

## National Horizon Scanning Centre

# Ecallantide (DX-88) for acute hereditary angioedema

August 2008



This technology summary 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.

## **Ecallantide for acute hereditary angioedema**

### **Target group**

- Hereditary angioedema (HAE) – acute attacks in patients 10 years and above.

### **Background**

HAE is a rare genetic disease characterised by spontaneous and recurrent attacks of oedema in various parts of the body including: the upper airway, hands, feet, face, genitals and abdomen. Precipitants of attacks of angioedema include:

- Stress (both physical and mental)
- Trauma (including minor and major surgery)
- Infection
- Menstruation
- Pregnancy
- Oestrogen containing medications including: oral contraceptives and hormone replacement therapy
- ACE inhibitors

HAE is caused by an autosomal dominant mutation of the gene for C1-INH. C1-INH is a serine protease inhibitor that plays a central role in the regulation of the complement, coagulation and kallikrein-kinin cascades. Dysregulation of the kallikrein cascade can lead to the excess production of bradykinin. This causes the typical symptoms of inflammation including: swelling, reddening, warmth and pain.

### **Technology description**

Ecallantide (DX-88, EPI-KAL2) is a recombinant protein that inhibits the activity of plasma kallikrein. For the treatment of acute HAE attacks 30mg of ecallantide is administered SC as a divided dose.

Ecallantide is also in phase II development in the US for haemorrhage during surgery.

### **Innovation and/or advantages**

Ecallantide is first-in-class for this indication. The SC route of administration distinguishes it from existing products that are administered IV. Use of ecallantide may avoid concerns over the microbiological safety of using blood derived C1 inhibitor concentrates.

### **Developer**

Dyax Corporation.

### **Availability, launch or marketing dates, and licensing plans:**

The company anticipate a licence application to the FDA in Q4 2008. Filing for an EU licence will occur at a later date.

Ecallantide is a designated orphan drug for this indication in the EU and has fast-track designation in the US.

### **Relevant guidance**

- Clinical Knowledge Summaries (formerly PRODIGY). Angioedema and anaphylaxis. 2007<sup>1</sup>.

- Clinical and Experimental Immunology. C1 inhibitor deficiency. 2005<sup>2</sup>.

### Clinical need and burden of disease

HAE attacks affecting the face, hands and feet are disfiguring, interfere with activities of daily living and may be uncomfortable. Abdominal attacks are marked by severe abdominal pain, nausea, vomiting and/or diarrhoea. Attacks affecting the throat can be life-threatening, as swelling can constrict the larynx and enlarge the tongue.

The prevalence of HAE has been estimated as between 1 in 10,000 and 1 in 50,000 of the population<sup>3</sup>. This equates to between 1,075 and 5,373 people in England and Wales with the condition. On average, patients suffer 12 attacks per year each lasting 2-5 days if left untreated. In 2006/7 there were 546 hospital admissions where the primary diagnosis was defects in the complement system and one death was recorded for 2005<sup>4</sup>.

### Existing comparators and treatments

- Prophylaxis for frequent and troublesome attacks - synthetic androgens (danazol and stanozolol); tranexamic acid.
- Acute attacks - C<sub>1</sub> esterase inhibitor in fresh frozen plasma or in partially purified form; icatibant (bradykinin B2 receptor antagonist; Jerini AG; recently approved but not yet marketed).

### Efficacy and safety

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| Trial code, name, phase | DX-88/4 EDEMA1; IV DX-88 vs. placebo; phase II.  | DX-88/5 EDEMA2; IV or SC DX-88; phase II.   | DX-88/14 EDEMA3- stage 1 <sup>5</sup> ; SC DX-88 vs. placebo; phase III.   |
| Sponsor                 | Dyax   | Dyax  | Dyax   |
| Status                  | Published <sup>6</sup> .   | Completed, press release <sup>7</sup>   | Completed, abstract and poster <sup>8</sup> .  |
| Location                | Belgium, Israel, US.   | Canada, US  | Canada, EU, Israel, US.  |
| Design                  | Double-blind, placebo controlled.  | Open label.   | Randomised, double-blind, placebo controlled.  |
| Participants in trial   | n=48; 10 years and older; moderate or severe HAE attack.<br>DX-88 5, 10, 20 or 40mg/m <sup>2</sup> IV or placebo (saline). | n=77; a total of 240 attacks; 10 years and older; moderate or severe HAE attack.<br>DX-88 5, 10, 20mg/m <sup>2</sup> IV or 30mg SC. | n=72; 10 years and older; moderate or severe HAE attack.<br>Randomised to DX-88 30mg SC or placebo.                        |
| Follow-up               | 4, 12 and 24 hours; in week 1; and weeks 1, 2 and 4.   | 4 and 24 hours; in first week, and weeks 1 and 4.   | 4 hours, 24 hours, in first week, and weeks 1, 4 and 12-13.  |
| Primary outcome         | Significant improvement at the primary attack location within 4 hours.   | Clinical response within 4 hours.   | Treatment Outcome Score (TOS) <sup>a</sup> at 4 hours.   |
| Secondary outcomes      | Pharmacokinetic parameters.  | Time to onset of clinical response.   | Mean Symptom Complex Severity (MSCS) <sup>b</sup> at 4 hours; time in minutes to report significant improvement in overall |

<sup>a</sup>Treatment Outcome Score (TOS) is a composite score that captures the response to treatments across symptom complexes, accounts for the complexity and variability of symptom manifestations, and quantifies patient-reported outcomes.

<sup>b</sup>Mean Symptom Complex Severity (MSCS) is the arithmetic mean of grades of severity of individual symptom complexes.

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|                 |  |   | response.  |
| Key results     | A significantly higher proportion of patients treated with ecallantide reported significant improvement at the primary attack location within 4 hours after drug infusion compared to placebo (p= 0.0169). Pharmacokinetics of ecallantide were consistent with values expected for a protein therapeutic. | Of the 240 attacks in 77 patients, clinical response rate in all IV administration groups (n=180) was >85% and in the SC administration group (n=60) response was >90%. Median time to onset of clinical response across all dose groups was <1 hour. | At 4 hours post-dose, ecallantide-treated patients had greater improvement as shown by the TOS as compared to placebo-treated patients (p=0.021). At 4 hours post-dose, ecallantide-treated patients showed greater improvement, as shown by changes in MSCS, as compared to placebo-treated patients (p=0.024). The estimated median time to significant improvement in overall response among ecallantide-treated patients was 149.0 minutes; the estimated median for placebo-treated patients was not reached by 240 minutes (p=0.04). |
| Adverse effects | Most AEs were mild or moderate in severity and not related to treatment. The most frequent AE was headache.  | Majority of AE were mild or moderate in severity.   | Adverse events were typically mild or moderate. There were no treatment related serious adverse events.  |

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|-------------------------|--|--|--|
| Trial code, name, phase | DX-88/14 EDEMA3 – stage 2 (repeat dosing): SC DX-88; phase III.  | DX-88/20 (EDEMA4) <sup>9</sup> ; SC DX-88 vs. placebo; phase III.  | DX-88/19 (continuation) <sup>10</sup> ; DX-88; phase III.  |
| Sponsor                 | Dyax   | Dyax   | Dyax   |
| Status                  | Completed, abstract and poster <sup>7</sup> .  | Completed, press release <sup>11</sup> .   | Ongoing  |
| Location                | Belgium, Canada, Israel, Italy, US.  | Canada, US.  | Canada, Jordan, US.  |
| Design                  | Open label.  | Randomised, double-blind, placebo control.   | Open label.  |
| Participants in trial   | n=67 (48 from EDEMA3 stage 1); 160 attacks. DX-88 30mg SC.   | n=96; 10 years and older; moderate or severe HAE attack. Randomised to DX-88 30mg SC or placebo.   | n=150 (planned); 10 years and older; acute HAE attack. DX-88 30mg SC.  |
| Follow-up               | 4 hours, 24 hours, in first week, and weeks 1, 4 and 12-13.  | 4 hours, 2 days and 1 week   | 4 hours; 7, 28 and 90 days.  |
| Primary outcome         | TOS at 4 hours.  | MSCS at 4 hours.   | MSCS at 4 hours.   |
| Secondary outcomes      | Change from baseline in MSCS at 4 hours post-dosing; time in minutes to report of the first significant improvement in overall response. | TOS; time in minutes to report of the first significant improvement in overall response; maintenance of significant improvement in overall | TOS; time in minutes to report of the first significant improvement in overall response; maintenance of significant improvement in overall |

|                         |   |   |  |
|-------------------------|---|---|--|
|                         |   | response; proportion of responders at 4 hours post dosing.  | response; proportion of responders at 4 hours post dosing. |
| Key results             | Mean TOS, MSCS changes and time to onset of improvement seen in the repeat dosing stage (attacks 2-6) were consistent with ecallantide in the double-blind stage. | MSCS ecallantide vs. placebo p=0.010. TOS ecallantide vs. placebo p=0.003. Response at four hours was 93.8% for DX-88 vs. 59.6% for placebo (p=0.001). At 24 hours proportion maintaining significant response 43.8% for DX-88 vs. 20.8% for placebo (p=0.022). | -  |
| Expected reporting date | Q4 2008.  | Publication date unknown.   | Q1 2009 (estimated study completion date).                 |
| Adverse effects         | Adverse events were typically mild or moderate; 10% had mild, moderate injection site reactions; 1 patient had a treatment-related anaphylactic reaction.         | DX-88 was well tolerated. There were no drug-related serious adverse events reported.   | -  |

### Estimated cost and cost impact

The cost of ecallantide is yet to be determined.

### Potential or intended impact – speculative

#### Patients

- |   |  |   |
|---|--|---|
| <input checked="" type="checkbox"/> Reduced morbidity   | <input type="checkbox"/> Reduced mortality or increased survival | <input checked="" type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker, earlier or more accurate diagnosis or identification of disease | <input type="checkbox"/> Other:                                  | <input type="checkbox"/> None identified  |

#### Services

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> Increased use   | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input checked="" type="checkbox"/> Decreased use: fewer or shorter hospital admissions. | <input type="checkbox"/> Other:                          | <input type="checkbox"/> None identified            |

#### Costs

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input type="checkbox"/> Increased costs: more patients coming for treatment       | <input type="checkbox"/> Increased costs: capital investment needed |
| <input type="checkbox"/> New costs:                                  | <input checked="" type="checkbox"/> Savings: fewer or shorter hospital admissions. | <input type="checkbox"/> Other:                                     |

### References

<sup>1</sup> Clinical Knowledge Summaries (formerly PRODIGY). Angio-oedema and anaphylaxis. April 2007.

<sup>2</sup> Gompels, M.M. *et al.* C1 inhibitor deficiency: consensus document. *Clinical and Experimental Immunology*, 139: 379-394.

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- <sup>3</sup> Bowen, T., Cicardi, M., Bork, K. et al. Hereditary angioedema: a current state of the art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Annals of Allergy, Asthma and Immunology*. 2008; 100: S30-40.
- <sup>4</sup> Office of National Statistics. DH2 table No. 32. Available at:  
[http://www.statistics.gov.uk/downloads/theme\\_health/Dh2\\_32/DH2\\_No32\\_2005.pdf](http://www.statistics.gov.uk/downloads/theme_health/Dh2_32/DH2_No32_2005.pdf) (Accessed 15/05/08).
- <sup>5</sup> NCT00262080 Efficacy and Safety Study of DX-88 to Treat Hereditary Angioedema (HAE) Available at:  
<http://clinicaltrials.gov/show/NCT00262080> (Accessed 17/06/08).
- <sup>6</sup> Schneider L, Lumry W, Vegh A et al. Critical role of kallikrein in hereditary angioedema pathogenesis: a clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunology* 2007;120:416-22.
- <sup>7</sup> Dyax Corporation. Positive final results from EDEMA2 trial with DX-88 for the treatment of hereditary angioedema presented at ACAAI meeting. Press release. November 2006.
- <sup>8</sup> Levy R, McNeil D, Li H et al. Results of a 2-stage, phase 3 pivotal trial, EDEMA3: a study of subcutaneous DX-88 (ecallantide), a plasma kallikrein inhibitor, in patients with hereditary angioedema (HAE). *J Allergy Clin Immunology* 2008; 121(2) S1: S231. Poster presented at American Academy of Allergy, Asthma & Immunology Annual Meeting 2008.
- <sup>9</sup> Clinical Trials. NCT00457015; Efficacy Study of DX-88 (Ecallantide) to Treat Attacks of Hereditary Angioedema (HAE) Available at:  
<http://clinicaltrials.gov/ct2/show/NCT00457015?term=NCT00457015&rank=1> (Accessed 17/06/08).
- <sup>10</sup> Clinical Trials. NCT00456508 Safety and Efficacy Study of Repeated Doses of DX-88 (Ecallantide) to Treat Attacks of Hereditary Angioedema (HAE) Available at:  
<http://clinicaltrials.gov/ct2/show/NCT00456508?term=NCT00456508&rank=1> (Accessed 17/06/08).
- <sup>11</sup> Dyax Corporation. Dyax announces DX-88 for hereditary angioedema meets primary and secondary endpoints in phase 3 trial (EDEMA4R). Press release. August 2008.