Health Technology Briefing
November 2021

Baloxavir marboxil for treating paediatric patients 1 to <12 years of age with influenza

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26906	NICE ID: 10712	UKPS ID: 661761

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Baloxavir marboxil is in clinical development for the treatment of paediatric patients 1 to <12 years of age with influenza. 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. 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.

Baloxavir marboxil is given by mouth as tablets or as a liquid that is swallowed (oral suspension) 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 medications need to be taken over several days. If licensed, baloxavir marboxil may offer an additional treatment option for pediatric patients with influenza.

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.
Copyright © National Institute for Health Research Innovation Observatory, The University of Newcastle upon Tyne.

Proposed Indication

Treatment of paediatric patients 1 to <12 years of age with influenza.[1]

Technology

Description

Baloxavir marboxil (Xofluza, RG6152) is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza activity against seasonal influenza A and B viruses.[2] 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.[3]

In the phase III clinical trials (NCT03653364, NCT03629184), baloxavir marboxil was administered at a single oral dose (tablets and oral suspension) based on body weight and age.[1,4]

- <12 years weighing ≥20 kg: 40 mg
- <12 years weighing <20 kg: 2 mg/kg

Key Innovation

Baloxavir marboxil is a novel treatment for influenza that targets the polymerase complex of influenza A and B viruses. Its mechanism of action allows for use in patients who may have oseltamivir resistance. Baloxavir marboxil is indicated for patients 12 years of age and older, which may limit its use in a younger population that is highly susceptible to influenza, as oseltamivir is approved for use in patients as young as 2 weeks old. Clinical benefits of baloxavir marboxil are similar to those of oseltamivir. Studies revealed that a single dose of baloxavir marboxil resulted in a shorter time to alleviation of symptoms and greater reductions in levels of influenza virus at one and two days after administration. Additionally, patients may be more adherent to baloxavir because only one dose is necessary for treatment as opposed to oseltamivir twice-daily dosing for five days.[5]

If licenced, baloxavir marboxil will provide an additional therapeutic option for treating flu in children aged 1 to <12 years.

Regulatory & Development Status

Baloxavir marboxil is indicated for the treatment of uncomplicated influenza and post-exposure prophylaxis of influenza in individuals aged 12 years and above.[3]

Patient Group

Disease Area and Clinical Need

Seasonal influenza is an acute respiratory infection caused by influenza viruses which circulate in all parts of the world.[6] 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.[7] 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

Copyright © National Institute for Health Research Innovation Observatory, The University of Newcastle upon Tyne.

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.[8] 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.[7] Complications of influenza can include pneumonia, ear infections, sinus infections and worsening of chronic medical conditions (e.g. congestive heart failure or asthma).[8] Children play a central role in influenza dissemination in the community because of their relative susceptibility to infection, high illness attack rates, prolonged viral shedding, and high contact rates between others in the household and community.[1] Influenza illness also causes children to lose school time, and their parents to lose work time, causing a socioeconomic as well as a clinical burden.[9]

In winter 2020-2021, in assessing influenza vaccination at GP surgeries, it was extrapolated that in England there were 8,296,775 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 3,897,995 were not vaccinated).[10] In terms of primary care, in England in 2019-2020, weekly rates of GP consultations for influenza-like illness (ILI) across the whole population peaked at 19.4 per 100,000 per week.[11] The ILI rate for 2020 to 2021 remained much lower than rates observed in previous seasons.[12] Estimates for the specific population group (1 to < 12 years) could not be found.

Recommended Treatment Options

Influenza is usually self-limiting in healthy individuals. Treatment of uncomplicated disease in healthy individuals is supportive and includes antipyretics, adequate fluid intake, rest, and staying off work or school until 24 hours after resolution of fever to limit spread to others.[7]

Amantadine, oseltamivir and zanamivir are recommended, within their marketing authorisations, for the treatment of influenza in adults and children if all the following circumstances apply:[13]

- National surveillance schemes indicate that influenza virus A or B is circulating
- The person is in an 'at-risk' group as defined below
- The person presents with an influenza-like illness and can start treatment within 48 hours (or within 36 hours for zanamivir treatment in children) of the onset of symptoms as per licensed indications.

Clinical Trial Information

Trial	**CP40559; NCT03653364, 2018-002154-70;** A Multicenter, Single-Arm, Open-Label Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients From Birth to < 1 Year With Influenza-Like Symptoms **Phase III** - Recruiting **Location(s):** 3 EU countries, United States, and other countries **Study completion date**: August 2022
Trial Design	Single group assignment, open label
Population	N = 30 (estimated), diagnosis of influenza virus infection, aged up to 1 year.
Intervention(s)	Participants will receive single oral dose of baloxavir marboxil on day 1 (based on body weight and age).
Comparator(s)	None

Copyright © National Institute for Health Research Innovation Observatory, The University of Newcastle upon Tyne.

Outcome(s)	Primary outcomes; • Percentage of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time frame: Up to day 29] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**CP40563; NCT03629184, 2018-002169-21;** A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients 1 to <12 Years of Age With Influenza-Like Symptoms **Phase III** - Completed **Location(s):** 2 EU countries, United States, and other countries **Study completion date:** April 2019
Trial Design	Randomised, parallel assignment, double-blind
Population	N = 173, diagnosis of influenza virus infection, aged 1 year to 11 years.
Intervention(s)	Participants will receive a single oral dose of baloxavir marboxil on day 1 (based on body weight). Oseltamivir matching placebo will also be administered orally twice daily (BID) for 5 days.
Comparator(s)	Participants will receive oseltamivir orally BID for 5 days (based on body weight). Baloxavir marboxil matching placebo will also be administered orally on day 1.
Outcome(s)	Primary outcomes; • Percentage of participants with AEs and SAEs [Time frame: Up to day 29] See trial record for full list of other outcomes.
Results (efficacy)	Median time (95% confidence interval) to alleviation of signs and symptoms of influenza was similar between groups: 138.1 (116.6–163.2) hours with baloxavir marboxil versus 150.0 (115.0–165.7) hours with oseltamivir.[1]
Results (safety)	Overall, 122 AEs were reported in 84 (48.6%) children. Incidence of AEs was similar between baloxavir marboxil and oseltamivir groups (46.1% vs. 53.4%, respectively). The most common AEs were gastrointestinal (vomiting/diarrhoea) in both groups [baloxavir: 12 children (10.4%); oseltamivir: 10 children (17.2%)]. No deaths, serious AEs or hospitalizations were reported.[1]

Trial	Japic CTI-163417; An Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of S-033188 after Administration of a Single Dose to Otherwise Healthy Pediatric Patients Aged 6 Months to < 12 Years with Influenza **Phase III** - Completed **Location(s):** Japan

Copyright © National Institute for Health Research Innovation Observatory, The University of Newcastle upon Tyne.

	Study completion date: December 2017
Trial Design	Single group assignment, open-label
Population	N = 107, diagnosis of influenza illness, aged 1 year to 11 years.[14]
Intervention(s)	Participants received 1 weight-adjusted dose of baloxavir marboxil on day 1.[14]
Comparator(s)	None
Outcome(s)	Primary outcomes; • Time to illness alleviation (TTIA), defined as time from baloxavir marboxil administration until the following criteria were reached and sustained for at least 21.5 hours: cough and nasal discharge/nasal congestion, both assessed as 0 (absent) or 1 (mild), and axillary temperature <37.5°C.[14] See trial record for full list of other outcomes.
Results (efficacy)	The median time to TTIA was 44.6 hours (95% CI, 38.9-62.5 hours), with 81.6% of patients being alleviated by 120 hours after treatment.[14]
Results (safety)	There were no serious AEs or AEs leading to discontinuation reported. 49 AEs were reported in 37 (34.6%) patients. Most common category was GI disorders (15.0%) with vomiting (all grade 1) reported in 8 patients (7.5%). Treatment-related AEs were reported in 4 (3.7%) patients; all judged grade 1 and resolved spontaneously.[14]

Trial	Japic CTI-173811; An Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of S-033188 2% Granules after Administration of a Single Dose to Otherwise Healthy Pediatric Patients with Influenza **Phase III** - Completed **Location(s):** Japan **Study completion date:** February 2019
Trial Design	Single group assignment, open-label
Population	N = 33, diagnosis of influenza illness, aged 0-<12 years
Intervention(s)	Participants received single oral dose of baloxavir marboxil 2% granules on day 1.
Comparator(s)	None
Outcome(s)	Primary clinical outcome; • Time to illness alleviation (TTIA), defined as time from baloxavir marboxil administration until the following criteria were reached and sustained for at least 21.5 hours: cough and nasal discharge/nasal congestion, both assessed as 0 (absent) or 1 (mild), and axillary temperature <37.5°C.[15] See trial record for full list of other outcomes.
Results (efficacy)	The median (95% CI) TTIA was 45.3 (28.5–64.1) hours, with approximately 80% of children being alleviated 120 hours after treatment.[15]
Results (safety)	No serious AEs or AEs leading to study discontinuation were reported. AEs were reported in 18 (54.5%) of 33 children. All AEs were of mild or moderate (grade 1 or 2)

Copyright © National Institute for Health Research Innovation Observatory, The University of Newcastle upon Tyne.

	severity. The most common AE, vomiting (all mild), was reported in 6 children (18.2%) and was considered not related to study drug. One child had an increase in platelet count on day 12 that was considered a mild treatment-related AE. There was no apparent difference in the incidence of AEs between children weighing <10 kg and 10 to <20 kg. No clinically meaningful findings were observed in clinical laboratory tests and vital signs.[15]

Estimated Cost

The cost of baloxavir marboxil is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Amatadine, oseltamivir 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- update. August 2020.

Other Guidance

- Public Health England (PHE). PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza. September 2019.[16]
- NICE Clinical Knowledge Summaries (CKS). Influenza – seasonal: Scenario: Post-exposure prophylaxis of influenza. 2019.[17]
- Healthcare Associated Infection & Antimicrobial resistance & Prescribing Programme (HARP). Managing Seasonal Influenza: Infection: Prevention and Control Guidance in Healthcare Settings. 2018.[18]
- World Health Organisation. WHO guidance document: Pandemic influenza preparedness and response. 2009.[19]

Additional Information

References

1 Baker J, Block SL, Matharu B, Burleigh Macutkiewicz L, Wildum S, Dimonaco S, et al. Baloxavir Marboxil Single-dose Treatment in Influenza-infected Children: A Randomized, Double-blind, Active Controlled Phase 3 Safety and Efficacy Trial (miniSTONE-2). *The Pediatric Infectious Disease Journal*. 2020;39(8). Available from:

Copyright © National Institute for Health Research Innovation Observatory, The University of Newcastle upon Tyne.

https://journals.lww.com/pidj/Fulltext/2020/08000/Baloxavir_Marboxil_Single_dose_Treatment_in.12.aspx.

2 Roche. *Product Development Portfolio.* 2021. Available from: https://www.roche.com/research_and_development/who_we_are_how_we_work/pipeline.htm [Accessed 3 October 2021].

3 electronic Medicines Compendium. *Xofluza 20 mg & 40 mg film coated tablets.* 2021. Available from: https://www.medicines.org.uk/emc/product/12879/smpc#gref [Accessed 3 October 2021].

4 Clinicaltrials.gov. *Comparison of efficacy and safety and anti-PD-1 antibody BGB-A317 versus docetaxel as treatment in the second- or third-line setting in participants with NSCLC. Trial ID: NCT03358875*. 2017. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03358875 [Accessed 3 October 2021].

5 Ng K. Xofluza (Baloxavir Marboxil) for the Treatment Of Acute Uncomplicated Influenza. *Pharmacy and Therapeutics*. 2019;44(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6336199/.

6 World Health Organization (WHO). *Influenza (Seasonal).* 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal) [Accessed 3 October 2021].

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

8 Centers for Disease Control and Prevention (CDC). *Key Facts About Influenza (Flu).* 2021. Available from: https://www.cdc.gov/flu/about/keyfacts.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Fkeyfacts.htm [Accessed 3 October 2021].

9 Ruf BR, Knuf M. The burden of seasonal and pandemic influenza in infants and children. *European journal of pediatrics*. 2014;173(3):265-76. Available from: https://doi.org/10.1007/s00431-013-2023-6.

10 Public Health England. *Seasonal influenza vaccine uptake in GP patients: winter season 2020 to 2021.* 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/996033/Annual-Report_SeasonalFlu-Vaccine_GPs_2020_to_2021.pdf [Accessed 13 October 2021].

11 Public Health England. *Surveillance of influenza and other respiratory viruses in the UK Winter 2019 to 2020.* 2020. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/895233/Surveillance_Influenza_and_other_respiratory_viruses_in_the_UK_2019_to_2020_FINAL.pdf [Accessed 13 October 2021].

12 Public Health England. *Surveillance of influenza and other seasonal respiratory viruses in the UK Winter 2020 to 2021.* 2021. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/995284/Surveillance_of_influenza_and_other_seasonal_respiratory_viruses_in_the_UK_2020_to_2021-1.pdf [Accessed 13 October 2021].

13 National Institute for Health and Care Excellence (NICE). *Influenza - Treatment.* 2020. Available from: https://pathways.nice.org.uk/pathways/influenza#content=view-node%3Anodes-treatment [Accessed 13 October 2021].

14 Hirotsu N, Sakaguchi H, Sato C, Ishibashi T, Baba K, Omoto S, et al. Baloxavir Marboxil in Japanese Pediatric Patients With Influenza: Safety and Clinical and Virologic Outcomes. *Clinical Infectious Diseases*. 2020;71(4):971-81. Available from: https://doi.org/10.1093/cid/ciz908.

15 Yokoyama T, Sakaguchi H, Ishibashi T, Shishido T, Piedra PA, Sato C, et al. Baloxavir Marboxil 2% Granules in Japanese Children With Influenza: An Open-label Phase 3 Study. *Pediatr*

Copyright © National Institute for Health Research Innovation Observatory, The University of Newcastle upon Tyne.

Infect Dis J. 2020 Aug;39(8):706-12. Available from: https://doi.org/10.1097/inf.0000000000002748.

16 Public Health England. *PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza.* Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/833572/PHE_guidance_antivirals_influenza_201920.pdf [Accessed 13 October 2021].

17 National Insititute for Health and Care Excellence (NICE). *Influenza - seasonal.* Available from: https://cks.nice.org.uk/topics/influenza-seasonal/ [Accessed 13 October 2021].

18 Healthcare Associated Infection & Antimicrobial resistance & Prescribing Programme (HARP). *Managing Seasonal Influenza: Infection Prevention and Control Guidance in Healthcare Settings.* Available from: http://www.wales.nhs.uk/sitesplus/documents/888/Managing%20Seasonal%20Influenza%20HARP.pdf [Accessed 13 October 2021].

19 World Health Organisation (WHO). *Global Influenza Programme.* Available from: https://apps.who.int/iris/bitstream/handle/10665/44123/9789241547680_eng.pdf;jsessionid=A92BADE6387E56767E216B4C36E1D177?sequence=1 [Accessed 13 October 2021].

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

Copyright © National Institute for Health Research Innovation Observatory, The University of Newcastle upon Tyne.