23 April 2009
EMA/208737/2009
Committee for Medicinal Products for Human Use (CHMP)

# Fasturtec

(rasburicase)

Procedure No. EMEA/H/C/000331/A45/39

# CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

# I. EXECUTIVE SUMMARY

On 15 December 2008, the MAH submitted two completed paediatric studies for **Rasburicase (Fasturtec, SR29142)**, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. With the exception of the EFC5339 and ACT5080 study reports, no further documentation has been provided by the MAH.
No critical expert overview neither an annex with SPC has been provided by the MAH.
The MAH stated that the submitted paediatric studies do no influence the benefit risk for Fasturtec and that there is no consequential regulatory action.

# II. RECOMMENDATION

In view of the Rapporteur, the analyses of the results of studies ACT5080 and EFC5339 do not affect the benefit/risk for Fasturtec under the currently authorized indication in the European Union. Therefore, no further regulatory action is required.

# III. INTRODUCTION

In patients with rapid proliferating malignancies hyperuricemia can be caused by the increased cell turnover with high catabolism of nucleic acids and/or may be the result of rapid tumor cell lysis following chemotherapy regimens.
Tumor lysis syndrome (TLS) is a metabolic disorder caused by the rapid destruction of malignant cells and release of intracellular contents into the extra-cellular space. TLS is characterized by hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and acute renal failure. Acute renal failure is essentially caused by precipitation of crystals of uric acid in renal tubules and is the most feared immediate complication occurring during treatment of haematological malignancies (frequency up to 30% in absence of prevention/treatment of hyperuricemia). Lethal cardiac arrhythmias are also reported in patients with TLS as consequence of hyperkaliemia.
The combination of allopurinol with alkaline hydration (facilitating the renal clearance of uric acid) has been used for the prophylaxis/treatment of hyperuricemia in patients with hematologic malignancies at risk of TLS. However, allopurinol (a xanthine oxidase inhibitor) blocks further uric acid production but has no effect on the existing hyperuricemia.

Rasburicase is a recombinant form of the enzyme urate oxidase produced in Saccharomyces cerevisiae cloned with cDNA of Aspergillus flavus. Rasburicase catalyses the oxidation of uric acid to allantoin (a water-soluble product that is easily excreted by the kidney), thus acting as uricolytic agent.
In clinical studies treatment with rasburicase has been associated with more rapid onset of anti-hyperuricemic action and significantly lower mean plasma uric acid levels compared with allopurinol, especially in patients presenting hyperuricemia prior to chemotherapy. In several trials, control of uric acid level was obtained in 95-99% of patients treated with rasburicase for prophylaxis/treatment of hyperuricemia.

Fasturtec was approved for the E.U. in February 2001 for the “treatment and prophylaxis of acute hyperuricemia, in order to prevent acute renal failure, in patients with hematological malignancy with a high tumor burden and at risk of a rapid tumor lysis or shrinkage at initiation of chemotherapy”.

In July 2002 also the U.S. Food and Drug Administration (FDA) approved rasburicase for the "initial management of plasma uric acid levels in paediatric patients with leukemia, lymphoma, and solid malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid" (trade name: Elitek).

The recommended posology for Fasturtec, either in adult and paediatric patients, is 0.20 mg/kg/day as a 30 minute intravenous infusion; the duration of treatment may be up to 7 days, based upon adequate monitoring of uric acid levels in plasma and clinical judgment. It is recommended to use rasburicase immediately prior to and during the initiation of chemotherapy only, as at the present, there is insufficient data to recommend multiple treatment courses.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the clinical studies

### 1. Introduction

The MAH submitted reports for:

- Study ACT5080: open-label, multicenter study of rasburicase as uricolytic therapy/profylaxis for hyperuricemia in paediatric patients with newly diagnosed haematological malignancies at high risk for Tumor Lysis Syndrome;

- Study EFC5339: evaluation of single agent resburicase in treatment/prevention of hyperuricemia associated with tumor lysis syndrome in adult and paediatric patients with lymphoma/leukemia/solid malignancies at their first relapse or refractory disease.

### 2. Clinical studies

**Study ACT5080: open-label, multicenter study of resburicase as uricolytic therapy/prophylaxis for hyperuricemia in paediatric patients with newly diagnosed haematological malignancies at high risk for Tumor Lysis Syndrome;**

- **Description - study ACT5080**

Study ACT5080 was a multicenter, randomized, open-label study conducted in 30 paediatric Japanese patients with haematological malignancies and at high risk of TLS in order to evaluate efficacy and safety of raburicase as urocolytic agent (i.e., in prevention and/or treatment of hyperuricemia) when administered at two dose levels (0.15 mg/kg/day and 0.20 mg/kg/day) for five days.

- **Methods - study ACT5080**

  - Objective(s)

  Primary objective of study ACT5080 was response rate. Responders were defined as patients with a plasma uric acid level decreased to the endpoint (uric acid: ≤ 7.5 mg/dL in patients ≥13 years and ≤ 6.5 mg/dL in patients <13 years) by 48 hours after the start of first drug infusion and lasting until 24 hours after the final (day 5) drug infusion.
  Patients who fail to complete the 5-days treatment for reason other than hyperuricemia were counted as non-evaluable for response rate.

Secondary endpoints were safety, evaluation of AUC of plasma uric acid and rate of uric acid reduction at 4 hours after study drug infusion, evaluation of anti-SR29142 and anti-SCP (Saccaromyces cerevisiae protein) antibody, pharmacokinetics.

- Study design

Study ACT5080 was a open-label, multicenter, parallel group and repeated dose trial conducted in three centers in Japan. Thirty paediatric patients with haematological malignancies and at high risk of TLS were randomized to two rasburicase dose groups (0.15 mg/kg/day or 0.20 mg/kg/day, respectively). Response rate and pharmacokinetic parameters were evaluated.
The original protocol of study ACT5080 was amended twice, on August 4th, 2005 and November 17th, 2005. Both amendments were introduced after inclusion of some patients and they consisted of modification in inclusion and exclusion criteria, preparation of the compound, modification of prohibited concomitant treatments and corrections of the statistical model of accumulation of PK parameters. Evaluation of pharmacokinetics was performed in 10 evaluable patients at each dose level which had a weight > 10 kg at time of enrolment.

- Study population /Sample size

The ACT5080 study population included 30 patients < 18 years of age with newly diagnosed haematological malignancies presenting with hyperuricemia (as defined as uric acid > 7.5 mg/dL in patients ≥13 years or > 6.5 mg/dL in patients <13 years) OR with high tumor burden, defined as:
a) Non-Hodgkin's lymphoma stage IV (according to modified Murphy's classification); or
b) Non-Hodgkin's lymphoma stage III with at least one lymph node or mass >5 cm in diameter or lactate dehydrogenase (LDH) ≥ 3 x ULN (IU/L); or
c) acute leukemia with white blood cell (WBC) count ≥ 50000/mm3 or LDH ≥ 3 x ULN (IU/L)).

Patients were required to receive induction chemotherapy (including cytoreductive corticosteroids) no sooner than 4 hours and no later than 24 hours after resburicase administration, and to have a Performance Status (PS) ≤ 3 according to ECOG scale or ≥ 30 according to the Lansky score. Patients who had received allopurinol within 72 hours prior to the first dose of rasburicase, with known history of allergic reaction and/or severe asthma, with personal of family history of G6P-deficiency or hemolysis and methemoglobinuria, as well as patients with severe liver and kidney disorders were excluded from the study.
Of note: patients were stratified by body weight at time of enrolment.

- Treatments

Patients were randomized to two rasburicase dose groups (0.15 mg/kg or 0.20 mg/kg, respectively) which received rasburicase as 30 minutes intravenous infusion once daily for 5 days. Whenever possible rasburicase was administered via a separate line in order to prevent drug-drug interactions. Chemotherapy including cytoreductive corticosteroids were to be started no sooner than 4 hours and no later than 24 hours after rasburicase administration. Corticosteroids as supportive treatment and anti-emetics were allowed.
Other anti-hyperuricemia agents (e.g., allopurinol) or treatment with sodium bicarbonate for urine alkalization was not permitted from start of the trial until the final blood sampling for plasma uric acid level at day 6.

- Statistical Methods

Assuming a response rate of 95% in each dose group (0.15 mg/kg and 0.20 mg/kg), a sample size of 15 patients per group had the following statistical properties:
- probability of observing at least 1 failure in the study was 0.79.
- expected lower 95% confidence limit for response rate in each dose group was 0.71.

The probability of observing at least one Adverse Event (AE) for various incidence rates is reported in Table 1. For example, when a rare event occurred 3% of the time, the probability that at least 1 patient in a treatment group reported the event would have been 36% for N=15.

**Table 1. Probability of observing at least 1 adverse event for various incidence rates (N=15 per dose group)**

| Incidence Rate | 0.01 | 0.03 | 0.05 | 0.10 | 0.15 | 0.30 |
|---|---|---|---|---|---|---|
| | 0.14 | 0.36 | 0.53 | 0.79 | 0.91 | 0.99 |

## ➢ Results - study ACT5080

- Recruitment/ Number analysed

Thirty-one patients were enrolled and 30 patients were randomized and treated. Fifteen patients were allocated to each treatment group. One patient did not fulfil the inclusion criteria prior to randomization (elevated ALT level).

One patient in the 0.20 mg/kg group discontinued treatment while on study due to lack of white blood cell count at baseline found on day 1 after the first administration of the study drug. A total of 13 patients presented protocol deviations: of note: one patient enrolled in the 0.15 mg/kg group had concomitant use of other anti-hyperuricemic agents, and one patient in the 0.20 mg/kg group did not fulfil all the inclusion criteria.

- Baseline data

Overall, the mean age of the patients enrolled was 8.8 years (range: 2 months-17 years), about two-thirds of the patients (63.3%) were male, and the majority of patients had an ECOG scale PS of 0 (40%) or 1 (40%). There were no notable differences between the two dose groups in terms of demographic and baseline characteristics, whereas differences in diagnosis and baseline disease status between the two study arms were observed (see Table 2). At baseline, 43.3% of patients were hyperuricemic. All patients (100%) were classified as at high risk for TLS.

**Table 2. Summary of initial diagnosis and baseline disease status**

| | 0.15 mg/kg N=15 | | 0.20 mg/kg N=15 | | Total N=30 | |
|---|---|---|---|---|---|---|
| Hyperuricemic at baseline | | | | | | |
| No | 7 | (46.7%) | 10 | (66.7%) | 17 | (56.7%) |
| Yes | 8 | (53.3%) | 5 | (33.3%) | 13 | (43.3%) |
| Diagnosis | | | | | | |
| Malignant lymphoma | 6 | (40.0%) | 2 | (13.3%) | 8 | (26.7%) |
| Acute leukemia | 9 | (60.0%) | 13 | (86.7%) | 22 | (73.3%) |
| Other | 0 | (0%) | 0 | (0%) | 0 | (0%) |
| Stage of lymphoma | | | | | | |
| I | 0 | (0%) | 0 | (0%) | 0 | (0%) |
| II | 0 | (0%) | 0 | (0%) | 0 | (0%) |
| III | 3 | (20.0%) | 1 | (6.7%) | 4 | (13.3%) |
| IV | 2 | (13.3%) | 1 | (6.7%) | 3 | (10.0%) |
| Unknown | 1 | (6.7%) | 0 | (0%) | 1 | (3.3%) |
| Acute leukemia | | | | | | |
| Lymphatic | 5 | (33.3%) | 12 | (80.0%) | 17 | (56.7%) |
| Myelogenic | 4 | (26.7%) | 0 | (0%) | 4 | (13.3%) |
| Other | 0 | (0%) | 1 | (6.7%) | 1 | (3.3%) |
| Risk category | | | | | | |
| High | 15 | (100%) | 15 | (100%) | 30 | (100%) |
| Potential | 0 | (0%) | 0 | (0%) | 0 | (0%) |

No significant differences were observed in prior and concomitant medications between the two study groups. A list of chemotherapeutic regimens co-administered to the patients during study ACT5080 has also been provided.

- Pharmacokinetics

In 20 of the 30 Japanese patients enrolled in study ACT5080 (10 patients in the 0.15 mg/kg, 10 patients in the 0.20 mg/kg dose group) blood samples for the determination of plasma concentrations of rasburicase were obtained. The mean age of the patients was 10 years (range: 3-16 years) in the 0.15 mg/kg group and 7 years (range: 2-16 years) in the 0.20 mg/kg group. The weight range of the patients was 11.8 kg to 58.8 kg. Plasma sampling was performed on :

- Day 1: Before administration (within 10 minutes), end of infusion (within 10 minutes), 4 hours ± 10 minutes after starting administration, 8 hours ± 10 minutes after starting administration;
- Day 2: Before administration (within 10 minutes).
- Day 5: Before administration (within 10 minutes), end of infusion (within 10 minutes), 4 hours ± 10 minutes after starting administration at day 5, 8 hours ± 10 minutes after starting administration at day 5.
- Day 6: 24 hours ± 10 minutes after starting administration at day 5.

The following pharmacokinetic parameters were determined:

- $AUC_{0-24}$ (Area under the plasma concentration versus time curve, calculated using the trapezoidal method from time zero to 24 hours after administration): day 1 and day 5;
- $C_{min}$ (plasma concentration observed before treatment administration during repeated dosing): day 1 and day 5;
- $C_{eoi}$ (plasma concentration observed at end of the i.v. infusion): day 1 and day 5;
- $t_{1/2z}$ (terminal half-life): day 5.

Rasburicase concentrations were measured using a validated ELISA method with a lower limit of quantification (LLOQ) of 1.4 ng/mL.
Mean plasma concentration time curves of rasburicase are shown in Figure 1 and descriptive statistics of the pharmacokinetic parameters are summarized in Table 3.

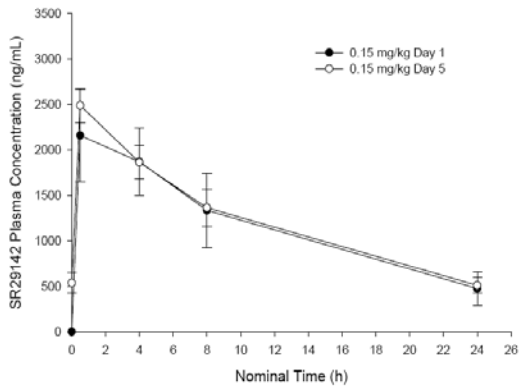
**Table 3. Mean (SD) pharmacokinetic parameters after once daily 30 min intravenous infusion of rasburicase (5-day treatment) in Japanese paediatric patients.**

| | Day 1 | | Day 5 | | | |
|---|---|---|---|---|---|---|
| Dose Group (mg/kg) | $C_{eoi}$ (ng/mL) | $AUC_{0-24}$ (ng•h/mL) | $C_{min}$ (ng/mL) | $C_{eoi}$ (ng/mL) | $AUC_{0-24}$ (ng*h /mL) | $t_{1.2z}$ (h) |
| 0.15 (n=10) | 2160 (512) | 28200 (7270) | 536 (218) | 2490 (373) | 29700 (6460) | 11.6 (4.96) |
| 0.20 (n=9) | 2580* (432) | 31500 (4540) | 780 (335) | 3050 (383) | 38100 (5640) | 11.2 (3.06) |

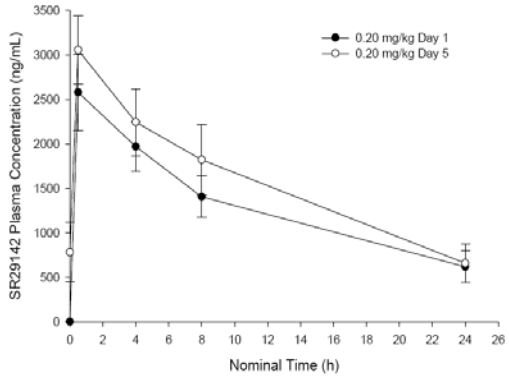
* n=10

Rasburicase pharmacokinetics was dose proportional. Rasburicase exhibited slight accumulation on day 5 as measured by $AUC_{0-24}$ and $C_{eoi}$ (mean ratios day 5/day 1 were 1.13 and 1.17, respectively); $t_{1/2z}$ was comparable for both groups. The elimination half life of 11 hours observed in study ACT5080 is shorter compared with data submitted previously ($t_{1/2}$: 16-21 hours in paediatric patients, see also Pui et al. J Clin. Onc, 2001) but this is most likely due to the shorter sampling period performed in study ACT5080. Variability in $AUC_{0-24}$ and $C_{eoi}$ values was small (total-patient variability < 20% for both parameters) indicating that dose administration based on kg bodyweight is adequate.

**Figure 1 Plasma concentration – time profile of rasburicase in Japanese paediatric patients (study ACT5080).**




* Mean (+/-SD) plasma concentration – time profile on Day 1 and Day 5 for SR29142 0.15 mg/kg dose group cartesian scale (n=10)




* Mean (+/-SD) plasma concentration – time profile on Day 1 and Day 5 for SR29142 0.20 mg/kg dose group cartesian scale (n=9)

In conclusion, after five days of administration of rasburicase as a 30-min intravenous infusion to Japanese paediatric patients at the doses of 0.15 and 0.20 mg/kg/day, no unexpected accumulation was observed. Variability in $AUC_{0-24}$ and $C_{eoi}$ values were small (total-patient variability < 20% for both parameters). Elimination half-life was comparable for both groups (11 hours). The results of ACT5080 study performed in Japanese paediatric patients are in line with the data described in section 5.2 of the currently approved SPC.

- Efficacy results

The population included in the efficacy and safety analyses consisted of all patients who received at least one dose of study drug. Fifteen patients for the 0.15 mg/kg group and 15 for the 0.20 mg/kg group were considered evaluable for response.

Primary Objective: Response Rate

The overall response rate was 96.6%. Response rate was 93.3% (14/15) and 100% (14/14) in the 0.15 mg/kg and 0.20 mg/kg groups, respectively. One patient in the 0.20 mg/kg group withdrew from the study after the first administration of study drug due to violation of inclusion criteria and was classified as non-evaluable for response rate. One patient in the 0.15 mg/kg group did not meet the primary endpoint, therefore was considered as a non-responder. See Table 4.

**Table 4. Response Rate Study ACT5080**

| | 0.15 mg/kg N= 15 | 0.20 mg/kg N= 14 | Total N= 29 |
|---|---|---|---|
| Response rate(%) | 93.3% | 100.0% | 96.6% |
| 95% C.I. | [ 68.1 , 99.8 ] | [ 76.8 , 100.0 ] | [ 82.2 , 99.9 ] |

Response rate in patients with hyperuricemia at baseline was 87.5% (7/8) in the 0.15 mg/kg and 100% (5/5) in the 0.20 mg/kg group. See Table 5.

**Table 5. Response Rate by hyperuricemia status at baseline, study ACT5080**

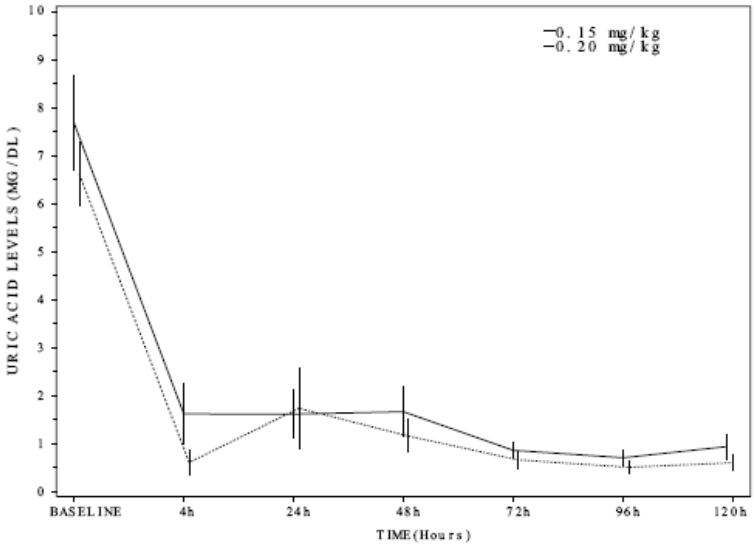
| | Hyperuricemic N= 13 | | Non-hyperuricemic N= 16 | | Total N= 29 | |
|---|---|---|---|---|---|---|
| | 0.15 mg/kg N= 8 | 0.20 mg/kg N= 5 | 0.15 mg/kg N= 7 | 0.20 mg/kg N= 9 | 0.15 mg/kg N= 15 | 0.20 mg/kg N= 14 |
| Response rate(%) | 87.5% | 100.0% | 100.0% | 100.0% | 93.3% | 100.0% |
| 95% C.I. | [ 47.3 , 99.7 ] | [ 47.8 , 100.0 ] | [ 59.0 , 100.0 ] | [ 66.4 , 100.0 ] | [ 68.1 , 99.8 ] | [ 76.8 , 100.0 ] |

Moreover in subgroup analyses, response rates by age category, sex, diagnosis, stage of lymphoma, acute leukemia and ECOG Performance Status were high and similar in both dose groups.

Secondary Objectives:

At both dose levels, rasburicase produced a rapid decrease in plasma uric acid concentrations with uric acid levels remaining low throughout treatment periods in all patients with the exception of a non-responder patient in the 0.15 mg/kg group. (Fig.2) Moreover, another patient in the 0.20 mg/kg group showed transient initial elevation of uric acid level (11.8 mg/dL) at 24 hours followed by low uric acid level from 48 hours through 120 hours (day 6). At 4 hours post the first dose of rasburicase, mean plasma uric acid concentration was reduced by 84.79% and 92.86% compared to baseline in the 0.15 mg/kg and the 0.20 mg/kg groups, respectively.

**Figure 2. Mean plasma uric acid concentrations by dose over time, study ACT5080**




- Safety results

All treated patients had at least 1 AE regardless of relationship to rasburicase. However, the majority of AEs could be attributed to the patients' underlying cancer state and/or to the concomitant administration of cytotoxic drugs. In general, AEs were similar at the two doses of rasburicase administered. Only one patient in the 0.15 mg/kg group reported Serious AEs (SAEs) of multiple cerebral haemorrhage, brain oedema, brain herniation, which have been considered not related to rasburicase. No patient died during study period.

Hypersensitivity-associated reactions, regardless of relationship to investigational product, occurred in 20 patients (66.7%), with grade 3 or 4 reactions in 2 patients (13.3%) in the 0.15 mg/kg group, and none in the 0.20 mg/kg group. The most frequent AE in hypersensitivity-associated reactions was pyrexia (40.0%).

Drug related AEs occurred in 6 patients (20.0%). Two patients in 0.15 mg/kg group had hypersensitivity and haemoglobin decreased before chemotherapy, respectively. One patient experienced hemolysis during the study that was judged by the Investigator to be related to rasburicase. However, a G6P-deficiency was not found in this patient.

Anti-SCP antibodies were detected before rasburicase administration in one patient. In another patient anti-SR29142 antibodies were found on day 29; however, anti-SR29142 were not detectable six months later. Moreover, both patients did not report any hypersensitivity-AEs. Of note: no deterioration of renal function parameters and serum electrolytes was observed.

**Study EFC5339: evaluation of single agent rasburicase in treatment/prevention of hyperuricemia associated with tumor lysis syndrome in adult and paediatric patients with lymphoma/leukemia/solid tumor malignancies at their first relapse or refractory disease**

- **Description - study EFC5339**

Study EFC5339 was a multicenter, open-label, two-arm trial conducted as post-marketing commitment requested by the US Food and Drug Administration (FDA) in order to evaluate/compare efficacy and safety of Rasburicase in adult and paediatric patients with haematological or solid malignancies at risk of tumor lysis syndrome (TLS), and being either previously treated or not previously treated with an uricolytic agent (Uricozyme or Fasturtec/Elitek).

- **Methods - study EFC5339**

  - Objective(s)

Primary objective of study EFC5339 was response rate. Responders were defined as patients who achieved and/or maintained plasma uric acid concentration ≤ 7.5 mg/dL within 48 hours from treatment with rasburicase up to 144 hours after the end of treatment. If at least 1 plasma uric acid level at 48h through 144h was >7.5 mg/dL, the patient was considered as treatment failure.

Secondary endpoints were safety, evaluation of AUC of plasma uric acid and rate of uric acid reduction at fixed time-points, incidence, duration, and type of immune response (immunoglobulin G [IgG], immunoglobulin E [IgE], and neutralizing antibody) as well as efficacy and safety of rasburicase in relation to antibody generation and antibody titer.
Of note: pharmacokinetic evaluation of rasburicase in adults was introduced as secondary objectives with protocol amendment 4; however, the study was stopped due to poor accrual before implementation of such amendment, therefore PK data were not collected.

  - Study design

Study EFC5339 is a multicenter, open-label, 2-arm study. In the original protocol 85 patients previously treated with an uricolytic agent (arm A, pretreated) and 85 patients not previously treated with an uricolytic agent (arm B, naïve) were to receive rasburicase at 0.20 mg/kg/day for 5 days and up to 7 days in case of uric acid plasma level above 7.5 mg/dL after the first 5 days of treatment.
On 16 May 2006, the DSMB recommended to early terminate the study due to poor accrual in arm A (patients previously treated with rasburicase). Due to the early stop of the study, evaluation of secondary endpoints has not been performed by the MAH.

  - Study population /Sample size

The EFC5339 study population included patients with recurrent or refractory malignancies, either at high or potential risk for TLS (according to specified criteria), previously treated or not with an uricolytic agent, and with a Performance Status (PS) ≤ 3 according to ECOG scale or ≥ 30 according to the Lansky score. Patients with known history of severe allergic reaction and/or severe asthma, with personal of family history of G6P-deficiency or hemolysis and methemoglobinuria, as well as patients in treatment or treated with rituximab within 12 months prior to study entry were excluded from the study.
A total of 85 patients were assigned to each study arm, with a minimum of 35 high-risk patients per arm.

  - Treatments

Patients were assigned to arm A or B by the Investigator depending on previous treatment with an uricolytic agent, and started rasburicase 0.20 mg/kg/day. Rasburicase treatment was administered i.v. over 30 minutes once a day for 5 days, and up to 7 days in case of uric acid plasma level above 7.5 mg/dL after 5 days of rasburicase. However, in this last case the patient was considered as non-responder in the primary efficacy analysis. All cytoreductive chemotherapy agents should have been initiated within 4-24 hours after the first dose of rasburicase. Recommendations for hydration before starting chemotherapy were provided in the protocol; however, optimal hydration was at the investigator's discretion. Concomitant administration of allopurinol, other uricolytic agents, or urine alkalinisation was not allowed.

- Statistical Methods

Based on combined data from previous studies with rasburicase showing an overall rate of uric acid maintenance at 48 hours of 96.6 % (256/265), response rate to rasburicase was estimated at 95% in both arms. To determine a minimum acceptable level of response with rasburicase, allopurinol has been used as a historical control: according to Smalley et al. response rate to allopurinol was 71.4% in hyperuricemic patients, and 93.5% in 46 non-hyperuricemic patients. Therefore, in a study with approximately 40% of patients being hyperuricemic the expected response rate for allopurinol would be 85%.If 85 patients were enrolled into each arm of EFC5339 study (minimum 35 high risk patients) and the expected 95% response rate was achieved, then the lower 95% confidence limit of the observed rate would have been 86.8%, exceeding the expected response rate of 85% with the historical control, allopurinol.
EFC5339 study protocol was amended four times, mostly due to requirements of the FDA.

➢ **Results - study EFC5339**

Analyses were performed in the following populations:

- Intent-to-Treat (ITT) Population, which consisted of all enrolled patients.
- Modified Intent-to-Treat (mITT) Population, which consisted of all patients who received at least one dose of study drug.
- Per Protocol (PP) Population, which excluded any patients who did not receive study therapy as planned, or who had one or more missing uric acid samples and no other samples showing lack of uric acid control.
- Safety (exposed) Population, which consisted of all patients who receive at least one dose of study drug.

- Recruitment/ Number analysed

A total of 94 patients were enrolled in the study, 9 in the pre-treated group and 85 in the naïve group: ITT, mITT, and safety populations all consisted of 94 patients (Table 6). No patients were excluded from any of the analyses.

Table 6. Overall patient disposition

| | Pretreated | | | Naïve | | |
|---|---|---|---|---|---|---|
| | Pediatric | Adult | Total | Pediatric | Adult | Total |
| Number enrolled | 6 | 3 | 9 | 10 | 75 | 85 |
| Number treated (mITT) | 6 | 3 | 9 | 10 | 75 | 85 |
| Number in per protocol population (PP) | 5 | 2 | 7 | 9 | 66 | 75 |
| Number previously enrolled in EFC4978 | 0 | 1 | 1 | 0 | 1 | 1 |

Treatment was stopped in six cases due to the following adverse events: bone pain, bradycardia, convulsions, AST increased, and panic attack. The bradycardia, convulsions, and AST increased were classified by the Investigator as related to rasburicase treatment. The sixth case was a patient who was classified as stopping treatment due to an AE (hemolysis) but was listed as having completed dosing by the Investigator. Treatment was stopped in 2 cases due to patient request. The remainder of patients completed the study period. Most patients stopped the trial because of death, but none of the deaths was related to rasburicase treatment. (See Table 7).

Table 7. Summary of reasons for stopping treatment and stopping EFC5339 trial

| Main reason for stopping treatment | Pretreated | | | | Naïve | | | |
|---|---|---|---|---|---|---|---|---|
| | Pediatric (N=6) | | Adult (N=3) | | Pediatric (N=10) | | Adult (N=75) | |
| Completed study treatment period [a] | 6 | (100) | 3 | (100) | 10 | (100) | 67 | (89.3) |
| Adverse event[b] | 0 | (0) | 0 | (0) | 0 | (0) | 6 | (8.0) |
| Subject's request | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2.7) |

| Main reason for stopping trial | Pretreated | | | | Naïve | | | |
|---|---|---|---|---|---|---|---|---|
| | Pediatric (N=6) | | Adult (N=3) | | Pediatric (N=10) | | Adult (N=75) | |
| Completed follow-up period | 3 | (50.0) | 0 | (0) | 8 | (80.0) | 15 | (20.0) |
| Subject lost to follow-up | 0 | (0) | 0 | (0) | 0 | (0) | 8 | (10.7) |
| Death | 2 | (33.3) | 3 | (100) | 2 | (20.0) | 48 | (64.0) |
| Subject's request | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1.3) |
| Other reason | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1.3) |
| Still in follow-up | 1 | (16.7) | 0 | (0) | 0 | (0) | 2 | (2.7) |

Two patients had protocol violations: one patient had received rituximab within 12 months prior to study entry, and in another patient of childbearing potential no pregnancy test was performed. Dosing irregularities were reported in a total of 10 patients: two patients (one pre-treated and one naïve) received an additional infusion day of resburicase; additional 8 naïve patients received resburicase for less than 5 days due to AEs (6 patients) or withdrawing of consent (2 patients).

- Baseline data

The median age of paediatric patients was 10 years in the pretreated arm and 9 years in the naïve arm. The median age of adult patients was 63 years in the pretreated arm and 49 years in the naïve arm. Across both arms most patients were male (50-67%), Caucasian (70-100%), and had an ECOG performance status of 0 or 1 (81-100%). Seventeen patients were hyperuricemic at baseline; over 90% of patients were at high risk of TLS. The majority were diagnosed with either AML or very aggressive B-cell lymphoma (Table 8).

Table 8. Summary of initial diagnosis and baseline disease status

| | Pretreated | | | | Naïve | | | |
|---|---|---|---|---|---|---|---|---|
| | Pediatric (N=6) | | Adult (N=3) | | Pediatric (N=10) | | Adult (N=75) | |
| Hyperuricemia of Malignancy | | | | | | | | |
| Plasma uric acid <= 7.5mg/dl | 5 | (83.3) | 1 | (33.3) | 9 | (90.0) | 62 | (82.7) |
| Plasma uric acid > 7.5mg/dl | 1 | (16.7) | 2 | (66.7) | 1 | (10.0) | 13 | (17.3) |
| TLS Risk | | | | | | | | |
| High | 6 | (100) | 3 | (100) | 9 | (90.0) | 73 | (97.3) |
| Potential | 0 | (0) | 0 | (0) | 1 | (10.0) | 2 | (2.7) |
| Diagnosis | | | | | | | | |
| Very aggressive B-cell Lymphoma | 1 | (16.7) | 0 | (0) | 6 | (60.0) | 18 | (24.0) |
| Very aggressive T-cell and NK cell lymphomas | 3 | (50.0) | 1 | (33.3) | 1 | (10.0) | 5 | (6.7) |
| Acute Myeloid Leukemias(AML) | 2 | (33.3) | 2 | (66.7) | 2 | (20.0) | 46 | (61.3) |
| Chronic Myeloid Leukemia in Blast Crisis (CML) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (1.3) |
| Myelodysplastic Syndrome (MDS) | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |
| Aggressive T-cell and NK cell lymphomas (intermediate risk) | 0 | (0) | 0 | (0) | 1 | (10.0) | 0 | (0) |
| Aggressive B-cell Lymphomas | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (2.7) |
| Other diagnosis | 0 | (0) | 0 | (0) | 0 | (0) | 3 | (4.0) |
| Time between diagnosis and 1st drug intake (weeks) | | | | | | | | |
| N | 6 | | 3 | | 10 | | 71 | |
| Median | 16.21 | | 17.43 | | 0.21 | | 1.29 | |
| Mean (SD) | 30.02 (37.08) | | 17.19 (16.93) | | 54.50 (135.65) | | 22.08 (74.78) | |
| Range [Min-Max] | 0.00- 86.71 | | 0.14- 34.00 | | 0.00- 426.14 | | 0.00- 503.86 | |
| LDH | | | | | | | | |
| < 2 X ULN | 3 | (50.0) | 1 | (33.3) | 4 | (40.0) | 45 | (60.0) |
| >= 2 X ULN | 3 | (50.0) | 2 | (66.7) | 6 | (60.0) | 30 | (40.0) |
| Stages | | | | | | | | |
| III | 0 | (0) | 0 | (0) | 3 | (30.0) | 2 | (2.7) |
| IV | 2 | (33.3) | 0 | (0) | 3 | (30.0) | 4 | (5.3) |
| Not applicable | 4 | (66.7) | 3 | (100) | 4 | (40.0) | 69 | (92.0) |
| Largest Tumor Size | | | | | | | | |
| < 5 cm | 0 | (0) | 0 | (0) | 1 | (10.0) | 3 | (4.0) |
| => 5 cm | 0 | (0) | 0 | (0) | 2 | (20.0) | 2 | (2.7) |
| Not applicable | 6 | (100) | 3 | (100) | 7 | (70.0) | 70 | (93.3) |

- Efficacy results

Primary endpoints: Response Rate

Ninety-four patients were included in the modified Intent-to-Treat (mITT) Population (see definition above) (Table 9).

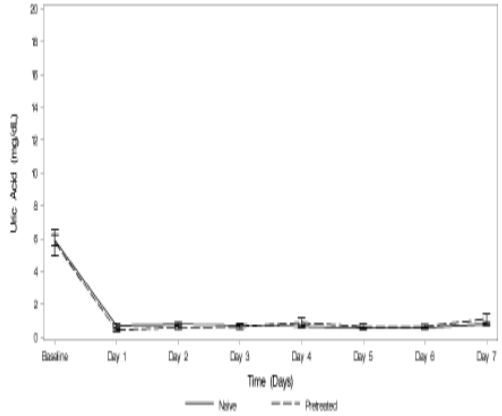
- In the rasburicase pre-treated arm a total of 8 patients (88.9%, 5 paediatric (83.3%) and 3 adults (100%)) were classified as responders. One patient was considered as 'treatment failure' due to extended dosing.
- In the rasburicase naïve arm, a total of 77 patients (90.6%, 10 paediatric (100%) and 67 adults (89.3%)) were classified as responders. Of the 8 who were classified as 'treatment failures' in the naïve arm, 5 were due to missing data, 2 were due to concomitant treatment with allopurinol, 1 was due to extended dosing. No patients were classified as 'treatment failures' due to failure of uric acid control.

Of note, similar results were obtained in the Per Protocol (PP) Population analysis.

**Table 9. Efficacy results EFC5339 study – mITT Population**

| Response Rate - mITT population | | | | | | |
|---|---|---|---|---|---|---|
| | Pre-treated | | | Naïve | | |
| | Pediatric N=6 | Adult N=3 | Total N=9 | Pediatric N=10 | Adult N=75 | Total N=85 |
| Response, n (%) | 5 (83.3%) | 3 (100%) | 8 (88.9%) | 10 (100%) | 67 (89.3%) | 77 (90.6%) |
| (95% CI) | 35.9-99.6 | 29.2-100 | 51.7-99.7 | 69.1-100 | 80-95.3 | 82.3-95.8 |
| | | | | | | |
| Response Rate by Hyperuricemia status - mITT population | | | | | | |
| | Pre-treated | | | Naïve | | |
| | Hyperuric N=3 | | Non-Hyper N=6 | Hyperuric N=14 | | Non-Hyper N=71 |
| Response, n (%) | 3 (100%) | | 5 (83.3%) | 10 (71.4%) | | 67 (94.4%) |
| (95% CI) | 29.2-100 | | 35.9-99.6 | 41.9-91.6 | | 86.2-98.4 |
| | | | | | | |
| Response Rate by TLS risk - mITT population | | | | | | |
| | Pre-treated | | | Naïve | | |
| | High N=9 | | Potential N=0 | High N=82 | | Potential N=3 |
| Response, n (%) | 8 (88.9%) | | 0 | 75 (91.5%) | | 2 (66.7%) |
| (95% CI) | 51.7-99.7 | | 0-0 | 83.2-96.5 | | 9.4-99.2 |

**Figure 3. Uric acid over time levels**




Secondary endpoints

Secondary endpoints have not been evaluated by the MAH due to limited number of patients enrolled in arm A (patients pre-treated with an uricolytic agent).

Time to ice for uric acid samples

Time to ice data for uric acid samples were provided considering that ex. vivo studies indicated that uric acid values in plasma samples from patients that received rasburicase could be affected by the time to ice. For each uric acid measurement time point ≥ 80% of the samples had a time to ice <10 minutes (a time within the effect on uric acid value is reported to be minimal) and <2% of plasma uric acid samples had time to ice ≥10 minutes in the two groups analyzed.

- Safety results

The median number of days of treatment per patient was 5 (range 2-6).

Overall, all patients experienced an AE, all grades. Within each arm and overall, most AEs were hematologic in nature (thrombocytopenia, anemia, and neutropenia) and most likely due to concomitant chemotherapy. Seven patients (8.2%) experienced an AE that was classified by the Investigator as related to study treatment; they were bradycardia, convulsions, hemolysis, AST increase, hypertension, TLS, and abnormal dreams.

Thirty-nine patients had a SAE (6 in the pretreated arm (66.7%) and 33 in the naïve arm (38.8%)): the most common SAEs were febrile neutropenia and neutropenic infection; one patient in the naïve arm experienced hemolysis.
Fifty-nine patients died during the study, mostly due to disease progression. Eight adult patients died within 30 days of last dose, 3 due to progressive disease and 5 due to AEs unrelated to rasburicase treatment (sepsis, neutropenic sepsis, pneumonia/hypoxia, neutropenic infection leading to respiratory failure, and veno-occlusive disease).
Five patients (all in the naïve arm) discontinued study treatment due to AEs (AST increased, convulsions, panic attack, bradycardia, and bone pain). The AST increased, bradycardia, and convulsions were classified as related to rasburicase by the Investigator. In addition, 1 patient interrupted rasburicase treatment due to an AE of hemolysis.

Regarding the AEs of special interest, defined as those associated with allergic reactions, in the naïve arm 2 adults experienced grade 2 hypersensitivity reactions. The hypersensitivity cases occurred 7 and 9 days after last rasburicase treatment and they were assessed as not related to rasburicase administration. A case of grade 3 hemolysis as well as a case of tumor lysis syndrome were reported, but no methemoglobinemia was observed.

In general, no clinically significant differences were observed between the safety profile of resburicase in pretreated and naïve patients. However, considering the very limited number of patients enrolled in the pretreated arm (9 subjects) no conclusion over efficacy and safety of rasburicase in this patient population can be made.

As a post marketing commitment for the approval of Elitek in U.S.A., Sanofi-Aventis agreed to develop quantitative immunogenicity assays (IgG, neutralizing, and IgE), the validation of which is still ongoing at the time of this report. As a result, immunogenity data have not been provided in the EFC5339 study report.

## 3. Discussion on clinical aspects

The analysis of the results of studies ACT5080 and EFC5339 does not raise any additional concern regarding efficacy and safety of rasburicase in the (paediatric) population under the conditions and with the dosing regimens currently approved in the European Union.
Pharmacokinetics of rasburicase in the Japanese paediatric patients enrolled in ACT5080 study was in line with data reported in previously study submitted and reported in section 5.2 of the currently approved SPC.

In study ACT5080 the overall response rate of rasburicase in paediatric patients with hematologic malignancies was 96.6%. Response rate was 93.3% (14/15) and 100% (14/14) in the 0.15 mg/kg and 0.20 mg/kg groups, respectively. In patients with hyperuricemia at baseline, response rate was 87.5% (7/8) in the 0.15 mg/kg and 100.0% (5/5) in the 0.20 mg/kg group. At 4 hours post the first dose of rasburicase, mean plasma uric acid concentration was reduced by 84.79% and 92.86% compared to baseline in the 0.15 mg/kg and the 0.20 mg/kg groups, respectively. These results are in accordance to data previously submitted.
Analogously, in study EFC5339 response rate of rasburicase was 90.6% (77/85) in non-pre-treated patients (100% (10/10) in paediatric and 89.3% (67/75) in adult patients). Similar response rates have been reported in the 9 patients previously treated with rasburicase and classified as responders (88.9% (8/9) overall response rate, 83.3% (5/6) in paediatric and 100% (3/3) in adult patients), but the study was prematurely stopped due to lack of accrual in the pre-treated arm and the limited number of patients enrolled in this group makes any conclusion on the efficacy of rasburicase in this subgroup of the population hazardous.

The safety of rasburicase as reported in ACT5080 and EFC5339 studies was similar to the profile observed in studies conducted previously. Almost all patients reported an AE, but the majority of AEs were hematologic in nature (thrombocytopenia, anemia, neutropenia) and could be attributed to the patients' underlying cancer state and/or to the concomitant administration of cytotoxic drugs. No deaths associated to study drug have been reported in both studies. Hypersensitivity reactions have been documented also, but they were of grade 1 or 2. One case of haemolysis has been reported in both studies, but no association with G6PD or metahemoglobinemia has been observed. No conclusive data have been submitted over the potential of immunogenicity with rasburicase, which remains a concern limiting recommendations on the use of rasburicase over multiple treatment courses.

# V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

The efficacy and safety results of ACT5080 and EFC5339 studies are consistent with previous studies conducted with rasburicase in naïve paediatric and adult patients. Also no major differences in efficacy or safety of rasburicase were observed in patients pre-treated with an uricolytic agent (Rasburicase or Uricozyme) in study EFC5339; however, due to the very limited number of patients enrolled in this group (6 paediatric and 3 adult subjects) any conclusion on this subgroup of the population is considered premature and, in line with the currently approved SPC (section 4.2), no recommendation on multiple treatment courses with rasburicase can be made.

- **Overall Conclusion**

The Rapporteur is of the opinion that the analyses of the results of studies ACT5080 and EFC5339 do not appear to affect the benefit/risk for Fasturtec under the currently authorized indication in the European Union. No further regulatory action is required.

- **Recommendation**

No further regulatory action is required.

# VI. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable.