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HEALTH TECHNOLOGY BRIEFING
MARCH 2020

Baloxavir marboxil for the treatment of influenza in patients aged 12 years and older and are at high risk of developing influenza complications

NIHRIO ID	28432	**NICE ID**	10316
Developer/Company	Roche Products Ltd	**UKPS ID**	653665

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

SUMMARY

Baloxavir marboxil is a medicinal product currently in development for the treatment of influenza patients aged 12 years and above including patients at high risk of developing influenza complications. 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 babies and in people with long term health conditions, such as heart disease, asthma or diabetes.

Baloxavir marboxil is given by mouth as tablets within 48 hours of symptom onset 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 licenced, baloxavir marboxil may offer an additional treatment option for patients with influenza.

PROPOSED INDICATION

Treatment of influenza in patients aged 12 and above who are at high risk of developing influenza-related complications.[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. Studies have shown that inhibiting this activity strongly decreased viral replication.[2]

Baloxavir marboxil is in development for the treatment of influenza in patients aged 12 years and above including patients at high risk of developing influenza complications. In the phase III randomised trial (NCT02949011; CAPSTONE 2) patients at high risk of developing influenza-related complications received either 40mg (if body weight <80 kg) or 80mg (if body weight ≥80 kg) of baloxavir marboxil tablets taken once on day 1 or 75mg oseltamivir tablets taken twice daily for 5 consecutive days or placebo.[3,4]

INNOVATION AND/OR ADVANTAGES

Oseltamivir and zanamivir are currently recommended for the treatment of influenza.[5] 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 is 75 mg twice daily for 5 days whilst, baloxavir marboxil is taken as a single dose.[3,6] 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, baloxavir marboxil's mechanism of action allows for use in patients who may have oseltamivir resistance.[8]

The magnitude and rapidity of antiviral effects of single doses of baloxavir marboxil in the CAPSTONE 1 + 2 studies were greater than those observed with systemic neuraminidase inhibitors in earlier studies involving adults with uncomplicated influenza.[9]

Baloxavir marboxil was associated with significantly more rapid declines in infectious viral load than placebo or oseltamivir. The median duration of infectious virus detection was shorter in the baloxavir marboxil group (24.0 hours) than in the oseltamivir group (72.0 hours, P<0.001) and the placebo group (96.0 hours, P<0.001).[9]

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 (flu) is an acute respiratory infection caused by influenza viruses which circulate in all parts of the world.[10] 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.[11]

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.[10]

Influenza can cause mild to severe illness, and at times can lead to death. Influenza is different from a cold. Influenza usually comes on suddenly. People who have influenza often feel some or all of these symptoms:[12]

- fever or feeling feverish/chills
- cough
- sore throat
- runny or stuffy nose
- muscle or body aches
- headaches
- fatigue (tiredness)
- some people may have vomiting and diarrhea, though this is more common in children than adults.

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.[12]

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.[11] Complications of influenza can include pneumonia, ear infections, sinus infections and worsening of chronic medical conditions e.g. congestive heart failure or asthma.[13] 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.[11]

Accoridng to NICE, people 'at risk' are defined as those who have one or more of the following:[14]

- Chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)
- Chronic heart disease
- Chronic renal disease
- Chronic liver disease
- Chronic neurological conditions
- Immunosuppression
- Diabetes mellitus
- Aged ≥65 years

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:[15]

- 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.[16]

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 these, 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.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

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.[11]

NICE, Public Health England, UK Chief Medical Officers, and the WHO recommend treatment of suspected and confirmed influenza for individuals at risk of complicated influenza.[11]

Individuals with complicated influenza may be helped by antiviral treatment. Treatment is most effective if started within 48 hours of symptom onset, and it should not be delayed while awaiting results of investigations. Meta-analysis of individual participant data found that, compared with late treatment, early treatment (within 48 hours of symptom onset) of hospitalised individuals with complicated influenza reduced the odds of mortality by 52%. Some individuals may require antibiotic therapy to treat secondary bacterial infections.[11]

CURRENT TREATMENT OPTIONS

Oseltamivir and zanamivir are recommended, within their marketing authorisations, for the treatment of influenza in adults and children if all the following circumstances apply:[14]

- 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.

PLACE OF TECHNOLOGY

If licenced, baloxavir marboxil may offer an additional treatment option for patients aged 12 years and older, who have been symptomatic for no more than 48 hours including patients at high risk of developing influenza complications.

CLINICAL TRIAL INFORMATION

Trial	**CAPSTONE 2; NCT02949011, 2016-002688-32;** A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared With Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients With Influenza at High Risk of Influenza Complications **Phase III** **Location(s): North America, other countries**
Trial design	- Randomised, parallel assignment, double-blind
Population	- Population size: 2184 (actual enrolled) - Patients with influenza with high risk of influenza complications - Aged 12 years and older
Intervention(s)	- Baloxavir marboxil (oral) - Oseltamivir (oral)
Comparator(s)	- Oseltamivir (oral) - Placebo to baloxavir marboxil (oral)
Outcome(s)	Time to improvement of influenza symptoms (TTIIS) [Time frame: from day 1 pretreatment up to day 22]
Results (efficacy)	- TTIIS was significantly shorter in Baloxavir marboxil than placebo (median 73.2 hours vs. 102.3 hours, $P < 0.0001$) and numerically shorter than Oseltamivir (81.0 hours, $P = 0.8347$). - TTIIS in Baloxavir marboxil patients with A/H3N2 virus (median: 75.4 hours) was significantly shorter than in placebo (100.4 hours; P =0.0141) and was significantly shorter in patients with influenza B (74.6 hours) than in either placebo (100.6 hours; $P = 0.0138$) or Oseltamivir (101.6 hours; $P = 0.0251$). For full results see trial record.
Results (safety)	- The incidence of any (25.1–29.7%) or serious adverse events (0.7–1.2%) did not differ significantly across the groups. For full results see trial record.

ESTIMATED COST

The cost range of baloxavir marboxil is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Peramivir for treating influenza (ID828). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Intravenous zanamivir for treating influenza in hospital (ID1196). Expected date of issue to be confirmed.

- NICE technology appraisal guidance in development. Baloxavir marboxil for treating influenza (ID1537). 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. Zanamivir for the treatment of influenza in adults (TA15). November 2000.

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: Treatment of influenza. April 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

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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.