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NHS National Institute for Health Research

EVIDENCE BRIEFING
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Baloxavir marboxil for treatment of influenza A or B infection in otherwise healthy patients aged 12 years and older

NIHRIO ID	12970	**NICE ID**	9921
Developer/Company	Roche Products Ltd	**UKPS ID**	649601

Licencing and market availability plans	Baloxavir marboxil is currently in phase III clinical trials for the treatment of Type A and B influenza infection in otherwise healthy patients

SUMMARY

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). There are two main types of virus which cause flu: Influenza A and Influenza B. Most cases of flu will resolve without the need for any treatment beyond self-care within three to seven days. However flu can be more severe in those who are older, in babies and in people with long term health conditions, such as heart disease, asthma or diabetes. There are currently two medications available to treat and prevent flu during epidemics.

Baloxavir marboxil is the first new flu medication to be developed within the last 20 years. It 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 (oseltamivir) do not work. Additionally, only one dose of baloxavir marboxil is needed whereas existing flu medications need to be taken over several days. If licenced, baloxavir marboxil may offer an additional treatment option for patients with influenza A or B infection and for people who have suspected oseltamivir-resistant influenza.

PROPOSED INDICATION

Influenza infection (type A and B, otherwise healthy patients aged 12 years and older)[1, 2]

TECHNOLOGY

DESCRIPTION

Baloxavir marboxil (Xofluza) is a CAP endonuclease inhibitor. The influenza endonuclease is an essential subdomain of the viral RNA polymerase enzyme. CAP endonuclease processes host pre-mRNAs to serve as primers for viral mRNA and therefore has been a common target for studies of anti-influenza drugs. Viral gene transcription is primed by short-capped oligonucleotides that are cleaved from host cell pre mRNA by endonuclease activity. The endonuclease domain binds the N-terminal half of PA subunit (PAN) and contains a two-metal (Mn2+) active site that selectively cleaves the pre-mRNA substrate at the 3' end of a guanine. The administration of a CAP endonuclease inhibitor, such as baloxavir marboxil, prevents the above process from occurring, exhibiting its action at the beginning of the pathway before CAP endonuclease may exert its action.[3]

In phase III trials (CAPSTONE 1 (NCT02954354), CAPSTONE 2 (NCT02949011), participants received two to four 20mg (40 or 80mg) baloxavir marboxil tablets orally on day 1 of the study.[1, 2] The proposed dose specified by the company is a 40mg single dose in those weighing 40 to <80kg and 80mg single dose in those weighing ≥80kg.[4]

INNOVATION AND/OR ADVANTAGES

It is has been reported that baloxavir marboxil is the first flu medication with a novel mechanism of action within the last 20 years.[5] Non-clinical studies have demonstrated that baloxavir marboxil may be effective against oseltamivir-resistant flu strains and avian flu strains, where there are limited treatment options available.[6] Additionally, baloxavir marboxil is delivered as a single dose as opposed to current treatment options (e.g. oseltamivir) which are taken over 5 days.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Baloxavir marboxil does not currently have Marketing Authorisation in the EU for any indication.[7]

Baloxavir marboxil was granted priority review status for treatment of acute, uncomplicated infections in patients aged 12 years and older by the FDA in June 2018.[5]

PATIENT GROUP

DISEASE BACKGROUND

Influenza infection or 'flu' is an acute viral infection of the respiratory tract that spreads easily from person to person, mainly by tiny droplets produced when people with the flu cough, sneeze or talk. These droplets can land in the noses and mouths of people nearby. Less commonly, a person might get flu by touching a surface or object that has flu virus on it and then touching their own mouth, nose or eyes.[8, 9] Influenza is caused by a family of RNA viruses called orthomyxoviridae. There are three different types of influenza virus which cause disease:[10]

- Influenza A: occurs most frequently and is the most virulent. It is responsible for most major epidemics and pandemics.
- Influenza B: often co-circulates with influenza A during yearly outbreaks. Influenza B generally causes less severe clinical illness although it can still be responsible for outbreaks. In children, the severity may be similar to that experienced with influenza A.
- Influenza C: usually causes mild or asymptomatic infection similar to the common cold.

Minor changes in the virus proteins between influenza seasons (antigenic drift) results in annual epidemics with winter peaks.[8] Influenza occurs most frequently in the UK in the winter months between October and May.[10] In contrast, pandemics occur when a new influenza A subtype emerges abruptly because of a major shift in the proteins on the virus surface (antigenic shift) often because of a combination with viruses which circulate in animals. As people have no immunity to the new subtype, the infection spreads quickly.[8]

Anyone can catch influenza, even healthy people, however some people are at increased risk of catching influenza and developing serious complications. People at risk include; people aged 65 years and older, people with chronic medical conditions (e.g. asthma, diabetes or heart disease), pregnant women and young children.[9] Common symptoms of influenza include sudden onset of fever, myalgia, headache, malaise, dry cough, sore throat, nasal congestion, nausea, vomiting and diarrhoea. The incubation period (time from infection to development of symptoms) for influenza is 1 to 4 days. Viral shedding (where the virus is infectious and can be passed on to others) usually occurs from one day before development of symptoms to 5 to 7 days after.[8]

Influenza is generally self-limiting in healthy people, with recovery occurring within 3 to 7 days. However those at high risk may develop more severe disease or complications, and may require antiviral therapy.[8] Complications of influenza can include bacterial pneumonia, ear infections, sinus infections and worsening of chronic medical conditions e.g. congestive heart failure, asthma or diabetes.[9] Influenza can sometimes cause death, and mortality is highest in those with influenza complications (necessitating hospital admission) and in infants aged 6 months and younger.[8]

CLINICAL NEED AND BURDEN OF DISEASE

According to Public Health England, winter 2016-17 data on influenza in England, the weekly rates of influenza-like illness peaked at 18 per 100,000 in week 1 of 2017 (includes GP in- and out-of-hours consultations, emergency department attendances and NHS 111 calls).[12] If this prevalence is applied to the mid-2017 UK population of 12 to 64 year olds of 47,414,919[11] this equates to a peak weekly flu prevalence of 8,535.

According to the UK Severe Influenza Surveillance System (USISS) mandatory scheme data for England, there were 3,175 influenza confirmed admissions to intensive care unit/high dependency unit (rate of 0.22 per 100,000) and 320 deaths due to influenza from week 40 2017 to week 15 2018.[12]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

As most cases of flu are self-limiting, self-care is the main recommendation for the treatment of influenza. This includes rest and sleep, keeping warm, taking paracetamol or ibruprofen to lower body temperature and treat aches and pains, and drinking plenty of water to avoid dehydration. Antibiotics are not recommended for the treatment of influenza.[13] There are currently two drugs available for the treatment and management of influenza: oseltamivir (Tamiflu) and zanamivir (Relenza).[14]

For an otherwise healthy person, antiviral drugs (oseltamivir or zanamivir) are not usually recommended (in accordance with NICE recommendation), unless the prescriber feels that the individual is at risk of developing serious complications from influenza. In this case, oseltamivir should be prescribed if national surveillance schemes indicate that influenza virus is circulating, and the person can start treatment within 48 hours.[10]

Oseltamivir and zanamivir are licenced for use within the first 48 hours of the first symptoms, and have been shown to reduce duration of symptoms in healthy adults by 1-1.5 days, and to reduce the risk of complications in the elderly and those with chronic disease. Oseltamivir and zanamivir are also licenced for post-exposure prophylaxis; oseltamivir should be given within 48 hours of exposure and zanamivir should be given within 36 hours of exposure (although both drugs may be given outside of these timeframes in cases of severe influenza or in the immunocompromised as an unlicensed indication).[14]

There is evidence that some influenza A virus strains may have reduced susceptibility to oseltamivir, but retain susceptibility to zanamivir. Therefore, zanamivir is usually reserved for immunocompromised patients or for when resistance to oseltamivir is suspected.[14]

CURRENT TREATMENT OPTIONS

- Oseltamivir (Tamiflu) is licenced for the treatment and prevention of influenza for children aged 1 month to 17 years and adults.[18]
- Zanamivir (Relenza) is licensed for the post-exposure prophylaxis of influenza, prevention of influenza during an epidemic and treatment of influenza in children aged 5 to 17 years old and adults aged 18 years and older. It also has unlicensed use for up to 10 days in cases of suspected resistance to oseltamivir.[15]

PLACE OF TECHNOLOGY

If licenced, baloxavir marboxil may offer an additional treatment option for patients with influenza A or B infection. It may also offer a treatment option for people who have suspected oseltamivir-resistant influenza.

CLINICAL TRIAL INFORMATION

Trial	CAPSTONE 1, NCT02954354, 1601T0831; Baloxavir marboxil vs Oseltamivir vs placebo; phase III
Sponsor	Shionogi
Status	Published in abstract
Source of Information	Trial registry[1], abstract[16], press release[17]
Location	Not stated
Design	Randomised, double blind, placebo-controlled, active-controlled
Participants	n=1,436; aged 12-64 years; diagnosis of influenza virus infection; within the last 48 hours from symptoms onset
Schedule	Adult participants (aged 20-64 years old) were randomised to one of three treatment arms: 1. Active treatment: Two or four 20mg baloxavir marboxil tablets orally on day 1 and one oseltamivir placebo capsule orally twice a day (BID) on days 1 to 5 2. Active comparator: 75mg oseltamivir twice a day on days 1 to 5 and two or four placebo tablets on day 1 3. Placebo: Two or four placebo tablets on day 1 and one oseltamivir placebo capsule orally twice a day on days 1 to 5. Adolescent participants (aged 12 to 19 years old) were randomised to one of two treatment arms: 1. Active treatment: Two or four baloxavir marboxil 20mg tablets on day 1. 2. Placebo: Two or four baloxavir marboxil placebo tablets on day 1.
Follow-up	Active treatment for 1 day (single dose). Follow-up 14 days
Primary Outcomes	Time to alleviation of symptoms [Time Frame: From day 1 pretreatment (baseline) up to day 14]
Secondary Outcomes	• Percentage of participants positive for influenza virus titer at each time point [Time Frame: days 1, 2, 3, 5 and 9] • Percentage of participants positive for influenza virus by RT-PCR at each time point [Time Frame: days 1, 2, 3, 5 and 9] • Change from baseline in virus titer at each time point [Time Frame: From day 1 pretreatment to days 2, 3, 5, and 9] • Change from baseline in virus RNA (RT-PCR) at each time point [Time Frame: From day 1 pretreatment to days 2, 3, 5, and 9]

	• Area under the curve (AUC) adjusted by baseline in virus titer [Time Frame: day 1 to day 9] • Area under the curve (AUC) adjusted by baseline of virus RNA [Time Frame: day 1 to day 9] • Time to cessation of viral shedding by virus titer [Time Frame: day 1 to day 9] • Time to cessation of viral shedding by virus RNA [Time Frame: day 1 to day 9] • Percentage of participants whose symptoms have been alleviated at each time point [Time Frame: days 2, 3, 4, 5, 6, 9, and 15] • Time to alleviation of the 4 systemic symptoms [Time Frame: Initiation of study treatment up to day 14] • Time to alleviation of the 3 respiratory symptoms [Time Frame: Initiation of study treatment up to day 14] • Change from baseline in composite symptom score at each time point [Time Frame: day 1 pretreatment to morning and evening on days 2 to 9 and evening on days 10 to 14] • Time to resolution of fever [Time Frame: Initiation of study treatment up to day 14] • Percentage of participants reporting normal temperature at each time point [Time Frame: days 1 to 3 at morning, noon, evening and bedtime, days 4 to 14 morning and evening] • Body temperature at each time point [Time Frame: days 1 to 3 at morning, noon, evening and bedtime, days 4 to 14 morning and evening] • Time to alleviation of individual symptoms [Time Frame: Initiation of study treatment up to day 14] • Time to return to preinfluenza health status [Time Frame: Initiation of study treatment up to day 14] • Percentage of participants with influenza-related complications [Time Frame: Initiation of study treatment up to day 14] • Number of participants with adverse events (AEs) [Time Frame: day 1 to day 22 plus or minus 3 days]
Key Results	A total of 1,436 patients were randomised. Time to alleviation of influenza symptoms (TTAS) was significantly shorter in the baloxavir marboxil group than in the placebo group (median TTAS: 53.7 hours vs 80.2 hours, p<0.0001). Median time to cessation of viral shedding was 24 hours in patients treated with baloxavir marboxil, compared to 72 hours in those treated with oseltamivir (p<0.0001) and 96 hours for placebo (p<0.0001). Patients in the baloxavir

	marboxil group had significantly greater reductions from baseline in both viral titre and RNA content than those in oseltamivir or placebo groups at all time-points until day 3 (compared with oseltamivir) or day 5 (compared with placebo).[16]
Adverse effects (AEs)	For patients treated with baloxavir marboxil, the incidence of treatment-related adverse events was comparable to those treated with placebo. Baloxavir marboxil demonstrated a statistically significant decrease in incidence of treatment-related adverse events compared to oseltamivir. Incidence of nausea was less frequent for patients treated with baloxavir marboxil compared to patients treated with oseltamivir.[17]
Expected reporting date	Company stated that publication is expected in August/September 2018.

Trial	CAPSTONE 2, NCT02949011, EudraCT2016-002688-32; Baloxavir marboxil vs Oseltamivir vs placebo; phase III
Sponsor	Shionogi
Status	Complete but unpublished
Source of Information	Trial registry[2]
Location	No countries listed
Design	Randomised, double blind, placebo-controlled, active-controlled
Participants	n=2,184 ; aged 12 years and above; diagnosis of influenza virus infection; within the last 48 hours from the onset of symptoms
Schedule	All participants were randomised to one of three treatment arms: 1. Active treatment: Two or four 20mg baloxavir marboxil tablets orally on day 1 and one oseltamivir placebo capsule orally twice a day (BID) on days 1 to 5 2. Active comparator: 75mg oseltamivir twice a day on days 1 to 5 and two or four placebo tablets on day 1 3. Placebo: Two or four placebo tablets on day 1 and one oseltamivir placebo capsule orally twice a day on days 1 to 5.
Follow-up	Active treatment for 1 day (single dose). Follow-up 14 days
Primary Outcomes	Time to improvement of symptoms [Time Frame: From day 1 pre-treatment up to day 14]
Secondary Outcomes	• Percentage of participants positive for influenza virus titer and viral RNA at each time point [Time Frame: days 1, 2, 3, 5 and 9] • Change from baseline in virus titer at each time point [Time Frame: from day 1 pretreatment to days 2, 3, 5, and 9]

	• Change from Baseline in viral RNA load at each time point [Time Frame: from day 1 pretreatment to days 2, 3, 5, and 9] • Area under the curve (AUC) adjusted by baseline in virus titer [Time Frame: day 1 to day 9] • Area under the curve (AUC) adjusted by baseline in viral RNA load [Time Frame: day 1 to day 9] • Time to cessation of viral shedding [Time Frame: From day 1 to day 9] • Percentage of participants whose symptoms have been improved at each time point [Time Frame: days 2-9, morning and evening, and days 10-14, evenings] • Time to alleviation of symptoms [Time Frame: day 1 pretreatment up to day 14] • Time to improvement in the 4 systemic symptoms [Time Frame: day 1 pretreatment up to day 14] • Time to improvement in the 3 respiratory symptoms [Time Frame: day 1 pretreatment up to day 14] • Time to resolution of fever [Time Frame: day 1 pretreatment up to day 14] • Percentage of participants reporting normal temperature at each time point [Time Frame: days 1 to 3 at morning, noon, evening and bedtime, days 4 to 14 morning and evening] • Body temperature at each time point [Time Frame: days 1 to 3 at morning, noon, evening and bedtime, days 4 to 14 morning and evening] • Time to improvement of each influenza symptom [Time Frame: day 1 pretreatment up to day 14] • Time to return to preinfluenza health status [Time Frame: day 1 pretreatment up to day 14] • Percentage of participants requiring systemic antibiotics for infections secondary to influenza infection [Time Frame: day 2 to day 22] • Percentage of participants with influenza-related complications [Time Frame: day 1 to day 22] • Number of participants with adverse events [Time Frame: day 1 to day 22 plus or minus 3 days]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date was reported as April 2018. Company stated results due to be presented at conference in Q3 2018.

ESTIMATED COST

The cost of baloxavir marboxil is not yet known.

The current direct comparator to this treatment, oseltamivir, costs £15.41 for a pack of ten 45mg capsules, and £15.41 for a pack of ten 75mg capsules.[18]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance proposed. Intravenous zanamivir for treating influenza in hospital (ID1196). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Peramivir for treating influenza (ID828). Expected date of issue to be confirmed.
- NICE technology appraisal. Amantadine, 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.
- NICE guideline in development. Flu vaccination: increasing uptake (GID-PHG96). Expected date of issue to be confirmed.
- NICE quality standard in development. Influenza (GID-TA10298). Expected March 2019.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified

OTHER GUIDANCE

- NHS England. Operating framework for managing the response to pandemic influenza. December 2017.[19]
- Public Health England. Influenza: treatment and prophylaxis using anti-viral agents. January 2014. Last updated October 2017.[20]
- National Institute for Communicable Diseases. Influenza: NICD recommendations for the diagnosis, prevention, management and public health response. May 2017.[21]
- Health Protection Scotland. Guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza 2016-17. October 2016.[22]
- NHS England. Pandemic Influenza: Guidance to the NHS on current and future preparedness for an influenza pandemic. April 2016.[23]
- NICE Clinical Knowledge Summaries. Influenza – seasonal. October 2015.[10]
- World Health Organisation. WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. February 2010.[24]
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