentospora Prolificans (L. profilicans)*, *Scedosporium Spp.*, *Aspergillus Spp.*, and other resistant fungi .[1]

Technology

Description

Olorofim (F901318) is the first member of the orotomide class of antifungals to be evaluated clinically for the treatment of invasive fungal infections. It acts as a reversible inhibitor of the enzyme dihydroorotate dehydrogenase, an oxidoreductase that catalyses the fourth step in the de novo synthesis of pyrimidine. The inhibition of pyrimidine biosynthesis results in the inhibition of the formation of uridine-5′-monophosphate (UMP) and uridine-5′-triphosphate (UTP). UMP and UTP are important for several cellular processes.[2] The inhibition of pyrimidine synthesis by olorofim may affect the fungal cell wall and result in cell lysis.[2,3]

Olorofim is currently in development for the treatment of patients aged 16 years and above with invasive fungal infections due to rare moulds. In a phase IIb clinical trial (FORMULA-OLS; NCT03583164), participants received 30mg oral olorofim tablets, with a maximum daily dose of 300mg.[1]

Key Innovation

Olorofim is the first novel antifungal class developed in the past 20 years.[4] Invasive *Scedosporium* spp. and *Lomentospora prolificans* infections are an emerging threat in immunocompromised and occasionally in healthy hosts. *Scedosporium* spp. is intrinsically resistant to most, *L. prolificans* to all the antifungal drugs currently approved, raising concerns about appropriate treatment decisions. High mortality rates of up to 90% underline the need for comprehensive diagnostic workup and even more for new, effective antifungal drugs to improve patient outcomes.[5]

One of the most promising aspects of olorofim is it's *in vitro* potency against fungi that are generally considered to have reduced susceptibility or frank resistance to currently available antifungal agents. This includes azole-resistant Aspergillus species, Scedosporium species and L. *prolificans*, which is pan-resistant to clinically available antifungals. [2] If licenced, olorofim may provide a new treatment option for patients with invasive fungi infections due to rare mould.

Regulatory & Development Status

Olorofim does not currently have marketing authorisation in the EU/UK for any indication.

Olorofim has the following regulatory designations/awards:

- orphan drug by the European Medicines Agency (EMA) in 2016 for the treatment of invasive aspergillosis[6]
- orphan drug by the EMA in 2016 for the treatment of scedosporiosis[7]
- orphan drug by the EMA in 2016 for the treatment of invasive scopulariopsis[8]
- breakthrough therapy by the US Food and Drug Administration (FDA) for the treatment of invasive mould infections in November 2019[9]
- qualified Infectious Disease Product (QIDP) designation by the US FDA for the treatment of multiple fungal infections in June 2020[10]

Olorofim is also in phase II development for other types of invasive fungi infections.[11]

Patient Group

Disease Area and Clinical Need

Invasive fungal infections are defined as systemic infections resulting from the establishment of yeasts or moulds (i.e., fungi) in deep-seated tissues. They are fatal conditions with high rates of morbidity and mortality. The population at risk for contracting an opportunistic fungal infection includes organ transplant recipients, haematologic patients requiring stem cell transplantation, acquired immune deficiency syndrome patients, diabetics, burn patients, neoplastic disease patients, patients on long-term immunosuppressive therapy, and those with chronic respiratory diseases, among others.[12] Fungi reproduce by spreading microscopic spores, which are often present in the air and soil, where they can be inhaled or come into contact with the surfaces of the body. When fungal organisms enter the body and the immune system is compromised these fungi grow, spread and invade into tissue and spread locally, where some yeast and mould species can invade the blood vessels, causing infection.[13] Symptoms of invasive fungal infections vary between the affecting species. Clinical symptoms can typically manifest as fever, cough, dyspnoea, chest pain, and haemoptysis.[14] *Scedosporium* spp, including *L. prolificans* (formerly *S. prolificans*) are species of pathogenic moulds that causes wide range of clinical manifestations in humans from superficial infection to severe invasive disease, as well as colonisation of the respiratory tract and allergic reactions. *Scedosporium* spp causes the invasive fungal disease scedosporiosis.[15] Invasive aspergillosis is caused by filamentous fungi of the *Aspergillus* species, which are found ubiquitously in soil. Inhalation of the aerosolised conidia (spores) causes the infection.[16] Scedosporiosis is classically associated with haematological malignancies, although patients with other forms of immune impairment (e.g. immunocompromised) may also contract the disease.[15,17] Individuals suffering from near-drowning events in water polluted with fungal propagules are also at risk of infections caused by *Scedosporium* spp with central nervous system involvement.[18]

Although there are estimates for the burden of invasive aspergillosis in the United Kingdom (UK) available, the burden of fungal disease by less common species in the UK is unknown. Only limited data are systematically collected.[19-21] Therefore, the population likely to be eligible to receive olorofim for this indication could not be estimated from available published sources.

Recommended Treatment Options

There is no treatment option recommended by the National Institute for Health and Care Excellence (NICE) for invasive fungal infections due to rare moulds.

For the treatment of Scedosporium/Lomentospora infections, the European guidelines recommend voriconazole as first-line treatment, together with surgical debridement when possible.[18]

Clinical Trial Information

Trial	**FORMULA-OLS; NCT03583164, EudraCT 2017-001290-17;** Phase IIb Study of F901318 as Treatment of Invasive Fungal Infections Due to Lomentospora Prolificans, Scedosporium Spp., Aspergillus Spp., and Other Resistant Fungi in Patients Lacking Suitable Alternative Treatment Options

	Phase II - Recruiting **Location(s):** Six EU countries, UK, USA, Australia, and others **Study Completion Date:** March 2023
Trial Design	Interventional, single-group assignment, and open-label
Population	N = 200 (estimated); patients aged 16 – 17 years weighing at least 40 kg, or patients aged 18 years and above, with invasive fungal disease who have limited alternative treatment options.
Intervention(s)	Olorofim: 30mg tablets, with a maximum daily dose of 300mg with dose adjustments according to plasma levels of olorofim and concomitant treatment with CYP inducers or inhibitors.
Comparator(s)	-
Outcome(s)	Primary outcome measures: - DRC adjudicated overall response at Day 42 using a combination of clinical, mycological, and radiological response [Time Frame: Day 42] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of olorofim is not yet known

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust. South Yorkshire and Bassetlaw Antifungal Guidelines for adult patients. 2022.[22]
- Hoenigl M., Salmanton-Garcia J., Walsh T.J. *et al*. Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiology. 2021.[23]
- Whittington Health NHS Trust. Antifungal Guideline for Invasive Fungal Infections in Adults. 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.