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HEALTH TECHNOLOGY BRIEFING
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Baloxavir marboxil for the post-exposure prevention of influenza in people aged 12 years and older

NIHRIO ID	28433	**NICE ID**	10321
Developer/Company	Roche Products Ltd	**UKPS ID**	653667

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Baloxavir marboxil is a medicinal product currently in development for the post-exposure prophylaxis (prevention) of influenza in individuals aged 12 years and above. Influenza or 'flu' is a common virus infection which causes high temperature, body aches, tiredness, cough, sore throat, headache, diarrhoea and nausea. Flu is usually spread by coughs and sneezes and occurs in annual flu seasons (commonly October to May). Most cases of flu will resolve within three to seven days. Although vaccines are the preferred method of flu prevention, they require continual evolution and may not provide protection to everyone. Other treatments are therefore also recommended for flu prevention and containment.

Baloxavir marboxil is given by mouth as tablets and works in a different way to existing flu medications by blocking a specific process which influenza viruses use to multiply within the body. There is evidence that this medication may be effective in people for whom existing flu medicines do not work. Additionally, only one dose of baloxavir marboxil is needed whereas existing flu prevention medications need to be taken over several days. If licenced, baloxavir marboxil may offer an additional prevention option for individuals who have been in contact with someone who has influenza.

PROPOSED INDICATION

The post-exposure prophylaxis of influenza in individuals aged 12 years and above.[1]

TECHNOLOGY

DESCRIPTION

Baloxavir marboxil (CapEndo, Xofluza) inhibits viral replication by targeting the cap-dependent endonuclease function encoded by the PA subunit of the viral polymerase complex. Influenza viruses have a trimeric polymerase complex composed of the PB1, PB2, and PA subunits, and the RNA-dependent RNA polymerase activity resides in the PB1 protein. The synthesis of viral mRNAs requires a host pre-mRNA to be used as a primer for viral transcription, and to achieve this the PB2 protein binds to the 5-cap structure of host pre-mRNAs in the nucleus of the infected cell.[2,a]

Baloxavir marboxil is in development for the post-exposure prophylaxis of influenza in individuals aged 12 years and above. In the phase III randomised trial (JapicCTI-184180; Blockstone), the household contacts (of an index patient with confirmed influenza) received baloxavir marboxil tablets taken as a single dose or a matched placebo.[3]

INNOVATION AND/OR ADVANTAGES

NICE currently recommends neuraminidase inhibitors oseltamivir and zanamivir for the post-exposure prophylaxis of influenza.[4] Unfortunately, influenza A and B viruses can develop resistance to oseltamivir by acquiring mutations in the neuraminidase active site (H274Y, E119V) that are critical for drug binding.[2] Futhermore, the recommended dose of oseltamivir for the post exposure prevention of influenza in individuals aged 13 and over is 75 mg once daily for 10 days, whilst baloxavir marboxil is taken as a single dose.[5,6] In contrast, zanamivir resistance is infrequent with only a few reported cases of resistant influenza A and B viruses from clinical samples. However, zanamivir is administered as an inhaled powder and is poorly tolerated in patients with underlying respiratory diseases.[2]

Baloxavir marboxil is a first-in-class, one-dose oral medicine with a novel proposed mechanism of action.[7] The key advantage of baloxavir marboxil is that only a single dose is required which should increase compliance.[2] Additionally, baloxivir marboxil's mechanism of action allows for use in patients who may have oseltamivir resistance.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Baloxavir marboxil does not currently have Marketing Authorisation in the EU/UK for any indication.

PATIENT GROUP

DISEASE BACKGROUND

Seasonal influenza is an acute respiratory infection caused by influenza viruses which circulate in all parts of the world.[9] There are four types of influenza viruses: influenza A, B, C, and D, but only influenza A and B viruses cause clinically important human disease and seasonal epidemics. Influenza A viruses cause the most severe clinical disease and are the commonest cause of seasonal epidemics and pandemics in human populations.[10]

In terms of transmission, seasonal influenza spreads easily, with rapid transmission in crowded areas including schools and nursing homes. When an infected person coughs or sneezes, droplets containing viruses (infectious droplets) are dispersed into the air and can spread up to one meter, and infect persons in close proximity who breathe these droplets in. The virus can also be spread by hands contaminated with influenza viruses.[9]

Anyone can get influenza, and serious problems related to influenza can happen at any age, but some people are at high risk of developing serious influenza-related complications if they get sick. This includes people 65 years and older, people of any age with certain chronic medical conditions (such as asthma, diabetes, or heart disease), pregnant women, and children younger than 5 years.[11]

Influenza is generally self-limiting in healthy people, with recovery occurring within 3 to 7 days. However people in high risk groups may benefit from antiviral therapy, hospitalisation, or intensive care.[10] Complications of influenza can include pneumonia, ear infections, sinus infections and worsening of chronic medical conditions e.g. congestive heart failure or asthma.[12] Influenza can cause severe illness or death, particularly in high risk populations. Mortality is higher among individuals with complicated influenza (illness necessitating hospital admission, or an exacerbation of an underlying chronic illness) across all age groups, but is highest in infants aged 6 months or younger.[10]

Vaccination is currently the most effective and economical method of controlling influenza virus infection. Vaccination may prevent infection by inducing production of specific antibodies that complex with the virus prior to infection of the respiratory epithelium or through cell-mediated destruction of infected cells early in the cycle of infection. However, several significant challenges are involved in vaccination against influenza, such as continual evolution of novel viral strains necessitates development of new vaccine preparations each year. Because the influenza virus can evolve rapidly and it is not possible to effectively vaccinate all vulnerable individuals, antiviral therapies will continue to fill an important role in the containment of influenza infections.[13]

CLINICAL NEED AND BURDEN OF DISEASE

In winter 2018-2019, in assessing influenza vaccination at GP surgeries, it was extrapolated that in England there were:[14]

- 10,435,319 people aged 65+ years (of which 2,924,732 weren't vaccinated)
- 7,055,771 people aged 6 months to <65 years in one or more clinical risk groups (excluding pregnant women without other risk factors and carers) (of which 3,666,362 weren't vaccinated)
- 61,411 pregnant women in one or more clinical risk groups (of which 24,416 weren't vaccinated)

In terms of primary care, in England in 2018-2019, weekly rates of GP consultations for influenza-like illness across the whole population peaked at 23.1 per 100,000 per week.[15]

In secondary care, a total of 5,505 hospitalised confirmed influenza cases (mean weekly incidence of 2.10 per 100,000 trust catchment population) were reported from 24 participating sentinel NHS acute trusts across England from week 40 in 2018 to week 15 in 2019. Of this, 2,924 were admissions to an intensive care unit (ICU) or high-dependency unit (HDU). 273 patients in ICU died due to influenza during the same period.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Vaccination is the most effective means of preventing influenza and its complications. Immunity developed in one influenza season may not provide protection in future years mainly because of

changes in circulating strains, antigenic drift, and waning immunity. Influenza vaccines are updated annually to include the viral strains that are predicted to circulate in winter.[10]

Influenza may also be prevented or rendered less severe by post-exposure prophylaxis with antivirals.[8]

CURRENT TREATMENT OPTIONS

Oseltamivir and zanamivir are recommended, within their marketing authorisations, for the post-exposure prophylaxis of influenza if all of the following circumstances apply:[16]

- National surveillance schemes have indicated that influenza virus is circulating
- The person is in an at-risk group
- The person has been exposed to an influenza-like illness and is able to begin prophylaxis within the timescale specified in the marketing authorisations of the individual drugs (within 36 hours of contact with an index case for zanamivir and within 48 hours of contact with an index case for oseltamivir)
- The person has not been effectively protected by vaccination

Exposure to an influenza-like illness is defined as close contact with a person in the same household or residential setting who has had recent symptoms of influenza.[16]

PLACE OF TECHNOLOGY

If licenced, baloxavir marboxil may offer an additional preventive option for the post-exposure prophylaxis of influenza in individuals aged 12 years and above.

CLINICAL TRIAL INFORMATION

Trial	**Blockstone; JapicCTI-184180; Study to confirm the efficacy of baloxavir marboxil versus placebo in the prevention of influenza virus infection** **Phase III** **Location(s): Japan**
Trial design	Randomised, double-blind
Population	- Population size: 749 (actual) - Subjects (household contacts) who had lived with the index patient with influenza virus infection for 48 hours or more prior to informed consent and who are not judged to have the influenza virus. - Patients aged 12 years and over.
Intervention(s)	Baloxavir marboxil (oral).
Comparator(s)	Matched placebo.
Outcome(s)	Proportion of subjects (household contacts) who are infected with influenza virus (RT-PCR positive), and present with fever and at least one respiratory symptom in the period from day 1 to day 10
Results (efficacy)	Among 545 index patients, 95.6% had influenza A infection, and 53.0%, 31.0%, or 16.0% received baloxavir marboxil (BXM), oseltamivir, or other neuraminidase inhibitors, respectively. Of 752 randomized household contacts (HHC), 749 (99.6%)

	constituted the modified intention to treat population (BXM n=374 vs. placebo n=375; 19.0% aged <12 years; and 13.1% had ⩾1 risk factor for complicated illness). The proportion of HHC who developed clinical influenza in the BXM group was significantly smaller (1.9%) than that in the placebo group (13.6%), with a risk ratio of 0.14 (95%CI: 0.06-0.30; p<0.0001). Similar findings were observed in subgroups of HHC <12 years and among those with risk factors, with risk ratios of 0.27 (95%CI: 0.08-0.90) and 0.13 (95%CI: 0.02-0.94), respectively. Similar results in subgroups of HHC with RT-PCR negative at baseline were also observed.[1]
Results (safety)	The incidence of adverse events was comparable in BXM and placebo groups (22.2% vs 20.5%, respectively).[1]

ESTIMATED COST

The cost of baloxavir marboxil is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

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

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- Public Health England (PHE). PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza. September 2019.[17]
- NICE Clinical Knowledge Summaries (CKS). Influenza – seasonal: Scenario: Post-exposure prophylaxis of influenza. 2019.[18]
- Healthcare Associated Infection & Antimicrobial resistance & Prescribing Programme (HARP). Managing Seasonal Influenza: Infection: Prevention and Control Guidance in Healthcare Settings. 2018.[19]
- World Health Organisation. WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. February 2010.[20]
- World Health Organisation. WHO guidance document: Pandemic influenza preparedness and response. 2009.[21]

ADDITIONAL INFORMATION

REFERENCES

1 Ikematsu H, et al. Single-dose baloxavir for the prevention of influenza among household contacts: a randomized, double-blinded, placebo controlled post-exposure prophylaxis study (BLOCKSTONE). *OPTIONS X*. 2019;Abstract #11718. Available from: https://isirv.org/site/images/conferences/Optionsx/Options%20X_Abstracts%20_Oral%20and%20Poster.pdf.

2 O'Hanlon R, Shaw M. Baloxavir marboxil: the new influenza drug on the market. *Current Opinion on Virology*. 2019;35:14-8. Available from: https://www.sciencedirect.com/science/article/pii/S1879625718301299?via%3Dihub.

3 NIPH Clinical Trials. *Study to confirm the efficacy of baloxavir marboxil versus placebo in the prevention of influenza virus infection*. *Trial ID: JapicCTI-184180*. 2018. Available from: https://rctportal.niph.go.jp/en/detail?trial_id=JapicCTI-184180 [Accessed 25 February 2020].

4 National Institute for Health and Care Excellence (NICE). *NICE Pathways: Influenza: Treatment* 2020. Available from: https://pathways.nice.org.uk/pathways/influenza#content=view-node%3Anodes-treatment [Accessed 11 February 2020].

5 electronic Medicies Compendium (eMC). *Tamiflu 75 mg Hard Capsules.* 2019. Available from: https://www.medicines.org.uk/emc/product/1194/smpc [Accessed 11 February 2020].

6 ClinicalTrials.gov. *Study of S-033188 (Baloxavir Marboxil) Compared With Placebo or Oseltamivir in Patients With Influenza at High Risk of Influenza Complications (CAPSTONE 2)*. *Trial ID: NCT02949011*. 2016. Status: Completed Available from: https://clinicaltrials.gov/ct2/show/study/NCT02949011 [Accessed 11 February 2020].

7 Genentech. *Genentech Announces FDA Approval of Xofluza (Baloxavir Marboxil) for People at High Risk of Developing Influenza-Related Complications.* 2019. Available from: https://www.gene.com/media/press-releases/14817/2019-10-17/genentech-announces-fda-approval-of-xofl [Accessed 25 February 2020].

8 Ng K. Xofluza (Baloxavir Marboxil) for the Treatment of Acute Uncomplicated Influenza. *Drug Forecast*. 2019;44(1):9-11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6336199/pdf/ptj4401009.pdf.

9 World Health Organization (WHO). *Influenza (Seasonal).* 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)) [Accessed 11 February 2020].

10 Ghebrehewet S, MacPherson P. Influenza. *BMJ*. 2016;355:i6258. Available from: https://doi.org/10.1136/bmj.i6258

11 Centers for Disease Control and Prevention (CDC). *Key Facts About Influenza (Flu).* 2019. Available from: https://www.cdc.gov/flu/about/keyfacts.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Fkeyfacts.htm [Accessed 11 February 2020].

12 Centers for Disease Control and Prevention (CDC). *People at High Risk For Flu Complications.* 2018. Available from: https://www.cdc.gov/flu/highrisk/index.htm [Accessed 11 February 2020].

13 Kandel R, Hartshorn K. Prophylaxis and Treatment of Influenza Virus Infection. *BioDrugs*. 2001;15(5):303–23. Available from: https://link.springer.com/article/10.2165%2F00063030-200115050-00003.

14 Public Health England (PHE). *Seasonal influenza vaccine uptake in GP patients: winter season 2018 to 2019* 2019. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/804889/Seasonal_influenza_vaccine_uptake_in_GP_patients_1819.pdf [Accessed 11 February 2020].

15 Public Health England (PHE). *Surveillance of influenza and other respiratory viruses in the UK Winter 2018 to 2019.* 2019. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/839350/Surveillance_of_influenza_and_other_respiratory_viruses_in_the_UK_2018_to_2019-FINAL.pdf [Accessed 11 February 2020].

16 National Institute for health and Care Excellence (NICE). *Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza.* 2008. Available from: https://www.nice.org.uk/guidance/ta158/chapter/1-Guidance [Accessed 12 February 2020].

17 Public Health England (PHE). *PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza.* 2019. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/833572/PHE_guidance_antivirals_influenza_201920.pdf [Accessed

18 NICE Clinical Knowledge Summaries (CKS). *Influenza - seasonal.* 2019. Available from: https://cks.nice.org.uk/influenza-seasonal [Accessed 12 February 2020]

19 Healthcare Associated Infection & Antimicrobial resistance & Prescribing Programme (HARP). *Managing Seasonal Influenza: Infection Prevention and Control Guidance in Healthcare Settings.* 2018. Available from: http://www.wales.nhs.uk/sitesplus/documents/888/Managing%20Seasonal%20Influenza%20HARP.pdf [Accessed 12 February 2020]

20 World Health Organization (WHO). *WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses.* 2010. Available from: https://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/ [Accessed 12 February 2020].

21 World Health Organization (WHO). *Pandemic influenza preparedness and response.* 2009. Available from: https://apps.who.int/iris/bitstream/handle/10665/44123/9789241547680_eng.pdf;jsessionid=A92BADE6387E56767E216B4C36E1D177?sequence=1 [Accessed 12 February 2020].

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