### Interferon beta-1a (Traumakine) for acute respiratory distress syndrome – first line

#### SUMMARY

Interferon beta-1a is intended to be used for the first line treatment of acute respiratory distress syndrome (ARDS) in adults. If licensed, interferon beta-1a will offer an additional treatment option for this patient group that directly targets the pathophysiological processes underlying ARDS. Interferon beta-1a is an interferon beta 1 agonist with the ability to up-regulate CD73, a molecule which yields anti-inflammatory adenosine, which enhances endothelial barrier function and leads to the prevention of vascular leakage, the predominant pathophysiological event in ARDS. Vascular leakage in ARDS allows plasma exudation into the alveolar space leading to potentially life-threatening hypoxaemia. Other preparations of interferon beta-1a are already licensed and available in the UK for patients with relapsing multiple sclerosis and with a single demyelinating event with an active inflammatory process.

The incidence of ARDS in the population is not clearly established. Estimates vary widely due to a number of reasons, including variation in patient demographics, healthcare delivery models and definitions of the condition. A total of 38 deaths from ARDS were registered in England and Wales during 2012. In England, there were 219 admissions (165 emergency admissions) for ARDS in 2012-13, resulting in 459 finished consultant episodes and 6,463 bed days, although these figures are unlikely to reflect the total number of patients treated for ARDS as the condition is often the result of another illness for which the patient has been hospitalised.

The management of ARDS aims to maintain oxygenation and support the patient whilst treating any underlying condition. Most patients will be admitted to an intensive care unit in order to effectively manage the condition and most will require mechanical ventilation. Treatment of the underlying cause of ARDS will depend on the condition, for example sepsis will be treated with appropriate antibiotics. A phase I/II dose escalation trial has been completed and results reported. A phase III clinical trial comparing the efficacy of interferon beta-1a and tolerability against placebo is planned for 2014.
TARGET GROUP

- Acute respiratory distress syndrome (ARDS): adults – first line.

TECHNOLOGY

DESCRIPTION

Interferon beta-1a (Traumakine; FP-1201; MR11-A8) is an interferon beta 1 agonist with the ability to up-regulate CD73 (also known as Ecto-5-nucleotidase) molecule expression. CD73, expressed on vascular endothelium, epithelial cells and a leucocyte subset, yields anti-inflammatory adenosine\(^1\), which acts to enhance endothelial barrier function via adenosine receptor activation, and prevents vascular leakage. ARDS is the result of severe direct or indirect lung injury, e.g. from infection leading to sepsis or trauma causing tissue injury. In ARDS the predominant pathophysiological event is increased vascular leakage caused by the inflammatory response to the underlying lung injury. This leakage allows plasma exudation into the alveolar space leading to potentially life-threatening hypoxaemia\(^1\). Interferon beta-1a has the potential to reduce the impact of ARDS by reducing vascular leakage. In the phase I/II dose escalation trial, the optimal tolerated dose (OTD) of interferon beta-1a was 10µg administered intravenously (IV) once daily for six days. A phase III clinical trial is planned for 2014.

Interferon beta-1a is already licensed and available in the UK as AVONEX and Rebif for patients with relapsing multiple sclerosis and for patients with a single demyelinating event with an active inflammatory process\(^2,3\). A number of common and very common adverse effects are associated with the currently available formulations of interferon beta-1a including:

**AVONEX**

- Headache, flu-like symptoms, pyrexia, chills, sweating, decreased lymphocyte count, decreased white blood cell, decreased neutrophil count, decreased haematocrit, increased blood potassium, increased blood urea nitrogen, muscle spasticity, hypoesthesia, rhinorrhea, vomiting, diarrhoea, nausea, rash, sweating, contusion, muscle cramp, neck pain, myalgia, arthralgia, pain in extremity, back pain, muscle stiffness, musculoskeletal stiffness, anorexia, flushing, injection site pain, injection site erythema, injection site bruising, asthenia, pain, fatigue, malaise, night sweats, depression, insomnia\(^2\).

**Rebif**

- Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia, increased transaminase, headache, injection site inflammation, injection site reaction, influenza-like symptoms, severe elevations in transaminases, depression, insomnia, diarrhoea, vomiting, nausea, pruritus, rash, erythematous rash, maculo-papular rash, alopecia, myalgia, arthralgia, injection site pain, fatigue, rigors, fever\(^3\).

INNOVATION and/or ADVANTAGES

If licensed, interferon beta-1a will offer an additional treatment option for this patient group that directly targets the pathophysiological processes underlying ARDS.
AVAILABILITY, LAUNCH OR MARKETING

Interferon beta-1a is a designated orphan drug in the EU for acute lung injury, including ARDS.

A phase III clinical trial is planned for 2014.

PATIENT GROUP

BACKGROUND

ARDS is a life-threatening condition where respiration fails to provide sufficient oxygen to the body as a result of the lungs becoming severely inflamed due to infection or injury. The inflammation leads to vascular leakage, allowing fluid to enter the alveoli thereby reducing the capacity of the lungs and making breathing increasingly difficult. The majority of ARDS cases develop in hospital as a result of a condition that has already led to admission, however ARDS may also develop quickly due to infection (e.g. pneumonia) or the accidental inhalation of vomit. Other conditions that can result in ARDS include: severe influenza, sepsis, severe chest injury, accidental inhalation of smoke or toxic chemicals, near drowning, acute pancreatitis and an adverse reaction to the transfusion of a blood product. Symptoms of ARDS can include: severe shortness of breath, rapid, shallow breathing, tiredness, drowsiness or confusion, and feeling faint. Approximately one in three people who develop ARDS will die, however most of these will be due to the underlying serious illness rather than ARDS alone. A number of complications are often faced by those who survive ARDS, including nerve and muscle damage resulting in weakness and pain. Psychological problems such as post-traumatic stress disorder (PTSD) and depression also develop in some patients. Chronic lung failure is rare after ARDS, as the lung generally recovers within 6-12 months, but some patients may experience persistent reduced vital capacity or obstructive lung disease.

The clinical definition of ARDS has varied and developed over time with changes to the specific diagnostic criteria used. Until recently, the majority of clinicians and researchers used the American-European Consensus Conference (AECC) definition; this has now been further developed to produce the ‘Berlin Definition’, which addresses a number of problems found in the AECC definition.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

The incidence of ARDS in the population is not clearly established. Estimates vary widely from 64.2 to 78.9 cases/100,000 person-years in US cohort studies, 13.5 cases/100,000 population per year in Northern Europe, 7.2 cases/100,000 population per year in Spain, and 28 cases/100,000 population per year in Australia/New Zealand. This is potentially due to a number of reasons, including variation in patient demographics, healthcare delivery models and definitions of the condition. A total of 38 deaths from ARDS were registered in England and Wales during 2012 (ICD-10 J80). In England, there were 219 admissions (165 emergency admissions) for ARDS (ICD-10 J80) in 2012-13, resulting in 459 finished consultant episodes and 6,463 bed days, although these figures are unlikely to reflect the total number of patients treated for ARDS as the condition is often the result of another illness for which the patient has been hospitalised.

The population likely to be eligible to receive interferon beta-1a could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**Other Guidance**

None found.

**CURRENT TREATMENT OPTIONS**

The management of ARDS aims to maintain oxygenation and support the patient whilst treating any underlying condition. Most patients will be admitted to an intensive care unit in order to effectively manage the condition. Most patients will require mechanical ventilation. Low tidal volume ventilation (≤6mL/kg predicted body weight) is the only form of mechanical ventilation associated with improved survival; large tidal volumes (10-15mL/kg) from conventional ventilation may lead to high peak airway pressure and pneumothorax. Other options for respiratory support include: inverse ratio ventilation (inspiration>expiration), permissive hypercapnia, prone position and high frequency jet ventilation. Other support for patients includes invasive monitoring of haemodynamic variables e.g. pulmonary capillary wedge pressure and cardiac output, the use of inotropes, vasodilators, blood transfusion, and careful fluid rehydration. Treatment of the underlying cause of the ARDS will depend on the condition, for example sepsis will be treated with appropriate antibiotics.
EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00789685, EudraCT – 2008-000140-13, FPCLI001; interferon beta-1a; phase I/II.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Faron Pharmaceuticals Ltd.</td>
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<tr>
<td>Status</td>
<td>Published.</td>
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<tr>
<td>Source of information</td>
<td>Publication¹, Trial registry¹².</td>
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<tr>
<td>Location</td>
<td>EU (incl. UK).</td>
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<tr>
<td>Design</td>
<td>Single arm.</td>
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<tr>
<td>Participants</td>
<td>n=37; aged ≥18; patients with acute lung injury/ARDS confirmed with the following diagnostic criteria: an initiating condition, acute onset, bilateral infiltrates documented by chest radiograph at end-aspiratory position, absence of clinical evidence of left atrial hypertension, in ALI PaO₂/FIO₂ ratio ≤300mmHg, and in ARDS PaO₂/FIO₂ ratio ≤200mmHg.</td>
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<tr>
<td>Schedule</td>
<td>Interferon beta-1a administered IV, daily for 6 days as a dose escalation. Doses included 0.44µg, 4.4µg, 10µg and 22µg.</td>
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<td>Follow-up</td>
<td>Active treatment for 6 days, follow-up 28 days.</td>
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<td>Primary outcome/s</td>
<td>28-day mortality; clinically significant treatment emergent events.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>None reported.</td>
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<td>Key results</td>
<td>No drug related toxicity reported with daily doses of 0.44µg, 4.4µg, or 10µg; administration of the drug was associated with improvement in: PaO₂/FIO₂ ratio (18.5 kPa [SE1.4] at screening to 38.2 kPa [4.1] on day 27; p&lt;0.0001); 28 day mortality (19 (32%) in the control group vs 3 (8%) in the treatment group); and reduction in odds of 28-day mortality (OR 0.19, 95% CI 0.03-0.72).</td>
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<td>Adverse effects (AEs)</td>
<td>AEs only reported in those receiving the highest dose (22µg per day) including fever, rigors and tachycardia: no systemic drug-related events were reported in those given 10µg dose per day (considered the optimal tolerated dose).</td>
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ESTIMATED COST and IMPACT

COST

The cost of interferon beta-1a (Traumakine) has not yet been determined for this indication. Interferon beta-1a is already marketed in the UK for the treatment of relapsing multiple sclerosis and patients with a single demyelinating event with an active inflammatory process. AVONEX costs £163.50 for a 30µg (6 million unit)/mL 0.5mL prefilled syringe, Rebif costs £48.16 for a 22µg (6 million unit) prefilled syringe.

IMPACT - SPECULATIVE

<table>
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<tr>
<th>Impact on Patients and Carers</th>
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<td>☑ Reduced mortality/increased length of survival</td>
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<tr>
<td>☐ Other:</td>
</tr>
</tbody>
</table>

¹ Ratio of arterial partial pressure of oxygen (PaO₂) to fraction of inspired oxygen (FIO₂)
Impact on Health and Social Care Services

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other: Expert opinion states that this drug would have limited service implications if used to manage ARDS as it would be administered easily on the intensive care units where ARDS patients are treated.
- No impact identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs: Expert opinion suggests the drug would have a considerable impact on training (early recognition of ARDS) and resources.
- Other reduction in costs:
- Other:
- No impact identified

Other Issues

- Clinical uncertainty or other research question identified: A large prospective randomised trial is required to support the use of interferon beta-1a for management of patients with ARDS.
- None identified

REFERENCES


b Expert personal opinion