Health Technology Briefing
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Baloxavir marboxil for reducing direct transmission of influenza

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27430	NICE ID: Not Available	UKPS ID: 671425

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Baloxavir marboxil is in clinical development for reducing direct transmission of influenza. Influenza commonly known as flu is an infection of the nose, throat, and lungs, which are a part of the respiratory system. There are three types of viruses that cause influenza; type A, B and C. Type A and B influenza viruses cause the main outbreaks of flu each year. Flu is very infectious and easily spread to other people. It is usually transmitted to others within the first five days of infection. It is spread by germs from cough and sneezes, which can live on hands and surfaces for 24 hours. Households and other close contact settings are important sites for the transmission of influenza virus. The most common symptoms of flu are fever, chills, headache, aches and pains in the joints and muscles, and extreme tiredness. Most cases of flu will resolve within three to seven days. However, flu can be more severe in those who are older, in children and in people with long term health conditions, such as heart disease, asthma or diabetes. There are currently no approved treatments proven to reduce influenza transmission.

Baloxavir marboxil is administered orally as a single-dose tablet or as an oral suspension. It works by blocking an enzyme known as cap-dependent endonuclease which the influenza virus uses to produce more copies of itself. By interfering with the activity of this enzyme, baloxavir marboxil can prevent the virus from multiplying thereby reducing its transmission to patients exposed to the virus. If licensed, baloxavir marboxil will offer a treatment option to reduce influenza transmission.

Proposed Indication

Reduction of direct transmission of influenza A and B from otherwise healthy people aged 5 to 64 years.[1]

Technology

Description

Baloxavir marboxil (Xofluza) is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza activity. Baloxavir acts on the cap-dependent endonuclease (CEN), an influenza virus-specific enzyme in the polymerase acidic (PA) subunit of the viral RNA polymerase complex and thereby inhibits the transcription of influenza virus genomes resulting in inhibition of influenza virus replication.[2,3]

Baloxavir marboxil is in clinical development for the reduction of direct transmission of influenza. In the phase III clinical trial (NCT03969212), patients younger than 12 years old will receive either 2 mg/kg (if weight less than 20 kg) or 40 mg (if weight more than or equal to 20 kg) of baloxavir marboxil as an oral suspension. Patients that are 12 years or older will receive either 40 mg (if weight less than 80 kg) or 80 mg (if weight more than or equal to 80 kg) of baloxavir marboxil as tablets.[1]

Key Innovation

Household transmission is one of the major ways of spreading the influenza virus. Early reduction of viral load may be necessary to avoid influenza transmission.[4] Influenza A and B infections are seasonal and highly contagious. Most individuals are advised to stay at home until their fever has subsided for at least 24 hours, which puts other household members at risk of infection. There are currently no approved treatments proven to reduce influenza transmission.[5] Baloxavir marboxil is a single-dose oral medicine with a novel proposed mechanism of action that has demonstrated efficacy against a wide range of influenza viruses.[3]

If licensed, baloxavir marboxil will offer a novel treatment option for reducing direct transmission of influenza A and B.

Regulatory & Development Status

In the UK, baloxavir marboxil has Marketing Authorisation for the treatment and post-exposure prophylaxis of influenza in patients aged 1 year and above.[6]

Baloxavir marboxil is not in clinical development for any other indication.

Patient Group

Disease Area and Clinical Need

Influenza is an acute respiratory illness caused by RNA viruses of the family Orthomyxoviridae (influenza viruses). There are three strains of influenza virus: A, B, and C.[7] Influenza A is the most frequently seen and is the cause of major influenza outbreaks. Influenza B tends to circulate with influenza A in yearly outbreaks and causes less severe illness. Influenza C causes a mild or asymptomatic illness similar to the common cold.[8] Influenza A and B infections are seasonal and highly contagious.[9] Influenza is commonly spread by droplets, aerosols and direct contact with respiratory secretions.[10] Droplets from coughs and sneezes can live on surfaces or objects for several hours. People with influenza are typically infectious from around one day before symptoms develop to three to seven days after symptoms appear. Children

and people with weaker immune systems may remain infectious for longer.[11] Households and other close-contact settings such as dormitories and schools are important sites for seasonal and pandemic transmission of influenza virus. School-age children often introduce the virus into households, with subsequent spread to younger siblings and adults.[12] Symptoms of influenza include fever of 38°C or above, cough, sore throat, runny or stuffy nose, headache, myalgia, fatigue, diarrhoea and vomiting in some cases.[13] Healthy individuals usually recover within 2 to 7 days, but for some the disease can lead to hospitalisation, permanent disability or even death.[14]

Influenza usually occurs in the UK between December and May. In the UK 2022-23, high levels of influenza activity were observed in a short period between December 2022 and January 2023, and the peak admission rates of influenza to hospital were higher compared to previous seasons.[15] In England (2022-23), there were 78,723 finished consultant episodes (FCEs) and 44,049 admissions for influenza due to identified seasonal influenza virus (ICD-10 code J10), which resulted in 376 day cases and 267,086 FCE bed days.[16]

Recommended Treatment Options
There is currently no recommended treatment option by the National Institute for Health and Care Excellence (NICE) for reducing the transmission of influenza. NICE recommends oseltamivir and zanamivir for the post-exposure prophylaxis of influenza.[17]

Clinical Trial Information

Trial	NCT03969212, **EudraCT** 2018-004056-37; A Phase IIIB, Multicentre, Randomized, Double-Blind, Placebo-Controlled, Clinical Efficacy Study of Baloxavir Marboxil for the Reduction of Direct Transmission of Influenza From Otherwise Healthy Patients to Household Contacts **Phase III-** Completed **Locations:** 6 EU countries, UK, USA, and other countries **Primary completion date:** May 2024
Trial Design	Randomised, parallel assignment, double masking
Population	N= 4,176 (actual); Subjects with acute influenza infection aged 5 to 64 years
Intervention(s)	Subjects aged 12 years and below will receive either 2 mg/kg (if weight less than 20 kg) or 40 mg (if weight more than or equal to 20 kg) of Baloxavir Marboxil as oral suspension. Subjects aged 12 years and older will receive either 40 mg (if weight less than 80 kg) or 80 mg (if weight more than or equal to 80 kg) of Baloxavir Marboxil as tablets.
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Virological Transmission by Day 5 [Time Frame: Baseline to Day 5 (5 days)] See trial record for full list of outcomes
Results (efficacy)	The proportion of families with household transmission was 17.98% (15,226 of 84,672) in the baloxavir group and 24.16% (14,983 of 62,004) in the oseltamivir

	group. The covariate-adjusted odds ratio (oseltamivir/baloxavir) was 1.09 (95% confidence interval [95% CI], 1.05 - 1.12), which indicated significantly lower incidence in the baloxavir group. The adjusted odds ratios (controls/baloxavir) against zanamivir and laninamivir were 0.93 (95% CI, 0.89 - 0.97) and 0.99 (95% CI, 0.96 - 1.02), respectively.[18]
Results (safety)	-

Estimated Cost

The NHS indicative price of 2 tablets of baloxavir marboxil 40mg is £100.[19]

Relevant Guidance

NICE Guidance

- NICE Technology Appraisal. Oseltamivir, amantadine (review) and zanamivir for the treatment of influenza (TA168). February 2009.
- NICE Technology Appraisal. Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza (TA158). September 2008.

NHS England (Policy/Commissioning) Guidance

- NHS England. The national flu immunisation programme 2020 to 2021. May 2020.

Other Guidance

- Public Health England (PHE). PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza. November 2021.[20]
- Healthcare Associated Infection & Antimicrobial resistance & Prescribing Programme (HARP). Managing Seasonal Influenza: Infection: Prevention and Control Guidance in Healthcare Settings. 2019.[21]
- World Health Organisation. WHO guidance document: Pandemic influenza preparedness and response. 2009.[22]

Additional Information

References

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