20 September 2012
EMA/CHMP/647431/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fasturtec

rasburicase

Procedure No.: EMEA/H/C/000331/II/0034

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi-aventis groupe submitted to the European Medicines Agency on 3 May 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Fasturtec	rasburicase	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.3.z	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation	II

The MAH proposed the update of section 4.1 and 5.1 of the SmPC in order to clarify the age range of paediatric patients following CHMP request made further to the assessment of a study submitted in accordance with Article 46 of Regulation (EC) No1901/2006 (P46-042). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	3 May 2012
Start of procedure:	20 May 2012
Rapporteur's assessment report circulated on:	12 June 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 July 2012
MAH's responses submitted to the CHMP on:	15 August 2012
Rapporteur's assessment report on the MAH's responses circulated on:	13 September 2012
CHMP opinion:	20 September 2012

2. Scientific discussion

2.1. Introduction

Rasburicase is a recombinant urate-oxidase enzyme able to convert uric acid into allantoin, a water soluble product, easily excreted in the urine. In this way rasburicase is expected to reduce hyperuricemia and prevent development of a tumour lysis syndrome during cytoreductive chemotherapy, a life-threatening complication in this patient population. Indeed, the acute increase of uric acid plasma levels following quick and massive lysis of malignant cells may lead to renal impairment due to precipitation of crystal of uric acids in renal tubules.

Fasturtec (rasburicase), 1.5 mg/ml powder and solvent for concentrate for solution for infusion, is administered at a dose of 0.20 mg/kg/day as a 30 minute intravenous infusion in 50 ml of a sodium chloride 9 mg/ml (0.9%) solution. The duration of treatment may be up to 7 days, based upon adequate monitoring of uric acid levels in plasma and clinical judgment.

Fasturtec was granted a marketing authorisation in the EU on 23 February 2001 for the treatment and prophylaxis of acute hyperuricaemia, in order to prevent acute renal failure, in patients with haematological malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy. Safety and efficacy of rasburicase have been assessed in studies in adults and paediatric patients (<18 years).

On 6 December 2011, the MAH submitted the results of a paediatric phase IV study (L9436) for rasburicase (Fasturtec), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use (P46-042).

On 16 February 2012, the CHMP adopted the conclusions on this study, requiring supplementary information as well as an update of the product information.

In this variation application, the MAH has submitted the requested supplementary information and proposed to update section 4.1 and 5.1 of the SmPC to clarify the age range of paediatric patients.

2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

Study L9436, a Phase IV, multicentre, non-comparative, open-label study of rasburicase in paediatric (<18 years) patients with acute hyperuricemia before or during chemotherapy for hematologic malignancies, or who have risk factors for development of tumour lysis.

This multicenter study was conducted at 3 centers in Brazil. The study started on 16 February 2006 and ended on 30 October 2006.

- **Objectives**

The primary objective was to determine efficacy of rasburicase in treating hyperuricemia and protecting renal function (through evaluation of serum creatinine levels) in patients at risk of tumour lysis syndrome during chemotherapy for hematologic malignancies.

Secondary objectives consisted of evaluation of safety of rasburicase as well as evaluation of other laboratory parameters (i.e., calcium, phosphorus, potassium, haemoglobin, platelet and leucocyte counts), some of which are altered in case of tumour lysis syndrome.

- **Study population /Sample size**

Since only a descriptive analysis was planned, no specific methodology for defining the sample size was applied. A total of 40 patients were initially planned.

Patients allowed to be enrolled in the study were subjects < 18 years old with acute hyperuricemia (uric acid > 8.0 mg/dL) before or during chemotherapy for hematologic malignancies, or who had risk factors for development of tumour lysis (lactate dehydrogenase (LDH) > 2 x upper limit of normality and/or serum creatinine > upper limit of normality and/or leukocyte count above 50,000/mm^3 in patients with leukaemia). Patients with hypersensibility to uricase or excipients or with known history of G6PD deficiency were excluded.

- **Treatments**

All patients received the best anticancer treatment according to each investigator. During 1-7 days of treatment, patients received rasburicase 0.20 mg/kg/day, once daily, as a 30 minutes intravenous infusion. Rasburicase doses every 12 hours were allowed during the first 72 hours of chemotherapy in case of persistent hyperuricemia or if the patient was considered at significant risk of tumour lysis complications. The extension of treatment (up to 7 days) was assessed according to the uric acid levels. Patients were then followed for 4 weeks after last medication dose. Two post-treatment evaluations were planned: at 24-48 hours and 28 ± 3 days after last rasburicase dose.

Patients should have discontinued previous hypouricemic treatment before starting rasburicase. All patients should receive proper hydration according to the clinical practice; alkaline hydration (with NaHCO3) was deemed at discretion of the investigator. Patients who had leucophoresis or transfusion with exchange of hyperleucocytosis within 12 hours after receiving rasburicase dose were allowed to receive an additional dose of study drug.

- **Outcomes/endpoints**

Primary endpoint was of evaluation of uric acid levels and renal protection (through serum creatinin levels) after treatment with rasburicase in patients with hyperuricemia and/or at risk of tumour lysis syndrome. Uric acid levels and renal function were evaluated at 24-48 hours and 28 ± 3 days after last medication dose.

Secondary endpoints were evaluation of safety and of several laboratory parameters (i.e., calcium, phosphorus, potassium, haemoglobin, platelet and white cell counts), some of which are mainly altered during a tumour lysis syndrome (i.e., hyperphosphataemia, hyperkalaemia, hypocalcaemia).

- **Statistical Methods**

The continuous variables were described by medians, means, standard deviation and ranges (maximum and minimum values), while the discrete variables were summarized in frequency tables. All tests were bilateral at 5% significance level. Descriptive levels were considered as statistically significant if $p<0.05$. The uric acid and creatinine values at baseline and at 24-48 hours post-treatment visit were compared by McNemar test for both ITT (Intent to Treat) and PP (Per Protocol) populations. The analyses were performed according to ITT, PP and Safety population according to the following definitions:

- ITT (Intent To Treat Population): subjects who received at least one dose of rasburicase, performed baseline and 24-48 hours and/or 28±3 days uric acid exam;
- PP (Per Protocol Population): all patients who received at least one dose of rasburicase, performed baseline and 24-48 hours uric acid exams and did not fit in any relevant protocol violation criteria;
- Safety Population: all patients who received at least one dose of study drug.

In the analysis provided, patients with normal / under / undetectable / undefined uric acid levels comparing to NRV (normal reference values) were assorted to be analyzed by McNemar test. In cases where uric acid results were expressed as "not detectable" or "less than a specific value" (i.e., less than the upper NRV), they were considered in the analysis as with normal or under the NRV.

2.2.2. Results

- **Recruitment/ Number analysed**

Between 16 February 2006 and 30 October 2006 a total of 33 patients were included in the study, of which 21 were included in the ITT population, 20 in the PP Population, and 32 in the Safety population.

Patients were enrolled from 3 different centers, of which 11 patients (33.3%) in center No 1, 21 patients (63.6%) in center No 2 and 1 patient (3.0%) in center No 4.

Seven patients (21.2%) have withdrawn the study observation before the trial completion, the most frequent reason for withdrawn being death.

- **Baseline data**

Of the 33 patients enrolled, 18 (45.5%) patients were female, 19 (57.6%) patients were black-Caucasian biracial, with a median age of 7.0 years (range 6 months – 16 years). Weight range was 8 – 97.5 kg, or 8 – 61.5 kg excluding patient n. 16. Twenty-one (63.6%) patients presented leukaemia (51.5% acute lymphocytic leukaemia and 12.1% acute myeloid leukaemia) as tumour diagnosis, 10 (30.3%) patients lymphoma (12.1% Burkitt lymphoma, 15.2% Non-Hodgkin lymphoma and 3.0% Hodgkin lymphoma) and 2 (6.1%) patients neuroblastoma. Of the patients enrolled, chemotherapy was given as initial therapy in 27 patients (81.8%) and as induction therapy in 32 patients (97.0%).

- **Efficacy results**

At baseline visit mean value of uric acid was 8.2 mg/dL (range: 1.2 – 27.4), of creatinine was 0.9 mg/dL (range: 0.3 – 5.3) and of LDH was 3240.9 U/L (range: 634 - 19378).

The first post-treatment visit should have been done in 24-48 hours after the last rasburicase dose, however two patients did not accomplished the routine and performed the above mentioned visit 3 and 4 days after the end of treatment. The mean time spent was 1.6 days (range: 1-4 days).

The second visit should be done after 28±3 days and it was done in 28.7 days average (range 24 – 36 days). In 3 patients, Day 28 visit has occurred in an interval not foreseen in the protocol (i.e., 32 days, 24 days, and 36 days, respectively).

Patients were treated for a mean of 5.3 days (SD: 1.7 days, range: 1 – 7 days), receiving a mean of 20.4 bottles of rasburicase (range: 6 – 78 bottles).

Four (12.1%) patients of the 33 included in the screening period have not completed the minimum time treatment (3 days) required: one patient due to death before receiving rasburicase dose, one patient due to transfer to other institution, and two patients due to development of adverse events (allergic reaction and cerebral bleeding, respectively). One patient did not receive rasburicase at day 5 although he continued treatment until day 7.

Uric acid evaluation

Of the 21 patients included in the ITT population, 13 (61.9%) patients had hyperuricemia at baseline and no (0%) patient at 24-48 hours visit. Similarly, in the PP analysis, 13 (65%) patients presented hyperuricemia at baseline and, at 24-48 hours visit, none of them presented hyperuricemia any longer. A significant reduction of uric acid levels was observed at the MacNemar test when comparing uric acid

level at 24-48 hours post-treatment and baseline visits in ITT and PP population (χ^2_1 = 11.08 – p<0.001).

At day 28 ±3 post- treatment visit none of the 9 patients for which uric acid levels were available showed hyperuricemia. However, at that time point determination of uric acid levels was not available for the majority of patients (52.6%).

Table 1 – Percentage of patients with uric acid (mg/dL) levels compared to baseline values – ITT population

ITT	Under NRV		Normal		Upper NRV		Undefined / Undetectable		Not done / Damaged / Cancelled		Total
	N	%	N	%	N	%	N	%	N	%	
Baseline	2	9,5%	6	28,6%	13	61,9%	0	0,0%	0	0,0%	21
Day 1	5	23,8%	4	19,0%	11	52,4%	1	4,8%	0	0,0%	21
Day 2	13	61,9%	1	4,8%	1	4,8%	2	9,5%	4	19,1%	21
Day 3	16	80,0%	0	0,0%	1	5,0%	1	5,0%	2	10,0%	20
Day 4	16	84,2%	2	10,5%	0	0,0%	0	0,0%	1	5,3%	19
Day 5	12	75,0%	1	6,3%	0	0,0%	0	0,0%	3	18,8%	16
Day 6	4	40,0%	0	0,0%	1	10,0%	0	0,0%	5	50,0%	10
Day 7	4	57,1%	1	14,3%	0	0,0%	0	0,0%	2	28,6%	7
24-48 hours	19	90,5%	1	4,8%	0	0,0%	1	4,8%	0	0,0%	21
Day 28	2	10,5%	7	36,8%	0	0,0%	0	0,0%	10	52,6%	19

Creatinine evaluation

Creatinine levels were analyzed in order to evaluate renal protection after treatment with rasburicase.

At baseline, in the ITT population normal creatinine levels were observed in 15 (71.4%) patients, whereas levels above the normal reference values were observed in 5 patients (23.8%). One patient had creatinine below the normal range.

At 24-48 post-treatment visit, creatinine levels normal/under the normal reference values were observed in 14 patients (66.7%, 5/9), 4 patients (19%) presented values above the normal range and values of 3 patients were missing.

At day 28 ± 3 post-treatment visit, creatinine values from only 14 patients were available (73.8%), of which only 1 (5.3%) was above the normal range.

The stratification at normal (NRV values) / abnormal (under/upper NRV values) creatinine levels in comparison to laboratories references values showed no significant difference when analyzed at 24-48h and baseline visits by MacNemar test (χ^2_1= 0.57 – p=0.4497-ns).

Analysis of mean and median creatinine values observed show relatively stable parameters during the study, with the exception of day 6, where mean value was 6.11 mg/dL (range of values 0.75-43), essentially due to one patient suddenly experiencing serum creatinine of 43 mg/dL.

Table 2 – Percentage of patients with creatinine (mg/dL) levels under / upper of Normal Reference Values (NRV) - ITT population

ITT	Under NRV		Normal		Upper NRV		Not done		Total
	N	%	N	%	N	%	N	%	
Baseline	1	4.8%	15	71.4%	5	23.8%	0	0.0%	21
Day 1	2	9.5%	12	57.1%	7	33.3%	0	0.0%	21
Day 2	2	9.5%	11	52.4%	8	38.1%	0	0.0%	21
Day 3	1	5.0%	10	50.0%	8	40.0%	1	5.0%	20
Day 4	2	10.5%	11	57.9%	6	31.6%	0	0.0%	19
Day 5	2	12.5%	8	50.0%	4	25.0%	2	12.5%	16
Day 6	0	0.0%	5	50.0%	3	30.0%	2	20.0%	10
Day 7	0	0.0%	5	71.4%	1	14.3%	1	14.3%	7
24-48 hours	5	23.8%	9	42.9%	4	19.0%	3	14.3%	21
Day 28	4	21.1%	9	47.4%	1	5.3%	5	26.3%	19

2.2.3. Discussion

Rasburicase (Fasturtec) is a recombinant urate-oxidase enzyme approved in the EU for the treatment and prophylaxis of acute hyperuricemia, in order to prevent acute renal failure and tumour lysis syndrome, in patients with haematological malignancies with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy. Urate-oxidase is an enzyme able to convert uric acid into allantoin, a water soluble product, easily excreted in the urine. Safety and efficacy of rasburicase have been assessed in studies in adults and paediatric patients (<18 years). The recommended dose is 0.20 mg/kg/day as a once daily 30 minutes intravenous infusion for up to 7 days, dependently on uric acid levels and clinical judgment.

In a previously performed randomized, comparative, phase III study a significantly more rapid onset of action of rasburicase compared with allopurinol was reported in terms of reduction of serum uric acid levels. At 4 hours after the first dose, there was a significant difference in the percentage of change from baseline plasma acid uric concentration in the rasburicase group (86%) compared with the allopurinol group (12.1%). Moreover, the rasburicase versus allopurinol group experienced a 2.6-fold less exposure to uric acid (Goldman *et a*l, Blood. 2001; 97:2998-3003).

L9436 was a phase IV study was performed between February and October 2006 in order to assess efficacy (in terms of reduction of uric acid levels and renal protection) and safety of rasburicase in 40 paediatric Brazilian patients treated with chemotherapy due to haematological malignancies and presenting hyperuricemia or risk of tumour lysis syndrome. Only a descriptive analysis of the results was planned. A total of 33 patients were included, of which 32 were treated with rasburicase. Age ranged from 6 months to 16 years old (mean 8.4 years). The majority of patients were females (54.5%), of black-Caucasian race (57.6%), and with diagnosis of leukaemia (63.6%) or lymphoma (30.3%).

The primary outcome was the evaluation of reduction of uric acid levels and monitoring of renal function through evaluation of creatinine levels 24-48 hours and 28 ± 3 days after last dose of rasburicase.

The results showed a significant reduction of the uric acid levels 24-48 hours after the end of treatment: indeed, all the 13 patients presenting hyperuricemia at baseline, experienced normalization of values 24-48 hours after treatment with rasburicase (p=0.001 at MacNemar test). No patients presented hyperuricemia after 28 days, however interpretation of data at 28 days time point is hampered by the high number of missing data (>50%). In this variation application, the MAH

explained the handling of the uric acid blood samples and thus confirmed the samples were evaluated as necessary in order to minimise ex vivo degradation of the analyte by blocking the enzymatic activity of Rasburicase at the time of taking blood samples (e.g. by immediate separation of serum and freezing the sample), which would otherwise give misleading results.

No significant difference was observed when baseline creatinine values were compared with 24-48 hours post-treatment visit (p=0.4497 at MacNemar test). Analysis of mean and median creatinine values observed showed relatively stable parameters during the study, with the exception of day 6, where mean value was 6.11 mg/dL (range of values 0.75-43), essentially due to one patient enrolled in center 2 experiencing serum creatinine 43 mg/dL. In this variation application, the MAH clarified that for this patient the correct value for serum creatinine on Day 6 is 0,5 mg/dl. The value of 43 was inadvertently reported and actually refers to an urea exam. Therefore, the patient presented on Day 6 a serum creatinine value within normal range.

Moreover, it was noted that 23% of subjects displayed a serum creatinine above the quoted reference interval at baseline and this figure increased to 40% at day 3 of treatment. Thereafter, although the percentage of subjects with serum creatinine above the reference interval declined, the results of days 4 onwards were based on much reduced subject numbers and so may have been misleading.

In response to the CHMP's concern, the MAH highlighted that the natural history of Tumour lysis syndrome, and of the renal damage that occurs, is that there is a lag time between reduction of uric acid levels and decline of serum creatinine. Thus the elevated baseline values and the day 3 values are not indicative of lack of a renal protective effect of the product. As one would expect, the values did indeed decline over time. There are sufficient numbers of evaluable patients with follow up to confirm this finding.

The MAH initially tested for normality but decided to perform a Wilcoxon rank sum test as the hypothesis of normality was rejected.

This Wilcoxon rank sum test was statistically significant for the comparison of creatinine levels of:

1.) baseline vs. day 28 ($p < 0.0001$) and

2.) day 3 vs. day 28 ($p= 0.0176$) .

The statistical significance of the Wilcoxon test shows that the distributions are not equal. Upon examination, the variation in the creatinine levels is clearly lower at day 28 than at baseline and at day 3 (e.g. 75% of all subjects had values lower than 0.40 for day 28, while more than 75% had their values larger than 0.50 at baseline and at day 3).

Of note is that the Wilcoxon test cannot be interpreted as a test of difference in medians, since the distribution at 28 day is clearly less spread (SD=0.24; max-min= 1) than at baseline or at day 3 (SD > 1; max-min > 4.5), so that the condition 'the one distribution is a shifted version of the other" is not met (Hart. BMJ. 2001; 323: 391–393).

The number of patients with missing data is 7/21=33.3%, which is substantial. However, in most of the patients with missing data at day 28, there are indications of decreasing trends of creatinine present. Therefore, the impact of missing data is considered not to change the trend observed.

Overall, this additional analysis confirmed that the creatinine values did decline over time.

Other laboratory parameters usually altered in tumour lysis syndrome (phosphorus, potassium, calcium) appeared to remain relatively stable during the study, therefore supporting the protecting effect of rasburicase against the development of tumour lysis syndrome.

At the request of the CHMP, the MAH also provided efficacy and safety results reported by age ranges (infants [28 days-24 months], child [2-11 years], adolescents [12-18 years]). Concerning efficacy in each age-group, the use of Fasturtec showed efficacy, although the numbers were too small to allow performing a statistical test on these data and would not have allowed obtaining a powerful and relevant analysis.

Overall, the CHMP considered, the results of the L9436 study appeared to confirm efficacy of rasburicase in treating hyperuricemia and preventing tumour lysis syndrome. The CHMP also considered that the age range of paediatric patients should be clarified in sections 4.1 and 5.1 of the SmPC.

2.3. Clinical Safety aspects

2.3.1. Results

- **Adverse events (AEs)**

Of the 32 patients included in the safety population, 30 (93.7%) patients reported 135 AEs, of which only one (i.e., allergic reaction), observed in 2 patients (6.3%), was considered related to rasburicase.

The most frequently observed AEs were vomiting (16 events in 11 [34.4%] patients), followed by febrile neutropenia (6 events in 6 patients [18.8%]), fever (8 events in 5 [15.6%] patients) and nausea (5 events in 4 [12.5%] patients). Most non-serious AEs were of grade 1 severity (62.7%); grade 2 and 3 AEs were reported in 25.5% and 10.9% cases, respectively, whereas only one (0.9%) event was graded 4 (hepatic enzyme increase).

Twenty-five (25) Serious AEs (SAEs) were reported in 19 patients (59.4%), but none of them was considered related to the study drug. Regarding the severity of the SAEs, grade 4 SAEs were observed in 6 (24%) patients, grade 3 SAEs in 5 (20%) patients, grade 2 SAEs in 2 (8%) patients and grade 1 SAEs in 3 (12%) patients. In 9 SAEs (36%) intensity was not reported.

Two (6.3%) patients were withdrawn from treatment due to AEs (i.e., 1 related to allergic reaction, another 1 related to central nervous system bleeding).

Five (15.6%) patients died due to AEs (i.e., 2 patients due to sepsis, 1 due to renal failure and bleeding, 1 due to oliguria, hypovolaemia, acute lung oedema and cardiac congestive failure, and 1 patient due to central nervous system bleeding); none of the death events was assessed as related to rasburicase.

- **Laboratory findings**

A descriptive analysis was provided where laboratory results regarding uric acid, creatinine, potassium, calcium, phosphorus, haemoglobin, platelet, leucocyte and neutrophil counts were compared to normal reference values and baseline. Results regarding uric acid and creatinine levels were in line with what reported in the efficacy results section.

Overall, analysis of the levels of potassium, phosphorus and calcium through the study did not suggest any significant incidence of hyperkalaemia, hyperphosphataemia and hypocalcaemia, therefore indirectly supporting the claimed protective effect of rasburicase against development of tumour lysis syndrome. However, the absence of a control arm and the high number of missed determinations at 24-48 hours and at day 28±3 time points (31-57%) does not allow to drawn any firm conclusion over this issue.

Reduction in haemoglobin, platelet and white blood cell counts was frequently reported during the study, 24-48 hour and 28 days after treatment; however, as rasburicase is administered as supportive care to cytoreductive chemotherapy, the causality of these events is difficult to assess.

2.3.2. Discussion

The evaluation of the safety of the drug was hampered also by the concomitant administration of cytotoxic chemotherapy and by the lack of a control group in the study. However, the AEs reported were in line with the known safety profile of the drug. Allergic reactions clearly related to study drug were observed in 2 patients (6.3%). Other frequently reported AEs consist of vomiting (34.4%), fever (15.6%), nausea (12.5%), diarrhoea (12.5%), and headache (9.4%), which represent the most frequently reported with rasburicase in other studies too (refer also to SmPC). No new safety signals were observed. The MAH confirmed in this application that there were no cases of methaemoglobinaemia nor haemolysis reported in this study. Therefore these adverse events of special interest have not been mentioned in the L9436 CSR.

At the request of the CHMP, the MAH also provided efficacy and safety results reported by age ranges (infants [28 days-24 months], child [2-11 years], adolescents [12-18 years]). Concerning the safety, the numbers are very small but the frequency and type of AEs registered are acceptable and conform to the safety profile in adults. No additional or new AEs were reported. The safety of Fasturtec in this population and administered in such a specific serious disease, is acceptable.

2.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed (deletions in strikethrough and insertions in bold underlined):

- **Section 4.1 *Therapeutic indications* of the SmPC**

Treatment and prophylaxis of acute hyperuricaemia, in order to prevent acute renal failure, in ~~patients~~ **adults, children and adolescents (aged 0 to 17 years)** with haematological malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy.

- **Section 5.1 *Pharmacodynamic properties* of the SmPC**

Clinical efficacy and safety
In a~~A~~ randomised comparative phase III study, performed in ***52*** paediatric patients, **27 patients were treated with rasburicase at** ~~using~~ the recommended dose **of 0.20 mg/kg/day, intravenously, for 4 to 7 days (< 5 years: n=11; 6-12 years: n=11; 13-17 years: n=5), and 25 patients with allopurinol daily oral doses for 4 to 8 days**. **Results** showed a significantly more rapid onset of action of Fasturtec in comparison with allopurinol. At 4 hours post first dose, there was a significant difference in the mean percentage change from baseline plasma uric acid concentration ($p < 0.0001$) in the Fasturtec group (-86.0%) compared to that for the allopurinol group (-12.1%).

[…]

In pivotal clinical studies, 246 **paediatric** patients (~~<18~~ **mean age 7** years**, range 0 to17**) were treated with rasburicase at doses of 0.15 mg/kg/day or 0.20 mg/kg/day for 1 to 8 days (mainly 5 to 7 days). Efficacy results on 229 evaluable patients showed an overall response rate (normalization of plasma uric acid levels) of 96.1%. Safety results on 246 patients were consistent with the adverse events profile in the overall population.
In long term safety studies, an analysis of data from 867 **paediatric** patients (~~<18~~ **mean age 7.3** years**, range 0 to17**) treated with rasburicase at 0.20 mg/kg/day for 1 to 24 days (mainly 1 to 4 days) showed consistent findings with pivotal clinical studies in terms of efficacy and safety.

During the procedure, the CHMP requested further amendments to the PI in order to also update the package leaflet accordingly:

Section 1 *What Fasturtec is and what it is used for* of the Package Leaflet

Fasturtec contains the active ingredient rasburicase.
Rasburicase is used to treat or prevent high blood levels of uric acid from occurring in **adults, children and adolescents (aged 0 to 17 years)** ~~patients~~ with disorders of the blood cells (haematological diseases) who are about to receive or are receiving chemotherapy treatment.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Ireland and Portugal.

3. Overall conclusion and impact on the benefit/risk balance

Overall, the CHMP considered the results of the L9436 study appeared to confirm efficacy of rasburicase in treating hyperuricemia and preventing tumour lysis syndrome. The safety was in line with the known safety profile of the drug. The CHMP considered that the age range of paediatric patients should be clarified in sections 4.1 and 5.1 of the SmPC. The benefit-risk balance of Fasturtec remains unchanged.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation accepted		**Type**
C.I.3.z	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation	II

Update of section 4.1 and 5.1 of the SmPC in order to clarify the age range of paediatric patients following CHMP request made further to the assessment of a study submitted in accordance with Article 46 of Regulation (EC) No1901/2006 (P46-042). The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of section 4.1 and 5.1 of the SmPC in order to clarify the age range of paediatric patients following CHMP request made further to the assessment of a study submitted in accordance with Article 46 of Regulation (EC) No1901/2006 (P46-042). The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Summary

Please refer to EPAR – Assessment Report Fasturtec-H-C-331-II-0034.