Public Assessment Report

Scientific discussion

Erwinase, powder for solution for injection 10,000 IU/vial

(crisantasprase)

NL/H/3194/001/MR

Date: 14 September 2015

This module reflects the scientific discussion for the approval of Erwinase, powder for solution for injection 10,000 IU/vial. The procedure was finalised on 2 February 2015. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.

A list of literature references is given on pages 16-17 of this report.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ALL</td>
<td>Acute Lymphoblastic Leukaemia</td>
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<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>CALGB</td>
<td>Cancer and Leukemia Group B</td>
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<tr>
<td>CCG</td>
<td>Children’s Cancer Group</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<td>EFS</td>
<td>Event-free Survival</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>kDA</td>
<td>kilo Dalton</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>MRP</td>
<td>Mutual Recognition Procedure</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PK</td>
<td>Pharmacokinetics</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<tr>
<td>RH</td>
<td>Relative Humidity</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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</table>
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Erwinase, powder for solution for injection 10,000 IU/vial from EUSA Pharma SAS.

The product is indicated in combination with other chemotherapeutic agents, for the treatment of patients, mainly children, with acute lymphoblastic leukaemia who have developed (clinical allergy or silent inactivation) to native or pegylated asparaginase derived from *E. coli*.

A comprehensive description of the indications and posology is given in the SmPC.

The amino acid asparagine is incorporated into most proteins, and protein synthesis is halted in its absence, thereby inhibiting RNA and DNA synthesis which results in a halt to cellular proliferation. Neoplastic cells associated with ALL, acute myeloid leukaemia and non-Hodgkin's lymphoma (especially the lymphoblastic form) are lacking in asparagine synthetase activity and are dependent upon exogenous asparagine.

The anti-tumour activity of L-asparaginase is a result of the sustained depletion of exogenous asparagine. L-asparaginase catalyses the deamination of asparagine to aspartic acid and ammonia.

This mutual recognition procedure concerns an application based on a full dossier according to Article 8(3) of Directive 2001/83/EC. A national marketing authorisation for Erwinase was granted in the Netherlands on 19 September 1997.

The concerned member state (CMS) involved in this procedure was France.

II. QUALITY ASPECTS

II.1 Introduction

Erwinase is a white lyophilised powder. It contains crisantaspase (asparaginase from *Erwinia chrysanthemi*: Erwinia L-asparaginase) per 10,000 IU/vial.

After reconstitution with 2 ml sodium chloride 0.9% solution for injection, one ml of ready prepared solution contains 5,000 IU of crisantaspase and after reconstitution with 1 ml sodium chloride 0.9% solution for injection, one ml of ready prepared solution contains 10,000 IU of crisantaspase.

The powder is packed in vials with a nominal capacity of 3 ml made of transparent neutral type I glass, closed with a 13 mm halobutyl stopper for freeze-drying and an aluminium outer seal.

The excipients are: glucose monohydrate, sodium chloride, sodium hydroxide (E524) (for pH adjustment), acetic acid (E260) (for pH adjustment).

II.2 Drug Substance

The active substance L-asparaginase is an enzyme which is derived from *Erwinia chrysanthemi*, a gram negative bacteria belonging to the *Enterobacteriacea* family. It is an established active substance, not described in a pharmacopoeia. The MAH does not make use of an ASMF or CEP procedure; full documentation on the active substance has been included in the dossier.

The active substance contains primarily the native L-asparaginase which is a non-disulfide bonded, tetrameric protein consisting of four identical polypeptide chain subunits with a combined molecular weight of 140 kDa. Each individual subunit has a molecular weight of 35 kDa. The biological activity is directly related to the enzymatic properties of the enzyme. The active substance is freely soluble in water and insoluble in alcohol.

Manufacturing process

The manufacturing process comprises three main stages: fermentation, extraction and purification. The fermentation stage commences with expansion of a vial of *Erwinia chrysanthemi* from the working
cell bank (WCB) to produce a working seed inoculum. Each inoculum is further expanded in a fermentation process. Cells are harvested from the production fermentation by centrifugation to form a cell paste.

The extraction stage comprises processing of a cell paste to yield a crude enzyme preparation. For purification, extracts are pooled and processed through a series of column chromatography and other protein purification steps to yield a drug substance batch. The process is described in sufficient detail.

**Quality control of drug substance**

The drug substance specification has been established in-house by the MAH, and comprises appropriate tests and acceptance criteria. The specification is acceptable in view of the manufacturing process and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for at least three production-scale batches.

**Stability of drug substance**

Stability data on the active substance have been provided for five full-scale batches, stored during at least 12 months at -20°C (long term condition) and six months at 25°C/60%RH, stored in the proposed packaging. The study programme was according to ICH conditions.

No significant changes were observed. The stability results justify the storage conditions of 12 months at -20°C, in the proposed packaging.

### II.3 Medicinal Product

**Pharmaceutical development**

The development of the product has been described, the choice of excipients is justified and their functions explained. The rationale of the development, the product composition and manufacturing process are clear and sufficiently justified. A detailed description of historical development is provided starting from initial clinical batches. Detailed information is provided showing the effect of glucose on dissociation and reformation of the tetrameric form. The effect of sodium chloride on protein aggregation is discussed in detail.

A comprehensive characterisation of the structural, biophysical, and enzymatic properties of the naturally produced enzyme L-asparaginase derived from *Erwinia chrysanthemi* (Erwinase) has been performed. The final formulation is equivalent to the clinical batches.

The ongoing control of the aseptic processing steps of the drug product manufacture has been demonstrated, where sterility of growth media has been maintained during the filtration and filling/freeze drying stages. Coupled with the ongoing compliance of the final drug product with sterility testing requirements, the data demonstrate that the processes, equipment and facilities involved in the drug product manufacture minimise potential sources of microbial contamination.

**Manufacturing process**

Aliquots of bulk drug substance, sodium chloride and glucose monohydrate are processed and the bulk drug product is then sterile filtered and subsequently filled into sterile vials for freeze drying.

The critical experimental conditions at the different process steps and in-process controls, and their acceptance criteria are laid down. The manufacturing process is described in sufficient detail and has been adequately validated according to relevant European guidelines.

Process validation data on the product has been presented for at least three recent production-scale batches, including data regarding the critical steps and in-process controls, and product release parameters. Retrospective historical data have also been submitted for numerous batches produced during product development, including clinical batches.

**Control of excipients**

The excipients comply with the Ph. Eur., including the requirements regarding microbiological purity and bacterial endotoxins. These specifications are acceptable.

**Quality control of drug product**

The product specification includes tests for appearance, water content, particulate matter: visible and sub-visible particles, pH, identity, assay (protein content), content uniformity, purity, potency, glucose content, sodium chloride content, endotoxin and sterility. The release and shelf-life specification limits are identical. The analytical methods have been adequately described and validated.
Batch analytical data have been provided on at least three recent production-scale batches for the production site demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on at least three recent production-scale batches stored in the glass vials during 36 months at long term (5°C) conditions and six months at accelerated conditions (25°C/60%RH). The conditions used in the stability studies are according to the ICH stability guideline. No significant changes were observed. The results of photostability studies showed that protection from light is not necessary. Based on the provided data the following shelf-life and storage conditions have been approved: 36 months at 2-8°C, in the glass vial.

Compatibility studies have been performed with the proposed diluent in the SmPC (0.9% NaCl), diluted to the proposed concentration range, justifying the claimed in-use shelf-life of the diluted product from a chemical-physical point of view: 15 minutes in the original container, 4 hours in a sterile glass or polypropylene syringe and stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A list of the raw materials of biological origin has been provided, together with the process stages in which they are used and manufacturer’s certifications concerning the potential for TSE risk. The potential TSE risk from the Master Cell Bank has been assessed to be acceptably minimal, and certificates for TSE absence have been provided. TSE risk can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Erwinase, powder for solution for injection 10,000 IU/vial has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

The non-clinical programme consists of a review of previously conducted toxicology studies on Erwinia sp. asparaginas, generally from the 1960’s and 1970’s, combined with a review of the open literature on Erwinia sp. asparaginase studies. Although not all aspects of a classical non-clinical evaluation can be completely addressed, this abbreviated approach is considered justified on the fact that the lack of some data is superseded by the information gained from extensive human use over numerous years.

Erwinase is an asparaginase derived from the bacterium Er. chrysanthemi. The primary pharmacodynamic action is through the inability of leukaemia cells to make asparagines due to a lack of asparagine synthetase activity. Erwinase treatment reduces circulating asparagine concentrations near zero resulting in the starvation and death of the asparagine-dependent cells. Normal cells that can synthesise asparagine are not affected.

Er. chrysanthemi asparaginas have high specificity for asparagine, although somewhat lower affinity for glutamine. This suggests that there is minimal potential for side effects due to non-target reactions. The primary target organ identified in the non-clinical studies is immunosuppression. Erwinia sp. asparaginase treatment inhibits blastogenesis in vitro and the immune response in vivo. The mechanism by which immunosuppression is reached is uncertain, but it may be related to decrease of circulating asparagine. Immunosuppression was observed at doses as low as 800 IU/kg IM in rats. This dose is lower than the proposed clinical dose (1000 IU/kg IM). This suggests that there may be potential for immunosuppression in the clinic.

Erwinia sp. asparaginas have a relatively high toxicity in the rabbit but a low order of acute toxicity in rodents. The exact scientific mechanism for lower tolerance in rabbit is unknown. Human circulating
asparagine concentration is similar to rodents (7.3 μg/mL).

In repeat dose studies, dogs and monkeys tolerated doses as high as 5,000 and 10,000 IU/kg IV, for 28 or 5 days, respectively, with no death or notable toxicity. In contrast, the rabbit is much more sensitive; 1 out 5 rabbits administered 1000 IU/kg for 5 days was found dead 7 days post dosing (day 12 of the study); the cause of death was uncertain. The no-observed-effect level (NOEL) from the dog and monkey studies is 2,000 IU/kg, which is above the proposed clinical dose.

All 5 of 5 rabbits administered 100 IU/kg i.v. Er. carotovora asparaginase on gestation day 8 and 9 had complete litter resorptions on gestation day 28. The significance of this observation is uncertain. This is lower than the proposed clinical dose and suggests that there may be potential for embryofetal toxicity in the clinic.

III.2 Ecotoxicity/environmental risk assessment (ERA)

According to the “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use” (EMEA/HMP/SWP/4447/00, 1 June 2006) vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted from the evaluation of an environmental risk ‘because they are unlikely to result in significant risk to the environment’.

Therefore, in accordance with the stipulations given in this Guideline waiving an ERA for Erwinase is fully justified and appropriate from a regulatory point of view.

Waiving an ERA for "Erwinase" is further justified considering:

- **Erwinia** L-asparaginase is a protein of molecular weight of approx. 135,000 Daltons and is composed of four subunits (tetramers), each subunit having a molecular weight of about 35,000 Daltons. L-asparaginase is not excreted via the kidney to any marked extent (cut off for glomerular filtration is about 46 000 Daltons). Thus, only traces of an administered dose can be detected in urine.
- The mechanism for the elimination of L-asparaginase is unknown but from animal studies using *E. coli* asparaginase the drug is concentrated in the liver where it is likely that it undergoes the normal catabolic processes applied to proteins with the resultant amino acids being utilised by the body.
- Only trace amounts are excreted via the bile.
- L-asparaginase is unstable in solution and any trace amounts that are excreted into the environment will be quickly destroyed by hydrolysis to short peptide fragments and amino acids.
- L-asparaginase is a natural product that is produced by a wide range of microorganisms and is present in the environment as a consequence.
- There is no evidence that L-asparaginase possesses any properties that make the molecule an environmental toxin that requires special controls.

Taken together, there are no environmental concerns apparent regarding the use of Erwinase, and no change of the environmental risk is expected. Hence, the absence of an ERA for the medicinal product is justified based on scientific grounds.

IV. CLINICAL ASPECTS

IV.1 Introduction

There are no reports on randomized controlled trials comparing treatment including asparaginase versus not including asparaginase. However, the relation between response rate and the amount of asparaginase was already demonstrated in the 1970’s (a.o. Ertel et al., 1979). The efficacy data submitted to support the application for Erwinase are primarily taken from the published medical literature. A pharmacokinetic/pharmacodynamics (PK/PD) study (AALL07P2) was submitted in support of the proposed posology in the SmPC.

IV.2 Pharmacokinetics and pharmacodynamics

Crisantaspase is a well-known substance and has been the subject of several publications. Accordingly, for this application, the pharmacokinetics and pharmacodynamics were addressed by
bibliographical data. In addition, PK/PD information was obtained in the recently conducted EUSA PK/PD Study AALL07P2. reflect a slow absorption phase. It has been shown that crisantaspase penetrates into the cerebrospina
The elimination half-life of Erwinase after i.v. infusion is 6.4 ± 0.5 hours, whereas half-life after i.m. infusion is longer, i.e. 16 hours. The longer half-life from this route of administration may fluid of monkeys. Although the degree of penetration is small, it is pharmacodynamically active. Further, the formation of antibodies as a response to repeated administration of all L-asparaginases is well known. Such antibodies do not always lead to clinical hypersensitivity, but can result in rapid asparaginase inactivation and/or clearance.
In Study AALL07P2, in which patients received 25,000 IU/m² 3 times weekly for 2 weeks, the proportion of patients with a subtherapeutic trough crisantaspase level was lower than reported previously at a dose regimen of 20,000 IU/m², 3 times weekly for 3 weeks. In Study AALL07P2, in 92.5% and 88.5% of patients, trough crisantaspase activity was ≥100 IU/ml at 48 and 72 hours post-dose, respectively in course 1. For all cohorts, in 97.9% of the patients in Course 1, 96.8% of the patients Course 2, and 100% of the patients in Course 3 asparagine levels were suppressed to <0.396 μg/ml.

IV.3 Clinical efficacy

Currently L-asparaginase is one of the main components of paediatric leukaemia treatments. Extensive clinical data support the use of asparaginase therapy in (paediatric) ALL (Silverman et al., 2000; Pui et al., 2009; Pieters et al., 2008; Ertel et al., 1979; Clavell et al., 1986; Amylon et al., 1999).

Comparison between different studies indicates that the efficacy of ALL therapy depends partly on the intensity of asparaginase treatment, the event-free survival (EFS) for patients appears to be longer for patients treated with higher intensity of asparaginase (Pieters et al., 2010). The mode of action of asparaginase is the depletion of the circulation pool of L-asparagine and the resulting inhibition of protein syntheses. It is thought that continuous serum asparagine depletion is associated with better EFS than intermittent depletion. The importance of continuous and sustained asparagine depletion in the first 30-35 weeks of asparaginase therapy as a critical factor in improving outcomes in childhood ALL, is supported by the results of several studies using E. coli asparaginase and pegaspargase (Abshire et al., 2000; Avramis et al., 2002; Patil et al., 2010; Silverman et al., 2001). The generally accepted opinion is that adequate asparagine depletion, including depletion in the cerebrospinal fluid, is achieved if a serum level of asparaginase of >100 IU/L is achieved (Riccardi et al., 1981).

Three main types of asparaginase have been used so far:
- native asparaginase derived from Escherichia coli
- a pegylated form of the native E. coli asparaginase
- Erwinase.

It is suggested that the biological activity and relative potency among available asparaginases is different (Pieters et al.).

Boos et al. reported that the treatment with different asparaginase preparations (10,000 IU/m²) resulted in different levels of enzyme activities. For patients treated with E. coli-derived asparaginase, complete asparagine depletion was reached in 60-90% of the patients at day 3 of treatment, whereas at that time point only for 26% of the patients treated with Erwinase complete asparagine depletion was reported (Boos J., et al. 1996). Randomized studies conducted by Moghrabi et al. (2007) and Duval et al. (2002) have indicated that asparaginase preparations with a shorter half-life (Erwinase) result in a poorer event-free survival, albeit less toxicity, compared with the use of asparaginase preparation with a longer half-life (E. coli aspasginase) given at the same dose and frequency. Also results of the study by Kwak et al. (2005), indicate that the efficacy of Erwinase appears inferior in comparison to E. coli asparaginase, when both products were administered at the same dose and dosage frequency. It is suggested that due to the shorter half-life of Erwinia asparaginase compared with the E. coli-derived preparations, a higher dose and increased frequency of treatment is required to ensure adequate serum enzyme activity and complete serum asparagine depletion.

Whereas, by low doses (10,000 IU/m²) Erwinase in only 26% of the treated patients complete asparagine depletion is seen at day 3 of treatment, in the AALL07P2 study the majority (75-85%) of the patients treated with 25,000 IU/m² proved to have complete serum asparagine depletion until 72
hours after treatment. Also the asparaginase activity of most of these patients was above 100 IU/L until 72 hours after treatment. Moreover, a study by the Children’s Cancer Group (CCG), study CCG-1962 indicated that by the dose of 25,000 IU/m² Erwinase asparaginase activity and asparagine levels are reached comparable to the levels seen after treatment with E. coli-derived PEG-asparaginase. It is reported that the ability to tolerate asparaginase is an important predictor of clinical outcome. Silverman et al. have seen that patients who were able to receive 26 or more weeks of a planned 30-week treatment course of E. coli asparaginase had superior EFS compared with patients who stopped asparaginase early due to toxicity (Silverman et al., 2001), suggesting that an effective treatment with asparaginase is important for long results of the ALL treatment. The possibility of (second line) asparaginase treatment after failure of first line asparaginase treatment is considered crucial.

A substantial percentage of patients who are treated with E. coli-derived asparaginase, develop allergic symptoms during treatment. It has been demonstrated that most patients with E. coli asparaginase allergy also have a neutralizing antibody to the enzyme, resulting in sub-therapeutic systemic asparaginase activity. Studies in relapsed and frontline patients suggest that development of high titer anti-asparaginase antibodies is associated with inferior treatment response (Abshire et al., 2000; Hawkins et al., 2004; Kurtzberg, 2000). Studies have shown the immunological cross-reactivity between patients’ antibodies against E. coli asparaginase and pegaspargase, but not between those against E. coli asparaginase and Erwinase (Wang et al., 2003).

In study CCG-1961 with high-risk paediatric ALL patients, the efficacy of switching products after clinical hypersensitivity was investigated. At the moment of an interim analysis, 41% of the patients treated with E. coli asparaginase had developed allergic reactions with positive antibody formation. Silent hypersensitivity (i.e., antibody positive with no clinical allergies) was reported for 29% of the patients. Patients with silent hypersensitivity continued to receive E. coli asparaginase, whereas patients with clinical allergic reactions were switched to Erwinase. The hazard ratio for treatment failure was 3.2 for patients with silent hypersensitivity and only 0.6 for patients who were switched to Erwinase (Panosyan et al., 2004). The data are given in the table below.

### Interim analysis of anti-asparaginase antibodies and outcome in patients with high-risk ALL – CCG-1961

<table>
<thead>
<tr>
<th>Groups</th>
<th>Clinical Allergy</th>
<th>Antibody (+)</th>
<th>Number (%) of Patients</th>
<th>Events (30 months)</th>
<th>Hazard Ratio for Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No</td>
<td>No</td>
<td>57 (20%)</td>
<td>3/57</td>
<td>1.0</td>
</tr>
<tr>
<td>B*</td>
<td>Yes</td>
<td>No</td>
<td>27 (10%)</td>
<td>2/27</td>
<td>1.3</td>
</tr>
<tr>
<td>C*</td>
<td>Yes</td>
<td>Yes</td>
<td>115 (41%)</td>
<td>3/115</td>
<td>0.6</td>
</tr>
<tr>
<td>D**</td>
<td>No</td>
<td>Yes</td>
<td>81 (29%)</td>
<td>13/81</td>
<td>3.2***</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>280 (100%)</td>
<td>21/280</td>
<td></td>
<td>2.11</td>
</tr>
</tbody>
</table>

* Patients were treated with Erwinase after the clinical allergy symptoms appeared.
** Silent hypersensitivity patients. These patients had the highest hazard ratio for treatment failure, which was statistically significant over the other groups of patients.
*** Log rank p=0.01

Vrooman et al. have demonstrated that there is no significant difference in EFS in children who received Erwinase after E. coli asparaginase allergy and those without a history of E. coli asparaginase allergy (Vrooman et al., 2010). Although all patients who received Erwinase in the Vrooman study had a history of prior E. coli asparaginase allergy, two-third did not develop allergy to Erwinase.

The above mentioned studies indicate that Erwinase is effective as next-line therapy in patients who have developed a hypersensitivity to E. coli-derived asparaginase. Most of the clinical studies conducted with Erwinase include paediatric patients. To date, no data have been published specifically concerning the use of Erwinase in adolescents and young adults with ALL. Data for this age group comes from a retrospective comparison of 2 groups of protocols that used E. coli-derived asparaginase (native or pegylated) (Stock et al., 2008). Results of this study indicate that the percentage of patients with a 7 years EFS was higher for adolescents and young adults who received the paediatric protocol of the CCG than for patients who had received the adult protocols of the Cancer and Leukemia Group B (CALGB) (55% vs. 29%). As not only the doses of asparaginase

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treatment were different between the adult and paediatric protocol, the contributions of asparaginase for the better efficacy of the paediatric treatment protocol in adolescents is not clear.

The efficacy of asparaginase has recently been evaluated in adults using the approach of administering the more intensive paediatric protocols. In most clinical studies investigating the efficacy of asparaginase treatment in adults, *E. coli*-derived asparaginase was used. The UKALL X study in which adult ALL patients were treated with a paediatric ALL protocol using the (suboptimal) dose of 9 X 6,000 IU/m² Erwinase during induction therapy, the 5 year disease-free survival in the standard-risk group improved only marginally in comparison to historical controls (40% vs 30%) (Durrant *et al.*, 1997). In studies using *E. coli*-derived asparaginase the 5 year overall survival appeared to be better (63%-60% Silverman *et al.*, 2001 and Thomas *et al.*, 2004, respectively). These results suggest that asparaginase treatment could be important for long-control of adult ALL patients.

IV.4 Clinical safety

The safety data are obtained from exposure to Erwinase in MAH sponsored clinical trials, safety studies in the literature and exposure data from the global safety database held by the MAH.

Very common (≥1/10 patients) and common (≥1/100 to <1/10) adverse events (AEs) that occur in patients who have been treated with Erwinase include the following:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very common:</strong></td>
<td>Coagulopathies – abnormal clotting factor, decreased antithrombin III, protein C, protein S or blood fibrinogen [2].</td>
</tr>
<tr>
<td><strong>Common:</strong></td>
<td>Coagulopathies associated with bleeding or thrombotic complications, hypocoagulable state, asymptomatic coagulopathy, hypofibrinogenaemia, febrile neutropenia, leukopenia (including neutropenia).</td>
</tr>
<tr>
<td><strong>Immune system disorders:</strong></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td><strong>Metabolic and nutrition disorders:</strong></td>
<td>Increased serum amylase or lipase</td>
</tr>
<tr>
<td><strong>Nervous system disorders:</strong></td>
<td>Lethargy, somnolence, confusional state, dizziness, neurotoxicity [3], grand mal convulsion [4], partial seizures [4], headache.</td>
</tr>
<tr>
<td><strong>Vascular disorders:</strong></td>
<td>Pulmonary, venous, peripheral or cerebral thrombosis, pallor.</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders:</strong></td>
<td>Dysspnoea [5]</td>
</tr>
<tr>
<td><strong>Gastrointestinal system disorders:</strong></td>
<td>Diarrhoea, acute pancreatitis, nausea, vomiting, abdominal pain.</td>
</tr>
<tr>
<td><strong>Hepato-biliary disorders:</strong></td>
<td>Increases in bilirubin, transaminases and alkaline phosphatase, hepatotoxicity, hypercholesterolemia.</td>
</tr>
<tr>
<td><strong>Skin and sub-cutaneous tissue disorders:</strong></td>
<td>Rash, urticaria, pruritis, erythema, face oedema, lip swelling [5]</td>
</tr>
<tr>
<td><strong>General disorders:</strong></td>
<td>Pyrexia, chills, peripheral oedema, injection site reaction (including injection site pain, erythema, haematoma, or oedema), pain.</td>
</tr>
</tbody>
</table>

1. Very common (≥1/10) and common (≥1/100 to <1/10)
2. As a consequence of inhibition of protein synthesis.
3. Nervous system and cardiac disorders are often secondary to other adverse effects (e.g. thromboembolism) or synergistic to the effects of other chemotherapy drugs (e.g. delayed
methotrexate clearance).

4. Convulsions may be associated with cases of thrombosis or metabolic encephalopathy.
5. These symptoms are commonly associated with hypersensitivity reactions.

Hypersensitivity - including urticarial rash, fever, bronchospasm, arthralgia, laryngeal oedema, hypotension and anaphylactic shock, pancreatitis and coagulation disorders are the three most frequent adverse reactions to Erwinase.

Retreatment with asparaginase may be associated with an increased risk of allergic reactions. Hypersensitivity reactions to asparaginase occur almost exclusively in post-induction therapy (i.e., intensification, re-induction) when asparaginase has not been given for some weeks or months (Pieters et al., 2010).

Serious adverse advents that are reported for Erwinase treatment included:
- hypersensitivity reactions including anaphylactoid reaction, anaphylactic shock, and anaphylactic reaction
- coagulation disorders, primarily haemorrhage or thrombosis
- pancreatitis, including haemorrhagic pancreatitis, pancreatic pseudocysts
- hyperglycaemia and diabetes mellitus
- infection
- abdominal pain
- neutropenia.

Fatal adverse events included coagulation disorders (haemorrhage and thrombosis), fatal hepatic failure, fatal haemorrhagic and acute pancreatitis, fatal diabetic ketoacidosis and diabetes mellitus and fatal cases of infection following treatment of Erwinase.

The reported AEs for Erwinase were known adverse events of asparaginase products. In previous clinical studies the safety of Erwinase and *E. coli*-derived asparaginase products has been directly compared, using low dose Erwinase. In these studies it was concluded that the incidence of neurotoxicity, pancreatitis and life-threatening sepsis was significantly lower in children treated with *Erwinia* asparaginase compared with those who received *E. coli* asparaginase (Eden et al., 1990). Moreover, fewer coagulation disorders have been reported for patients treated with Erwinase than for patients treated with *E. coli* asparaginase (Avramis & Pansyan, 2005; Duval et al., 2002). Albertsen et al. has suggested that coagulation changes during asparaginase therapy may be more related to dose than the product used (Albertsen et al., 2002).

The AEs reported in the AALL07P2 study conducted with the (high) 25,000 IU/m² dose, are known AEs of asparaginase products and correspond with the AEs earlier mentioned reported for Erwinase when used at a lower dose. Only 58 patients were included in the AALL07P2 study, therefore the toxicity data coming from this study for the use of 25,000 IU/m², study is very limited. However, about 3000 patients have been treated in other (published) clinical studies with a dose per course close to the dose per course used in the AALL07P2 study.

When comparing the incidence of AEs reported for high dose and low dose Erwinase treatment, the incidence of infections and blood and lymphatic system disorders is slightly higher in case of high dose Erwinase. The occurrence of blood and lymphatic system disorders will be closely monitored and discussed in the next PSURs.

Moreover, in the AALL07P2 study QT prolongations were reported in some of the treated patients. After re-analysis of the QTc interval data from the ECGs as collected during study AALL07P2 using Fridericia's correction, none of the evaluable patients showed QTcF prolongation. Therefore, it was concluded that there is no evidence for a QTc prolongation-related safety risk associated with the use of high dose Erwinase. However, the MAH should closely monitor case reports of QTc prolongation and address these in the next PSUR.

Furthermore, an increased incidence of anaphylaxis after treatment with the high dose Erwinase in comparison to the incidences reported after the use of low dose Erwinase was seen. This might be explained by the switch to high dose Erwinase use only after the development of hypersensitivity to *E. coli*-derived asparaginase, by which possibly some cross-reactivity occurs, whereas initially low dose Erwinase treatment was also approved as first line treatment.
Finally an increased incidence of gastrointestinal system disorders for high dose Erwinase in comparison to low dose Erwinase was seen. These AEs could possibly include pancreatitis which is a known AE for asparaginase. The MAH should discuss reported cases of abdominal pain and pancreatitis in future PSURs.

As high dose Erwinase is not directly compared with *E. coli* asparaginase in a clinical trial, it is difficult to compare the safety profile of high dose Erwinase with that of other asparaginase products. However, by the provided data no additional safety concerns are raised for the use of high (25,000 IU/m²) dose Erwinase in comparison to other asparaginase products.

The toxicity and tolerability of asparaginase in the adult population is less well defined (Patil *et al.*, 2010). Given the absence of reliable evidence of the contrary, the current Erwinase SmPC states that the frequency, type and severity of adverse reactions in adults and children are expected to be the same.

### IV.5 Risk Management Plan

The MAH has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Erwinase.

- Summary table of safety concerns as approved in the RMP

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
</table>
| Important identified risks | • Hypersensitivity
|                            | • Coagulation disorders
|                            | • Pancreatic disorders, including hyperglycaemia
|                            | • Hepatotoxicity
|                            | • Infections
| Missing information        | • Use during pregnancy

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in the RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
</tr>
</thead>
</table>
| Hypersensitivity           | **Warning in SmPC section 4.4**
|                            | Although anaphylaxis occurs rarely, measures for treating an anaphylactic reaction, such as epinephrine, *i.v.* glucocorticoids and oxygen, must be available. If hypersensitivity reactions occur the treatment with Erwinase should be discontinued. In the case of repeated treatment the chance of hypersensitivity reactions is increased.
|                            | **Statement in SmPC section 4.8**
|                            | Hypersensitivity, including urticarial rash, fever, bronchospasm, arthralgia, laryngeal oedema, hypotension or other allergic reaction or even anaphylactic shock. In case of systemic hypersensitivity reaction, treatment should be discontinued immediately and withdrawn.

| Coagulation disorders      | **Warning in SmPC section 4.4**
|                            | Routine clotting parameters including prothrombin time, partial thromboplastin time, fibrinogen levels and antithrombin III levels may be performed before
treatment initiation and must be regularly monitored. If significant symptomatic coagulopathy occurs, withhold L-asparaginase treatment until resolved then continue according to protocol.

**Statement in SmPC section 4.8**
Coagulation abnormality due to impairment of protein synthesis, is the second most frequent class of adverse reaction. Clotting disorders as a result of falls in a number of clotting factors and clotting inhibitors (such as antithrombin III, Proteins C and S), hypofibrinogenemia, prolonged prothrombin time, prolonged partial thromboplastin time, and a fall in plasminogen content can lead to thromboembolic and haemorrhagic complications. Thromboses of peripheral, pulmonary or central nervous system blood vessels have been reported which are potentially fatal or associated with residual delayed effects dependent upon the location of the occlusion. Other risk factors contributing to coagulation abnormalities include the disease itself, concomitant steroid therapy and central venous catheters.

**Pancreatic disorders, including hyperglycaemia**

**Warning in SmPC section 4.4**
In the event of symptoms of pancreatitis the treatment should be discontinued. Serum amylase, lipase and/or insulin levels should be monitored to exclude hyperglycaemia and severe pancreatitis. Hyperglycaemia may be treated with insulin, if needed.

**Statement in SmPC section 4.8**
Pancreatic disorders – acute pancreatitis occurs in <10% of cases, and there have been isolated reports of pseudocyst formation up to 4 months after last treatment. In very rare cases, haemorrhagic or necrotising pancreatitis occurs, with fatal consequences. L-asparaginase can affect endocrine pancreatic function. Hyperglycaemia is the most commonly reported undesired effect and is readily controlled with hypoglycaemic agents including insulin. Rare cases of diabetic ketoacidosis have been reported.

**Hepatotoxicity**

**Warning in SmPC section 4.4**
Liver function tests should be monitored regularly during therapy.

**Statement in SmPC section 4.8**
Hepato-biliary disorders:
Common (≥ 1/100 to < 1/10): Increases in blood bilirubin, transaminases, and alkaline phosphatase, hepatotoxicity, hypercholesterolemia.

Rare (≥ 1/10.000 to < 1/1.000): Hepatic failure.
Not known: Hepatomegalgy, cholestatic jaundice, hypoproteninaemia, hypo-albuminaemia, hepatic steatosis.

**Infections**

**Warning in SmPC Section 4.4**
L-asparaginase has been reported to have immunosuppressive activity in animal models. Use of the drug in man may predispose to infection.

**Statement in SmPC section 4.8**
Infections and infestations:
Very rare (1/10.000): Infection, life-threatening sepsis.
Blood and lymphatic system disorders:
Very rare (1/10.000): Neutropenia, febrile neutropenia
Not known: leukopenia, bone marrow depression.

**Missing information**

**Use during pregnancy**

**Statement in SmPC section 4.6**
There are no adequate data from the use of crisantaspase in pregnant women. Limited reports in humans of the use of L-asparaginase in combination with other anti-neoplastics during pregnancy do not provide sufficient data to reach any conclusions.
Animal studies have shown adverse effects on embryonal/fetal development.
Erwinase should not be used during pregnancy unless clearly indicated.

**Statement in SmPC section 5.3**

Reproduction toxicity studies have shown placental transfer of L-asparaginase in rabbits. Teratogenic effects have been observed in rabbits, rats and mice at or below clinically relevant doses. In rabbits malformations of the lung, kidney and skeleton (spina bifida, abdominal extrusion, missing tail) were observed. Treatment of pregnant rats and mice produced ex-encephaly and skeletal abnormalities.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks.

The MAH committed to include updated questionnaires for follow-up of case reports of nausea, vomiting, abdominal pain and anaphylactic reactions as an appendix in the RMP. This commitment has been fulfilled through variation NL/H/3194/001/IA/001.

**IV.6 Discussion on the clinical aspects**

Extensive clinical data support the use of asparaginase therapy in (paediatric) ALL and L-asparaginase is one of the main components of paediatric leukaemia treatments. Several studies indicated that the efficacy of Erwinase is inferior in comparison to *E. coli* asparaginase, when both products were administered at the same dose and dosage frequency. On the other hand, previously conducted studies comparing Erwinase and *E. coli*-derived asparaginase show a better safety profile for Erwinase than for *E. coli* asparaginase (significantly lower incidence of neurotoxicity, pancreatitis and life-threatening sepsis). In these studies Erwinase was used at the same dose as *E. coli* asparaginase. It is thought that both the inferior efficacy and the better safety profile of Erwinase may be more related to dose than the product used.

It is suggested that due to the shorter half-life of *Erwinia* asparaginase compared with the *E. coli*-derived preparations, a higher dose and increased frequency of treatment is required to ensure adequate serum enzyme activity and complete serum asparagine depletion.

A substantial proportion of the patients treated with *E. coli* asparaginase develop antibodies against asparaginase. Studies in relapsed and frontline patients suggest that development of high titer anti-asparaginase antibodies is associated with inferior treatment response.

Studies in which patients with silent hypersensitivity continued to receive *E. coli* asparaginase and patients with clinical allergic reactions were switched to Erwinase, showed higher treatment failure for patients continuing treatment with *E. coli* asparaginase, than for patients who were switched to Erwinase after the development of antibodies to *E. coli* asparaginase. In other studies immunological cross-reactivity between patients’ antibodies against *E. coli* asparaginase and pegaspargase was observed, but not between those against *E. coli* asparaginase and Erwinase.

The observations from clinical studies indicate that Erwinase is effective as next-line therapy in patients who have developed a hypersensitivity to *E. coli*-derived asparaginase.

The reported adverse events for Erwinase were known AEs of asparaginase products. When comparing the incidence of AE reported for high dose Erwinase and for low dose Erwinase treatment, the incidence of hypersensitivity reaction, gastro-intestinal system disorder, possibly including pancreatitis and infections and blood and lymphatic system disorders, is higher in case of high dose Erwinase.

In the AALL07P2 study QT prolongation was reported in some of the treated patients. A re-analysis using Fridericia's correction showed no evidence for a QTc prolongation-related safety risk associated with the use of high dose Erwinase.

No direct comparison of AEs between *E. coli* asparaginase products and high dose Erwinase was conducted. However, the submitted safety data for high dose Erwinase does not raise specific safety concerns for the use of high dose Erwinase as second line treatment. Risk management is adequately addressed.
V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Erwinase, powder for solution for injection 10,000 IU/vial has a proven chemical-pharmaceutical quality. The non-clinical dossier contains sufficient data on pharmacology, pharmacokinetics and toxicology.

The data provided in the clinical dossier demonstrate an established efficacy and an acceptable level of safety in the indication ‘in combination with other chemotherapeutic agents, for the treatment of patients, mainly children, with acute lymphoblastic leukaemia who have developed (clinical allergy or silent inactivation) to native or pegylated asparaginase derived from E. coli.’

The Board followed the advice of the assessors and granted a marketing authorisation on 19 September 1997.

In the mutual recognition procedure agreement between member states was reached during a written procedure; there was no discussion in the CMD(h). The concerned member state, on the basis of the data submitted, considered that a positive benefit-risk balance has been demonstrated for Erwinase, powder for solution for injection 10,000 IU/vial, and has therefore granted a marketing authorisation. The MRP was finalised with a positive outcome on 2 February 2015.

The following post-approval commitment has been made during the procedure:
- The MAH committed to include updated questionnaires for follow-up of case reports of nausea, vomiting, abdominal pain and anaphylactic reactions as an appendix in the RMP. This commitment has been fulfilled (variation NL/H/3194/001/A/001, August 2015).
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
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<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non-approval</th>
<th>Assessment report attached</th>
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<td>Submission of a revised version of the RMP (version April 2015), incorporating amendments agreed during the mutual recognition procedure.</td>
<td>NL/H/3194/001/IA/001</td>
<td>IA</td>
<td>2-7-2015</td>
<td>1-8-2015</td>
<td>Approval</td>
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LITERATURE REFERENCES


