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Voraxaze™ - an enzyme that breaks down methotrexate (MTX)

Voraxaze™ fact sheet
Voraxaze™ US supplies

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Voraxaze™ (glucarpidase, previously known as carboxypeptidase G2 or CPG2) is a biological product designed to rapidly reduce the amount of blood levels of methotrexate (MTX), a commonly used cancer drug in the blood. High doses of MTX can cause kidney damage in some cancer patients and this can delay the elimination of MTX from the body. Prolonged exposure to high concentrations of MTX commonly results in serious toxic effects such as mucositis (painful mouth sores), reduced platelet and white blood counts (myelosuppression) , kidney failure and an increased risk of sepsis and in some instances death. A number of cancer patients die every year from MTX induced toxicity, mainly due to sepsis. Voraxaze™ is the only drug which can remove MTX from the blood; dialysis is the only other way to remove MTX from the blood.

Voraxaze™ is given via a simple intravenous infusion and rapidly reduces the amount of MTX in the bloodstream. Voraxaze™ contains a recombinant enzyme (glucarpidase) which rapidly cleaves MTX into a non-toxic form. In one pivotal and two supportive studies, Voraxaze™ was able to achieve a clinically important reduction (CIR) in MTX concentration to ≤1 µmol/L in the majority of patients treated. This concentration of MTX is a generally accepted threshold below which the risk of severe MTX toxicity is considered to be low. Voraxaze™ consistently reduced plasma or serum MTX concentrations by an average of >98% by the time of the first sample point, which was usually 15 minutes after Voraxaze administration in each of the three studies.

In clinical studies, a total 25/329 (8%) patients reported 50 adverse events with a possible relationship to Voraxaze™; about a third of these were considered to be allergic reactions (burning sensation, flushing, hot flush, allergic dermatitis, feeling hot, pruritis, hypersensitivity). Two of the adverse events were considered serious, hypertension and arrhythmia, but neither was definitively associated with use of Voraxaze™ and the latter was considered more likely to be associated with MTX.

Availability

As of 25 May 2007, Voraxaze™ is available for intravenous use in the US under an Open-Label Treatment Protocol and cost recovery program or the US Leucovorin PK study. The procedure for obtaining Voraxaze™ for treatment of patients with intrathecal overdose of methotrexate continues to be via an Emergency Use IND. In Canada,

Voraxaze™ can be obtained via SAP through our distributer, McKessen. Voraxaze™ is also available on a **named patient basis** in the US and other non-US countries through our distributer IDIS Pharmaceuticals.

Development status

Voraxaze™ was granted orphan drug status in both the US and Europe in 2003.

Voraxaze™ has been granted Fast Track Designation in the US and Protherics intends to resubmit a rolling submission of the Biological License Application (BLA) starting early in the second half of 2008, after additional manufacturing and stability data has been obtained. Protherics will also undertake a small 12 patient study to support a label claim regarding the dosing of leucovorin, a rescue agent routinely given to patients receiving high doses if MTX, following administration of Voraxaze™. Protherics intends to seek a Priority Review, reducing the time for the BLA review from 10 to 6 months from submission of the final part of the application and providing a potential approval in the US in 2010.

In Europe, Protherics submitted a Marketing Authorisation Application (MAA) for Voraxaze™ to the European Medicines Evaluation Agency (EMEA) in June 2005. The EMEA subsequently requested further manufacturing and stability data, in addition to data to assess the clinical relevance of the interaction between Voraxaze™ and leucovorin. These data could not be provided in the time permitted by the Centralized Procedure and so the MAA was withdrawn in May 2007.

The manufacturing and stability data being generated to support the BLA in the US are expected to also support a MAA in the EU. Protherics will consider resubmitting a MAA application if the 12 patient study to support the label claim for leucovorin dosing requested by the FDA is deemed acceptable by the EMEA to address their concern about the clinical relevance of the leucovorin interaction. Protherics will continue supplying Voraxaze™ on a named patient basis in Europe for intervention use in patients at risk of severe or life-threatening methotrexate toxicity due to delays in their elimination of MTX following high dose MTX therapy.

Planned Use

A development programme is ongoing to expand the indications for Voraxaze™ to include planned repeated use, a market opportunity which could be worth up to US$100-200 million per annum.

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Voraxaze™

for methotrexate toxicity

Voraxaze is a unique drug that allows clinicians to control patient exposure to methotrexate (MTX). Voraxaze contains a recombinant enzyme (glucarpidase; formerly known as carboxypeptidase-G2 or CPG2) which rapidly lowers blood levels of MTX, reducing its concentration to below the threshold for serious toxicity in the majority of patients.

Development status

- The resubmission of a marketing application in the US is expected to begin on a rolling basis in the second quarter of 2008. Additional clinical, manufacturing and stability data are planned to be generated during 2008 to 2009 to facilitate a potential approval from the first half of 2010. Discussions are ongoing with the EMEA and, depending on the outcome, an application may also be resubmitted in the EU.
- The initial indication for which approval will be sought is for the use of Voraxaze as an adjunctive treatment for patients experiencing or at risk of toxicity from MTX ("intervention use"). Patients are considered at risk of MTX toxicity if they have impaired renal function, which can lead to a delay in MTX elimination, or have evidence of delayed elimination based on MTX levels.
- Voraxaze may also prove suitable for more routine adjunctive use ("planned use") with high-dose MTX (HDMTX) to optimise the HDMTX therapy. The first planned use study is ongoing.

Market opportunity

- MTX is a widely used anti-cancer drug which is often used in high-doses (≥ 1 g/m^2) in certain types of cancer such as leukaemia, lymphoma and sarcoma.
- MTX can result in reduced kidney function, particularly when it is used in high doses. This delays the elimination of MTX from the body, often leading to serious side effects such as mucositis and haematological toxicity, increased risk of sepsis and in some instances, death.
- There are no other drug treatments available which are capable of reducing MTX levels in the blood of patients.
- Protherics estimates that the global market opportunity for intervention use is about US$25-$50m per annum. Protherics believes that Voraxaze could potentially be used as an adjunctive therapy with each cycle of high dose MTX therapy, an opportunity that could be worth more than US$100m per annum.

Mechanism of action

- Voraxaze reduces systemic MTX levels by rapidly converting MTX to glutamate and 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA). Compared with MTX, DAMPA is 25- to 100-fold less potent an inhibitor of dihydrofolate reductase (DHFR) and is significantly less cytotoxic.
- DAMPA and glutamate are metabolised by the liver, providing an alternative route of MTX elimination to renal clearance which is important in patients with reduced kidney function.
- Voraxaze is administered as a single dose of 50 Units/kg by bolus intravenous injection over five minutes.

Results to date

- Clinical trials in the US and EU have shown that Voraxaze rapidly and predictably reduces MTX levels in the blood of patients in whom its elimination has been delayed.
- In one pivotal and two supportive studies, Voraxaze achieved a clinically important reduction (CIR) in MTX to ≤ 1 µmol/L in the majority of patients treated.

Voraxaze™ Continued

This concentration is a generally accepted threshold below which the risk of severe MTX toxicity is considered to be reduced. Voraxaze consistently reduced plasma or serum MTX concentrations by an average of >98% by the time of the first sample point, which was usually 15 minutes after Voraxaze administration in each of the three studies.

- Voraxaze is well tolerated. In clinical studies, a total 25/329 (8%) patients reported 50 adverse events with a possible relationship to Voraxaze; about a third of these were considered transient allergic reactions (burning sensation, flushing, hot flush, allergic dermatitis, feeling hot, pruritis, hypersensitivity). Only 2 of these adverse events were considered serious, one case each of hypertension and arrhythmia, but neither was definitively associated with use of Voraxaze and the latter was considered more likely to be associated with MTX.

Next steps

- Q1 2008: Initiation of a 12 patient study requested by FDA to support a label claim regarding the dosing of leucovorin following administration of Voraxaze.
- Q1 2008: Establish whether a marketing authorisation application can be resubmitted to the EMEA using the same data package that is being prepared for the FDA.
- Q2 2008: Commencement of the resubmission of the marketing application to the FDA as a rolling submission.

Partnering status

- Protherics intends to sell Voraxaze using its own sales force in the US and EU, and through a network of specialist oncology local partners in some EU markets and elsewhere.
- In the US, Voraxaze is available for intravenous use under an Open-Label Treatment Protocol and cost recovery program, and for intrathecal use under an Emergency Use IND. Voraxaze is available outside of the US on a named patient basis. Further details can be found at http://www.protherics.com/products/voraxaze.aspx.

Intellectual property

- Protherics has filed for patents in multiple territories worldwide. Two related families of patents are undergoing PCT worldwide and were filed in 2005.
- Voraxaze has been granted orphan drug designation in the USA and EU, giving it seven and ten years market exclusivity respectively.

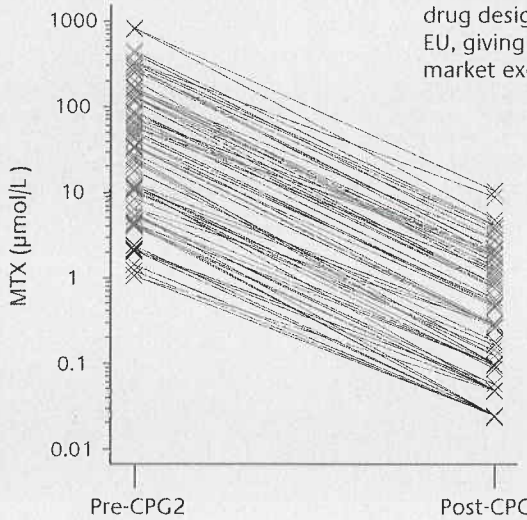

Figure 1: Voraxaze (previously CPG2) rapidly reduces blood levels of MTX

Source: 70 patients with paired data from US NCI Special Exception Protocol

*Post-CPG2 is approximately 15 mins after dosing

References

Widemann, B. C., Adamson, P. C. Understanding and managing methotrexate nephrotoxicity. Oncologist. Jun 2006 11: 694-703.

For other relevant references please visit: www.protherics.com/references

Available fact sheets

For the following fact sheets please visit: www.protherics.com/factsheets

- Protherics Overview
- Acadra™
- Angiotensin Therapeutic Vaccine
- CoVaccine HT™ Adjuvant
- CroFab™
- CytoFab™
- DigiFab™
- Digoxin Immune Fab
- OncoGel™
- ReGel™
- Prolarix™
- Sepsis

Further information

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Voraxaze for emergency use

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- For US Intrathecal Use & Canada contact Protherics Inc on: +1 888 327 1027
- For Europe & RoW contact David Briscoe on: +44 (0)7968 492 957
- Visit: www.protherics.com/products/voraxaze.aspx

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