Zanamivir (Relenza) as an intravenous formulation for the treatment of hospitalised patients with influenza

NIHR HSRIC ID: 6033

Lay summary

Zanamivir is a new drug to treat patients who have been admitted to hospital with influenza. It is for patients who are not responding to other antiviral medicines or who are only able to receive treatment via a drip; it is also an option for patients who are infected with influenza virus which is resistant to other medicines. Zanamivir is administered via a drip directly into the bloodstream.

This briefing is based on information available at the time of research 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.

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.
TARGET GROUP

- Patients requiring hospitalisation following influenza infection: patients who are not responding to either oral or inhaled currently authorised antiviral medicinal products; patients for whom drug delivery by a route other than intravenous (IV) infusion is not feasible; or patients infected with documented influenza virus resistant to other antiviral agents and not suitable for therapy with inhaled zanamivir.

TECHNOLOGY

DESCRIPTION

Zanamivir (Relenza; GG167; GR121167) is an inhibitor of the enzyme neuraminidase, a surface glycoprotein essential for the replication of type A and B influenza viruses. In phase III clinical trials, zanamivir is administered by IV at a dose of 600mg twice daily for adults with a treatment duration of 5-10 days¹.

Zanamivir IV is available in the EU for compassionate use to treat critically ill adults and children with a life-threatening condition due to suspected or confirmed pandemic influenza virus infection or infection due to seasonal influenza A or B².

Zanamivir (Relenza) is licensed in the UK as an inhalation powder for the treatment of influenza A and B in adults and children (≥ 5 years) who present with symptoms typical of influenza when influenza is circulating in the community; and for post-exposure prophylaxis of influenza A and B in adults and children (≥ 5 years) following contact with a clinically diagnosed case in a household. In exceptional circumstances, zanamivir may be considered for seasonal prophylaxis of influenza A and B during a community outbreak³.

A common side effect of zanamivir is skin rashes. Less common effects include allergic or vasovagal reactions, respiratory symptoms including breathlessness, and urticarial reactions. Rare adverse events include anaphylactic reactions, and skin problems such as Stevens-Johnson syndrome. There have been reports of convulsions and psychiatric events such as depressed level of consciousness, abnormal behaviour, hallucinations and delirium during zanamivir administration in patients with influenza. The frequency of these effects has not been reported and symptoms were mainly reported in children and adolescents.

INNOVATION and/or ADVANTAGES

If licensed, zanamivir IV will offer an additional treatment option for patients who have been hospitalised with influenza infections. The exact indication has not yet been decided⁴.

DEVELOPER

GlaxoSmithKline.

AVAILABILITY, LAUNCH OR MARKETING

Zanamivir IV is in phase III clinical trials for hospitalisation following influenza infection.

---

¹ Company information.
Influenza is an acute infection of the respiratory tract usually caused by the influenza A or B virus. Influenza is highly infectious with an incubation period of 1–3 days. The symptoms of uncomplicated influenza include fever, dry chesty cough, sore throat, tiredness, myalgia and headache. Influenza infection is usually self-limiting and lasts for 3–4 days, with some symptoms persisting for 1–2 weeks. The severity of the illness however, can vary from asymptomatic infection to life-threatening complications (known as ‘complicated influenza’).

Complicated influenza infection is defined as that requiring hospital admission and/or with symptoms of lower respiratory tract infection, central nervous system involvement and/or a significant exacerbation of an underlying medical condition. The most common complications include secondary bacterial infections such as otitis media, pneumonia and bronchitis. For certain ‘at risk’ groups, influenza infection can be very serious and require specific antiviral medication to reduce viral replication. Groups at risk include those over the age of 65; pregnant women; those with long term medical conditions such as diabetes, heart disease, lung disease, kidney disease and/or neurological disease; and those with a weakened immune system.

The impact of influenza infection on the population varies from year to year and is influenced by changes in the virus that, in turn, influence the proportion of the population that may be susceptible to infection and the severity of the illness.

In 2014-15, there were 4,122 hospital admissions for influenza (ICD-10 J10 and J11), resulting in 41,389 bed days and 7,902 finished consultant episodes. In 2014, there were 118 deaths from influenza (J09-J11) in England and Wales. In comparison with in 2013-14, when there were 1,863 hospital admissions for influenza (ICD-10 J10 and J11), resulting in 17,777 bed days and 3,188 finished consultant episodes. In 2013, there were 161 deaths from influenza (J09-J11) in England and Wales. The number of registered deaths from influenza is likely to be an underestimate of the impact of influenza virus circulating in the community on mortality; many deaths arising from influenza infections will be from complications e.g. pneumonia or exacerbations of underlying medical conditions.

The population likely to be eligible to receive zanamivir IV could not be estimated from available published sources.

NICE Guidance


**NHS England Policies and Guidance**


**Other Guidance**


**CURRENT TREATMENT OPTIONS**

In certain groups and individuals, influenza infection can progress from a mild illness manifesting as fever, cough, sore throat, headache, malaise, and muscle and joint pains to one in which there is shortness of breath, chest pain and/or confusion, which may be indicative of pneumonia. There may also be a significant exacerbation of an underlying medical condition, such as heart, liver, lung or renal insufficiency, or diabetes mellitus. Patients with signs and symptoms of suspected pneumonia are likely to need assessment and treatment in hospital. Treatment options will include antiviral drugs and intravenous antibiotics. Depending on the severity of the disease and any other co-morbidities, some form of ventilation may be required.

Pneumonia that is caused directly by the influenza virus is usually more serious and may require prolonged hospital admission and specialist ventilation techniques including extracorporeal membrane oxygenation (ECMO). ECMO provides both cardiac and respiratory support and involves removing blood from the patient, adding oxygen and removing carbon dioxide from the blood, and then pumping it back into the patient. ECMO can maintain pulmonary function while the lungs heal.
### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01231620, 114373; zanamivir vs oseltamivir; phase III.</th>
<th>NCT01527110, 115215; zanamivir; phase III.</th>
<th>NCT01014988, 113678; zanamivir; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Complete but unpublished.</td>
<td>Published.</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry[^6], manufacturer[^6].</td>
<td>Publication[^17], trial registry[^18].</td>
<td>Publication[^19], trial registry[^1].</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>Japan.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=626 (planned); aged ≥16 yrs; hospitalised; clinical symptoms of influenza; laboratory confirmed influenza or strong suspicion of influenza; no prior anti-viral agent; does not need ECMO or dialysis at baseline; potential survival ≥ 48 hours.</td>
<td>n=21; aged ≥16 yrs; hospitalised; laboratory confirmed influenza; does not need ECMO at baseline; potential survival ≥ 48 hours.</td>
<td>n=133; aged ≥6 mths; hospitalised; confirmed influenza.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to zanamivir IV 300mg plus oral placebo; or zanamivir IV 600mg plus oral placebo; or oseltamivir 75mg oral plus IV placebo. All administered twice daily for 5 days initially, with an extension for 5 more days if clinically warranted.</td>
<td>Pts receive zanamivir IV 600mg twice daily for 5 days initially, with an extension of 5 days if clinically warranted.</td>
<td>Pts receive zanamivir IV 600mg twice daily or age-adjusted, weight-based dose (not exceeding 600mg) for 5 days initially, with an extension of 5 days if clinically warranted.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment 24 days maximum, follow-up up to 48 days.</td>
<td>Active treatment 5-10 days, follow-up up to 33 days.</td>
<td>Active treatment 5-10 days, follow-up up to 33 days.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Time to clinical response (TTCR).</td>
<td>Adverse events (AEs); clinical chemistry and haematology data; treatment emergent toxicities; heart rate; blood pressure; oxygen saturation; respiration rate; temperature; ECG.</td>
<td>AEs; clinical chemistry and haematology data; heart rate, blood pressure, oxygen saturation, respiration rate and temperature; ECG.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Katz Index of Independence in Activities of Daily Living (ADL); mortality; disease progression and complications of influenza; duration of hospitalisation and intensive care unit (ICU) stay; time to improvement of vital signs; time to improvement in respiratory</td>
<td>TTCR; time to return to pre-morbid level of activity; ventilation status; length of ICU and hospital stay; viral susceptibility to zanamivir; resistance emergence; clinical symptoms of influenza; complications; antibiotic</td>
<td>Viral load and time to undetectable viral RNA; viral susceptibility to zanamivir; resistance emergence; mortality; complications; antibiotic use; ventilation status; time to resolution of all and individual vital signs; length of total ICU stay and</td>
</tr>
</tbody>
</table>

[^6]: Company information.
status; time to reduction in viral load and undetectable viral RNA; safety and tolerability; electrocardiogram (ECG); No quality of life measurement included in trial outcomes.

Key results

No statistically significant difference was observed for the difference in TTCR between any trial arms. Results for secondary efficacy variables were similar between treatment groups.

Median time to clinical response and time to virological improvement approximately 4 days (range 0.5-22) and 3 days (range 2-5), respectively.

Pts received zanamivir IV a median of 4.5 days (range 1-7) after onset of influenza; 83% required intensive care. Most common influenza type/subtype was A/H1N1pdm09 (71%). Dose adjustments for renal impairment yielded similar zanamivir exposures. 93 pts with PCR confirmed influenza had a median decrease in viral load of 1.42 log10 copies/mL after 2 days of treatment.

Adverse effects (AEs)

In the zanamivir 300mg IV group 44% pts reported non-serious AEs with the most frequently reported being diarrhoea and hypertension. In the zanamivir 600mg IV group, 45% pts reported non-serious AEs with the most frequently reported being diarrhoea and constipation. In the oseltamivir group 54% subjects reported non-serious adverse events with the most frequently reported being diarrhoea, constipation and increased aspartate aminotransferase. 8% subjects in the zanamivir 300mg IV group reported a serious adverse effect (SAE), the most common being acute respiratory distress syndrome, respiratory failure and acute kidney injury. 6% subjects in the zanamivir 600mg IV group reported an SAE, the most common being acute respiratory distress syndrome and respiratory failure. 7% subjects in the oseltamivir group reported an SAE, the most common being respiratory failure. There were 9 fatalities in the

Overall AEs and SAEs reported in 13 (62%) and 4 (19%), respectively. There were no reported patterns of AEs or SAEs.

AEs and SAEs reported in 85% and 34%, respectively; SAEs included bacterial pulmonary infections (8%), respiratory failure (7%), sepsis or septic shock (5%), and cardiogenic shock (5%). No drug-related trends in safety parameters identified. Protocol-defined liver AEs and SAEs were observed in 13%. The 14- and 28-day all-cause mortality rates were 13% and 17%. No fatalities were considered zanamivir IV related.
Zanamivir powder for inhalation is already marketed as Relenza in the UK; a pack of 20 x 5mg inhalation powder blisters costs £16.36\(^{20}\).

The cost of zanamivir IV is not yet known.

### IMPACT - SPECULATIVE

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified

**Impact on Health and Social Care Services**
- Increased use of existing services
- Decreased use of existing services
- Need for new services
- None identified

**Impact on Costs and Other Resource Use**
- Increased drug treatment costs
- Reduced drug treatment costs
- Other reduction in costs
- None identified

**Other Issues**
- Clinical uncertainty or other research question identified
- None identified

### REFERENCES


16 ClinicalTrials.gov. A phase III international, randomized, double-blind, double-dummy study to evaluate the efficacy and safety of 300 mg or 600 mg of intravenous zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily in the treatment of hospitalized adults and adolescents with influenza. [www.clinicaltrials.gov/ct2/show/NCT01231620](http://www.clinicaltrials.gov/ct2/show/NCT01231620) Accessed 1 November 2016.


