

PRODUCT MONOGRAPH

Pr **FASTURTEC**[®]
(rasburicase)
Powder for Injection
Professed Standard

1.5 mg/vial
(1.5 mg/mL/vial)

Uricosuric Agent

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(rasburicase)

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PHARMACOLOGIC CLASSIFICATION

Uricosolytic Agent

CAUTION: FASTURTEC® (RASBURICASE) SHOULD BE ADMINISTERED ONLY UNDER THE SUPERVISION OF A PHYSICIAN WHO IS EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS.

ACTIONS AND CLINICAL PHARMACOLOGY

FASTURTEC® (rasburicase) is a recombinant urate-oxidase enzyme produced by a genetically modified *Saccharomyces cerevisiae* strain. The cDNA coding for rasburicase was cloned from a strain of *Aspergillus flavus*.

FASTURTEC® is a highly potent uricosolytic agent that catalyzes enzymatic oxidation of uric acid into an inactive and soluble metabolite (allantoin) which is easily excreted by the kidneys in the urine. In humans, uric acid is the final step in the catabolic pathway of purines. Rasburicase is only active at the end of the purine catabolic pathway.

Pharmacokinetics

Pharmacokinetics of rasburicase were evaluated in two studies that enrolled patients with lymphoid leukemia (B and T cell), non-Hodgkin's lymphoma (including Burkitt's lymphoma) or acute myelogenous leukemia. Rasburicase exposure, as measured by AUC_{0-24} and C_{max} , tended to increase linearly with doses over a limited dose range (0.15 to 0.20 mg/kg). The overall elimination half-life was 18 hours. No accumulation of rasburicase was observed between days 1 and 5 of dosing. Rasburicase mean volume of distribution was 110 to 127 mL/kg.

INDICATIONS AND CLINICAL USE

FASTURTEC[®] (rasburicase) is indicated for the treatment and prophylaxis of hyperuricemia in pediatric and adult cancer patients.

CONTRAINDICATIONS

FASTURTEC[®] (rasburicase) should not be administered to patients with a known history of anaphylactic reactions or known history of hypersensitivity reactions to FASTURTEC[®] or any of the excipients. Studies have not been conducted in patients with severe allergies or asthma.

FASTURTEC[®] should not be administered to patients with a known history of glucose-6-phosphate dehydrogenase deficiency (G6PD) or other cellular metabolic disorders known to cause hemolytic anemia [See Actions and Clinical Pharmacology: Pharmacokinetics, Special Populations Section].

WARNINGS

Clinical experience with FASTURTEC[®] (rasburicase) demonstrates that FASTURTEC[®], like other proteins, has the potential to induce allergic responses in humans. Clinical experience with FASTURTEC[®] demonstrates that patients should be closely monitored for the onset of allergic-type adverse events, especially urticaria or bronchospasm. If any serious allergic or anaphylactic reaction occurs, FASTURTEC[®] therapy should be immediately and permanently discontinued, and appropriate therapy initiated.

The safety and efficacy of FASTURTEC[®] has been established for a treatment duration of up to seven days. Because the safety and efficacy of other schedules have not been established, dosing beyond seven days or administration of more than one course of FASTURTEC[®] is not currently recommended pending further clinical studies. Therefore, repeated treatment with interruptions is not recommended.

Hemolysis:

Hemolysis has been reported in patients receiving FASTURTEC[®].

FASTURTEC[®] administration should be immediately and permanently discontinued in any patient developing hemolysis and appropriate measures initiated.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

FASTURTEC[®] administered to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency can cause severe hemolysis. Therefore, FASTURTEC[®] is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD), in order to prevent hemolytic anemia in this patient population.

It is recommended that patients at higher risk for G6PD deficiency (e.g. patients of African or Mediterranean ancestry) be screened prior to starting FASTURTEC® therapy.

Methemoglobinemia:

FASTURTEC® use has been associated with methemoglobinemia on rare occasions. FASTURTEC® administration should be immediately and permanently discontinued in any patient identified as having developed methemoglobinemia and appropriate measures initiated.

Pregnancy:

FASTURTEC® has been shown to be teratogenic in rabbits given doses of 10, 50 and 100 times the human dose and in rats given doses 250 times the human dose.

Animal studies with respect to effects on parturition and postnatal development have not been conducted with FASTURTEC®. It is also not known whether FASTURTEC® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FASTURTEC® should be given to a pregnant woman only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, FASTURTEC® should not be used in breast-feeding women.

Immunogenicity:

Antibodies to FASTURTEC® have been detected in 24 of 28 (86%) healthy adult volunteers within 6 weeks of a single intravenous infusion. In clinical studies, 24 of 218 patients (11%) who received a single 5-7 day course of intravenous FASTURTEC® produced detectable antibody responses within 4 weeks of administration. Clinically significant allergic reactions to FASTURTEC® occurred in clinical studies; the relative

risk of an allergic reaction in patients who develop anti-FASTURTEC[®] antibodies has not been determined (refer to Table 1).

Pending further clinical trials to assess safety and efficacy in retreated patients, patients should not receive more than one course of FASTURTEC[®]. Any patient with a serious hypersensitivity reaction should have FASTURTEC[®] permanently discontinued.

PRECAUTIONS

General

Age and gender do not significantly affect the pharmacokinetics of FASTURTEC[®] (rasburicase) in healthy subjects and patients as indicated by population pharmacokinetic analysis.

Renal function revealed no clinically meaningful changes in population pharmacokinetic analysis. Therefore no dose adjustment is necessary for renally impaired patients.

Leukapheresis/Exchange Transfusions

Patients who require leukapheresis or exchange transfusion due to hyperleukocytosis within 12 hours of receiving a dose of FASTURTEC[®] (rasburicase), may require repeat dosing since these procedures may remove FASTURTEC[®] from the system.

Drug Interactions

No specific *in vivo* clinical drug interaction studies have been performed. FASTURTEC[®] does not metabolize allopurinol, methylprednisolone, etoposide, daunorubicin, cyclophosphamide and vincristine, or the following anti-metabolites, 6-mercaptopurine, methotrexate, cytarabine and thioguanine, *in vitro*. No metabolic-based drug interactions are therefore anticipated with these agents in patients.

FASTURTEC[®] is adjunct therapy administered to cancer chemotherapy patients and has been administered with concomitant medications. Given the efficacy of rasburicase in patients, it is judged that the concomitant administrations of cytotoxic drugs does not significantly modify the uricolytic activity of FASTURTEC[®].

Rasburicase did not affect the activity of the following isoenzymes: CYP1A, CYP2A, CYP2B, CYP2C, CYP2E, and CYP3A in animal studies, suggesting no induction nor inhibition potential. Clinically relevant P450-mediated drug-drug interactions are therefore not anticipated in patients based on the dosing schedule recommended.

Laboratory Test Interactions

Although use of FASTURTEC[®] does not require any special schedule of uric acid monitoring beyond standard practice, a special handling procedure for plasma samples is required to avoid *ex vivo* enzymatic degradation of uric acid by the drug at room temperature.

Procedure for blood collection: Blood must be collected into pre-chilled tubes containing heparin anticoagulant. Samples must be immediately immersed in an ice water bath. Plasma samples must be prepared by centrifugation in a pre-cooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within four hours.

FASTURTEC[®] is not known to alter the accuracy of any other laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

FASTURTEC[®] was non-genotoxic in the Ames, unscheduled DNA synthesis, chromosome analysis, mouse lymphoma, and micronucleus tests.

FASTURTEC[®] did not affect reproductive performance or fertility in male or female rats.

Pediatric Use

FASTURTEC[®] has been shown to be safe and effective in children over the age of one month.

Immunogenicity:

Caution should be used in patients with a history of atopic allergies.

ADVERSE REACTIONS

Adverse events were reported in pediatric and adult patients in various clinical efficacy and safety studies, as well as in one study, which was specifically designed to collect further safety and tolerability data of FASTURTEC[®] (rasburicase).

In a study of 28 healthy volunteers, only two adverse events (headache of moderate intensity) were reported.

In the clinical studies in patients, the adverse events that were judged to be at least in part related to FASTURTEC[®] include: allergic reactions, including anaphylaxis (with signs and symptoms which include chest pain, dyspnea, hypotension and/or urticaria), rash, rhinitis, bronchospasm, diarrhea, fever, headache, nausea, and vomiting. The incidence of these events are presented in the table below.

Table 1: Incidence of Adverse Events

Adverse Event	Comparator Study				Non-Comparator Studies	
	Allopurinol (N=25)		FASTURTEC® (N=27)		FASTURTEC® (N=320)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Any allergic reaction	12.0%	0	3.7%	0	2.5%	0.6%
Any rash	12.0%	0	14.8%	3.7%	23.4%	0.9%
Diarrhoea	16.0%	4.0%	29.6%	0	19.4%	0.9%
Fever	32.0%	4.0%	40.7%	0	37.5%	6.6%
Headache	12.0%	0	25.9%	0	25.3%	0.9%
Nausea	24.0%	8.0%	33.3%	3.7%	30.9%	1.6%
Vomiting	36.0%	4.0%	55.6%	3.7%	46.6%	1.3%

The following additional adverse events occurred in $\geq 5\%$ of patients (not considered related to FASTURTEC® treatment): abdominal pain, anemia, back pain, constipation, coughing, dyspnea, epistaxis, granulocytopenia, hyperglycemia, hypertension, hypocalcemia, hypotension, injection site pain, injection site reaction, mucositis, pain, pharyngitis, sepsis, skeletal pain, thrombocytopenia.

Uncommon cases of hemolysis which could be related to G6PD deficiency and methemoglobinemia have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The maximum dose of FASTURTEC[®] that has been administered as a single dose is 0.20 mg/kg; the maximum daily dose that has been administered is 0.40 mg/kg/day. According to the mechanism of action of FASTURTEC[®], an overdose will lead to low or undetectable plasma uric acid concentrations and increased production of hydrogen peroxide. Patients suspected of receiving an overdose should be monitored for hemolysis and general supportive measures should be initiated as no specific antidote for FASTURTEC[®] has been identified.

DOSAGE AND ADMINISTRATION

FASTURTEC[®] (rasburicase) should be administered as a single daily dose of 0.20 mg/kg daily for up to 7 days. Administration of FASTURTEC[®] does not require a change in chemotherapy timing or schedule and chemotherapy may be initiated as soon as four hours after the first dose. Age and gender do not significantly affect the pharmacokinetics of FASTURTEC[®] in patients as indicated by population pharmacokinetic analysis.

FASTURTEC[®] must first be reconstituted in the solvent provided. The reconstituted solution must then be diluted in sterile normal saline solution for injection and administered intravenously over 30 minutes (see below).

Reconstitution and dilution procedure

Add 1 mL of the provided reconstitution solution (solvent) to each vial containing 1.5 mg of FASTURTEC[®] and mix by swirling very gently. **Do not vortex.** The required quantity of solution (according to the patient's weight and the dose per kilogram) is to be further diluted with 50 mL sterile normal saline solution. This final solution is to be infused over

30 minutes. **No filters should be used for the infusion.** The reconstituted or diluted solution should be used immediately (within 3 hours), as FASTURTEC[®] does not contain any bacteriostatic agents. Although not recommended, they may be stored for up to 24 hours at 2-8°C.

DO NOT ADMINISTER AS A BOLUS INFUSION.

FASTURTEC[®] should be infused through a separate infusion line. If use of a separate line is not possible, the line should be flushed with at least 15 mL of saline solution prior to and after infusion with FASTURTEC[®].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Vial Size	Volume of Solvent to be Added to Vial	Nominal Concentration per mL
1.5 mg	1 mL	1.5 mg

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Rasburicase

Structural Formula: Rasburicase is a tetrameric protein with identical subunits. The monomer, made up of a single 301 amino acid polypeptide chain, has no intra- or inter-disulfide bridges and is N-terminal acetylated:

Ac-SAVKAARYGK	DNVRVYKVHK	DEKTGVQTV	EMTVCVLEGG	EIETSYTKAD
NSVIVATDSI	KNTIYITAKQ	NPVTPPELFG	SILGTHFIEK	YNHIHAAHVN
IVCHRWTRMD	IDGKPHPHSF	IRDSEEKRNK	QVDVVEGKGI	DIKSSLSGLT
VLKSTNSQFW	GFLRDEYTTL	KETWDRILST	DVDATWQWKN	FSGLQEVRSH
VPKFDATWAT	AREVTLKTFA	EDNSASVQAT	MYKMAEQILA	RQQLIETVEY
SLPNKHIFEI	DLSWHKGLQN	TGKNAEVFAP	QSDPNGLIKC	TVGRSSLKSKL

Molecular Formula: C₁₅₂₃ H₂₃₈₃ N₄₁₇ O₄₆₂ S₇

Molecular Weight: Monomer: Approximately 34 kDa.

Dosage Form:

Description: The drug product is a sterile, white to off-white, lyophilized powder intended for intravenous infusion following reconstitution.

Composition: Drug Product:

1.5 mg/vial

The 1.5 mg glass vial contains 1.5 mg rasburicase, 10.6 mg mannitol, 15.9 mg L-alanine, and between 12.6 and 14.3 mg of dibasic sodium phosphate.

The accompanying sterile solution for reconstitution is composed of 1.0 mL sterile water for injection, USP, and 1.0 mg poloxamer 188 (anti-aggregation agent).

Stability and Storage Recommendations

The lyophilized drug product and the solution for reconstitution should be stored at 2-8°C for a maximum of 36 months.

Do not freeze.

Protect from light.

The reconstituted or diluted solution should be used immediately (within 3 hours), as FASTURTEC® does not contain any bacteriostatic agents. Although not recommended, they may be stored for up to 24 hours at 2-8°C.

DO NOT ADMINISTER AS A BOLUS INFUSION.

AVAILABILITY OF DOSAGE FORMS

FASTURTEC® is supplied as a pack of:

1.5 mg/vial

3 vials of 1.5 mg rasburicase as a sterile lyophilized powder and 3 ampoules of 1 mL sterile solvent. The powder is supplied in a 3 mL colourless glass vial with a rubber stopper and the solvent in a 2 mL clear glass ampoule.

PHARMACOLOGY

Studies were carried out in both animals and humans and have been summarized below:

Animal Pharmacology:

Rasburicase is a biosynthetic urate oxidase obtained from a recombinant *S. cerevisiae* expressing a gene encoding *Aspergillus flavus* (*A. flavus*) urate oxidase. The recombinant urate oxidase is similar to the native *A. flavus* urate oxidase.

Toxicokinetics:

Exposure to rasburicase in rats and baboons following both single and multiple dosing, increased linearly with dose. After single and multiple doses, exposure levels (based on AUC) in the rat (3 mg/kg/day) and baboon (1.5 mg/kg/day) were 1.6 to 3.2 times greater than the exposure (AUC) observed in humans given the clinical dose of 0.2 mg/kg. The mean volume of distribution in baboons (0.05-0.06 L/kg) was similar to the plasma volume. The mean volumes of distribution in rats (0.06-0.07 L/kg) and healthy human subjects (0.06-0.1 L/kg) were twice the respective plasma volumes for these species. The mean terminal half-lives determined for rats and baboons (2-4 hours) were notably shorter than the mean terminal half-life observed for humans (~18 hours). The plasma clearance was low in all species including human with values much lower than hepatic blood flows (0.01-0.03 L/h/kg in animals and 0.002-0.004 L/h/kg in humans).

For the single-dose regimen, concentrations at 1 hour and the mean AUC, were similar to that achieved on Day 15 or 29 of the multiple-dose regimen. This is consistent with the short elimination half-life and the lack of plasma accumulation following multiple dosing.

Anti-SR29142 Antibodies:

Variable levels of circulating anti-rasburicase antibodies were detected in most of the plasma samples of rats (Day 29) and baboons (Days 21 and 29). No circulating anti-rasburicase antibodies were found in baboons after 7 days of treatment (0.15-1.5 mg/kg/day) and only very low levels of circulating antibodies were found in rats after 15 days of treatment (1-10 mg/kg/day).

Cytochrome P450 Activities:

Rasburicase neither modified liver weight nor had any effect on the activities of CYP1A, CYP2A, CYP2B, CYP2C, CYP2E, and CYP3A isozymes in rats and baboons, suggesting no induction nor inhibition potential.

Safety Pharmacology:

Studies in animals were performed by the intravenous route at a dosage of 1.5 mg/kg rasburicase. These studies showed that rasburicase did not modify neurobehavioral parameters (assessed by Irwin test or body temperature) in mice, hemodynamic parameters in anesthetized dogs, or hydroelectric balance in rats.

Clinical Pharmacology:

FASTURTEC[®] (rasburicase) is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD). Hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin, and therefore, FASTURTEC[®] is contraindicated in patients with G6PD deficiency, in order to prevent hemolytic anemia in this patient population.

Age and gender do not significantly affect the pharmacokinetics of FASTURTEC[®] in healthy subjects and patients as indicated by population pharmacokinetic analysis.

No dose adjustment is necessary for renally impaired patients.

FASTURTEC[®] is active at the end of the purine catabolic pathway and, therefore, should not modify the earlier steps of purine metabolism. Consequently, FASTURTEC[®] is not expected to induce accumulation of metabolites, such as xanthine or hypoxanthine. FASTURTEC[®] does not block any anabolic pathway involved in the synthesis of nucleic acids.

Pharmacokinetics:

FASTURTEC[®] exposure, as measured by AUC₀₋₂₄ and C_{max}, increased linearly with dose over a limited dose range in patients (0.15 to 0.20 mg/kg). Linearity over the larger dose range (0.05 to 0.20 mg/kg) was also seen in healthy volunteers.

Steady state plasma concentrations of FASTURTEC[®] were achieved on Day 2 in patients. The plasma concentrations declined slowly; the mean elimination half-life was approximately 17 to 21 hours. Because FASTURTEC[®] is a protein, peptide hydrolysis is the expected metabolic degradation pathway. Clearance of FASTURTEC[®] is low (4.6 - 5.0 mL/h/kg in patients). FASTURTEC[®] mean volume of distribution was 110 to 127 mL/kg in patients.

Pharmacokinetic parameters on Day 5 of the multiple dose portion of two studies in patients are displayed in the table below.

Table 2: Pharmacokinetic Parameters

Parameter	Pediatric and Adult Patients (Dose=0.20 mg/kg on Day 5)		
	N	Mean	SD
C_{max} ($\mu\text{g/mL}$)	15	4.5	1.15
AUC_{0-24} ($\mu\text{g}\cdot\text{h/mL}$)	10	47.3	21.7
CL (mL/h/kg)	10	4.87	1.64
V_z (mL/kg)	8	127	55.4
$t_{1/2}$ (hours)	14	21.1	12

Pharmacokinetics in Special Populations:

FASTURTEC[®], like other proteins, has the potential to be antigenic. It should not be administered in patients with a known history of hypersensitivity reactions. Studies have not been conducted in patients with severe allergies or asthma and therefore, FASTURTEC[®] is contraindicated in patients exhibiting allergic or anaphylactic reactions to FASTURTEC[®] or any of the excipients.

Clinical Trials:

FASTURTEC[®] was administered in three studies to 265 patients with acute leukemia or non-Hodgkin's lymphoma. The clinical studies were largely limited to pediatric patients (246 of 265). FASTURTEC[®] was administered as a 30-minute infusion once (n=251) or twice (n=14) daily at a dose of 0.15 or 0.20 mg/kg/dose (total daily dose 0.20-0.40 mg/kg/day). FASTURTEC[®] was administered prior to and concurrent with anti-tumor therapy, which consisted of either systemic chemotherapy (n=196) or steroids (n=69).

Study 1

Study 1 was a multi-institutional, single-arm study conducted in 130 pediatric patients and 1 adult patient with hematologic malignancies. Patients received FASTURTEC[®] at either a dose of 0.15 mg/kg/day (n=12) or 0.20 mg/kg/day (n=119). The primary efficacy

objective was determination of the proportion of patients with maintained plasma uric acid concentration at 48 hours where maintenance of uric acid concentration was defined as: 1) achievement of uric acid concentration ≤ 6.5 mg/dL (patients <13 years) or ≤ 7.5 mg/dL (patients ≥ 13 years) within a designated time point (48 hours) from initiation of FASTURTEC[®] and maintained until 24 hours after the last administration of study drug; and 2) control of uric acid level without the need for allopurinol or other agents.

The study population demographics were: age < 13 years (76%), Caucasian (83%), males (67%), ECOG = 0 (67%), and leukemia (88%).

The proportion of patients with maintenance of uric acid concentration at 48 hours in Study 1 was 92% in the 0.15-mg/kg group (n=12) and 95% in the 0.20 mg/kg group (n=119).

Study 2

Study 2 was a multi-institutional, single-arm study conducted in 89 pediatric and 18 adult patients with hematologic malignancies. Patients received FASTURTEC[®] at a dose of 0.15 mg/kg/day. The primary efficacy objective was determination of the proportion of patients with maintained plasma uric acid concentration at 48 hours as defined for Study 1 above.

The study population demographics were: age <13 years (76%), males (61%), Caucasian (91%), ECOG performance status = 0 (92%), and leukemia (89%).

The proportion of patients with maintenance of uric acid concentration at 48 hours in Study 2 was 99% (106/107).

Study 3

Study 3 was a randomized, open-label, controlled study conducted at six institutions, in which 52 pediatric patients were randomized to receive either FASTURTEC[®] (n=27) or allopurinol (n=25). The dose of allopurinol varied according to local institutional practice. FASTURTEC[®] was administered as an intravenous infusion over 30 minutes once (n=26) or twice (n=1) daily at a dose of 0.20 mg/kg/dose (total daily dose 0.20-0.40 mg/kg/day). Initiation of dosing was permitted at any time between 4 to 48 hours before the start of anti-tumor therapy and could be continued for 5 to 7 days after initiation of anti-tumor therapy. Patients were stratified at randomization on the basis of underlying malignant disease (leukemia or lymphoma) and baseline serum or plasma uric acid levels (< 8.0 mg/dL and 8.0 mg/dL [$< 472 \mu\text{mol/L}$ and $\geq 472 \mu\text{mol/L}$]¹).

¹Results are reported in mg/dL. To convert to SI units of $\mu\text{mol/L}$, multiply mg/dL by conversion factor 59 (i.e. 8 mg/dL x 59 = 472 $\mu\text{mol/L}$).

The primary study objective was to demonstrate a greater reduction in uric acid concentration over 96 hours ($\text{AUC}_{0-96 \text{ hr}}$) in the FASTURTEC[®] group as compared to the allopurinol group. Uric acid $\text{AUC}_{0-96 \text{ hr}}$ was defined as the area under the curve for plasma uric acid levels (mg•hr/dL), measured from the last value prior to the first dose of FASTURTEC[®] until 96 hours after that first dose. Plasma uric acid levels were used for all uric acid $\text{AUC}_{0-96 \text{ hr}}$ calculations.

The demographics of the two study arms (FASTURTEC[®] vs. allopurinol) were as follows: age < 13 years (82% vs. 76%), males (59% vs. 72%), Caucasian (59% vs. 72%), ECOG performance status 0 (89% vs. 84%), and leukemia (74% vs. 76%). The median interval, in hours, between initiation of FASTURTEC[®] and of anti-tumor treatment was 20 hours, with a range of 70 hours before to 10 hours after the initiation of anti-tumor treatment (n=24, data not reported for 3 patients).

The uric acid $\text{AUC}_{0-96 \text{ hr}}$ was significantly lower in the FASTURTEC[®] group ($128 \pm \text{s.e. } 14 \text{ mg}\cdot\text{hr/dL}$) as compared to the allopurinol group ($328 \pm \text{s.e. } 26 \text{ mg}\cdot\text{hr/dL}$). All but one patient in the FASTURTEC[®] arm had reduction and maintenance of uric acid levels to

within or below the normal range during the treatment. The incidence of renal dysfunction was similar in the two study arms; one patient in the allopurinol arm developed acute renal failure.

Pooled Analyses

Dosing

For the pooled data set of the 3 clinical studies (n=265), total daily dosing for FASTURTEC[®] ranged from 0.15 to 0.40 mg/kg/day with the majority receiving 0.20 mg/kg/day. The maximum daily doses received were 0.15 mg/kg/day in 116 patients, 0.20 mg/kg/day in 135 patients, 0.30 mg/kg/day (divided doses) in 3 patients, and 0.40 mg/kg/day (divided doses) in 11 patients. The safety and effectiveness of twice-daily dosing with FASTURTEC[®] have not been established due to insufficient data.

Reduction of Uric Acid Levels

Data from the 3 studies (n=265) were pooled and analyzed according to the plasma uric acid levels over time. The pre-treatment plasma uric acid concentration was ≥ 8 mg/dL in 61 patients and was < 8 mg/dL in 200 patients. The median uric acid concentration at baseline, at 4 hours following the first dose of FASTURTEC[®], and the per patient fall in plasma uric acid concentration from baseline to 4 hours were calculated in those patients with both pre-treatment and 4-hour post-treatment values. Among patients with pre-treatment uric acid ≥ 8.0 mg/dL [baseline median 10.6 mg/dL (range 8.1 - 36.4)], the median per-patient change in plasma uric acid concentration by 4 hours after the first dose was a decrease of 9.1 mg/dL (0.3 - 19.3 mg/dL). Among the patients with a pre-treatment plasma uric acid level < 8 mg/dL [baseline median 4.6 mg/dL (range 0.2 - 7.9 mg/dL)], the median per-patient change in plasma uric acid concentration by 4 hours after the first dose was a decrease of 4.1 mg/dL (0.1 - 7.6 mg/dL).

Of the 261 evaluable patients, plasma uric acid concentration was maintained (see “Clinical Trials”, Study 2 for the definition of uric acid concentration maintenance) by 4 hours for 92% of patients (240/261), by 24 hours for 93% of patients (245/261), by 48

hours for 97% of patients (254/261), by 72 hours for 99% of patients (260/261), and by 96 hours for 100% of patients (261/261). Of the subset of 61 patients whose plasma uric acid level was elevated at baseline (≥ 8 mg/dL), plasma uric acid concentration was maintained by 4 hours for 72% of patients (44/61), by 24 hours for 80% of patients (49/61), by 48 hours for 92% patients (56/61), by 72 hours for 98% patients (60/61), and by 96 hours for 100% (61/61).

Please refer to the table below for a summary of the clinical data:

Table 3: Summary of Clinical Trials:

	Study 1	Study 2	Study 3		Pooled Data - FASTURTEC	
Patients (n, type)	130 pediatric, 1 adult	89 pediatric, 18 adult	52 pediatric		n = 265 pediatric and adult (note: 4 patients did not have baseline plasma uric acid samples)	
			FASTURTEC (n=27)	Allopurinol (n=25)		
Dosage of FASTURTEC mg/kg/day (n)	0.2 mg/kg/day (n=109) 0.15 mg/kg/day (n=11) 0.3-0.4 mg/kg/day divided dose (n=11)*	0.15 mg/kg/day (n=105) 0.3-0.4mg/kg/day divided dose (n=2)*	0.2 mg/kg/day (n=26) 0.3-0.4 mg/kg/day divided dose (n=1)*		0.15 mg/kg/day (n=116) 0.20 mg/kg/day (n=135) 0.30 B 0.40 mg/kg/day divided dose (n=14)*	
Patient Demographics						
Age < 13 years (%)	76%	76%	82%	76%	77%	
Males (%)	67%	61%	82%	72%	64%	
Caucasian (%)	83%	91%	59%	72%	84%	
ECOG Status <1 (%)	67%	92%	89%	84%	79%	
Leukemia (%)	88%	89%	74%	76%	79%	
Outcome Measures						
					Pre-treatment uric acid < 8mg/dL (n=200)	Pre-treatment hyperuricemic patients ≥ 8mg/dL (n=61)
% Reduction in Uric Acid at 4 hours post first dose	85%	88%	86%	12%	98%	72%
Uric Acid Maintenance at 48 hours ** (% patients)	92% @ 0.15 mg/kg/day 95% @ 0.20 mg/kg/day	99%	96%	96%	99%	92%

* Note B safety and efficacy of divided dosing have not been established

** Uric Acid Maintenance at 48 hours defined as 1) uric acid concentrations of ≤ 6.5 mg/dL (patients < 13 years) or ≤ 7.5 mg/dL (patients ≥ 13 years) within 48 hours of drug administration and maintained 24 hours post last drug administration and control of uric acid level without the need for allopurinol or other agents

Immunogenicity:

FASTURTEC[®] is immunogenic in healthy volunteers and can elicit antibodies that inhibit the activity of rasburicase *in vitro*.

In a study of 28 healthy volunteers, the incidence of antibody responses to either a single dose or to 5 daily doses was assessed. Binding antibodies to rasburicase were detected in 17/28 (61%) volunteers and neutralizing antibodies were detected in 18/28 (64%) volunteers. Time to detection of antibodies ranged from 1 to 6 weeks after FASTURTEC[®] exposure. In two subjects with extended follow-up, antibodies persisted for 333 and 494 days.

In clinical trials of patients with hematologic malignancies, 24 of the 218 patients tested (11%) developed antibodies by day 28 following FASTURTEC[®] administration. However, this is not a reliable estimate of the true incidence of antibody responses in patients with hematologic malignancies, because the data from the healthy volunteer study indicate that antibody responses may not be detectable until some time point beyond day 28.

The observed incidence of antibody positivity in an assay may be influenced by several factors, including serum sampling, timing and methodology, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to FASTURTEC[®] with the incidence of antibodies to other products may be misleading.

TOXICOLOGY

Acute Toxicity

Rasburicase was well tolerated upon acute administration to mice and rats at the highest dosage administered (15 mg/kg). This dosage represents 75 times the proposed dosage of 0.2 mg/kg for clinical use based on body weight (6-12 times greater based on surface area). No untoward effects or mortality occurred following acute intravenous administration of rasburicase to mice or rats.

Long-Term Toxicity Studies

Rat: Rasburicase was well tolerated upon intravenous administration to male and female rats for 15 days at dosages up to 10 mg/kg/day. No adverse effects were detected at the highest dosage administered. Only very low levels of circulating anti-rasburicase antibodies were detected. Despite circulating anti-rasburicase antibody formation, exposure was not significantly altered between animals that produced circulating anti-rasburicase antibodies and those that did not, except for one high dosage female. Rasburicase plasma concentrations 1 h post-dosing on Day 15 increased with the dose administered and were consistent with dose proportionality.

Rasburicase was also well tolerated upon intravenous administration to male and female rats at dosages up to 3 mg/kg/day for 29 to 34 days. There were no adverse clinical signs or mortality attributable to drug treatment. No treatment-related changes were detected for body weight, feed intake, electrocardiography, ophthalmoscopy, hematology, clinical chemistry, organ weights, macroscopic pathology and histopathology. Circulating anti-rasburicase antibodies were detected in 75% to 95% of the animals on Day 29. There were no adverse clinical signs indicative of an anaphylactic response.

Baboon: Rasburicase was well tolerated upon intravenous administration to male and female baboons at dosages up to 1.5 mg/kg/day for 31 to 32 days. No treatment-related adverse clinical signs or mortality occurred. No treatment-related changes were detected for body weight, feed intake, electrocardiography, ophthalmoscopy, hematology, clinical chemistry, organ weights, macroscopic pathology and histopathology. No circulating anti-rasburicase antibodies were detected on Day 7, while circulating anti-rasburicase antibodies were detected at all dosages in all animals on Days 21 and 29. There were no adverse clinical signs indicative of an anaphylactic response.

Developmental and reproductive toxicity

Rasburicase did not affect reproductive performance or fertility following administration of dosages up to 10 mg/kg/day in male (62-64 days) or female (23-33 days) rats.

Rasburicase has been shown to be teratogenic in rabbits given doses of 10, 50 and 100 times the human dose and in rats given doses 250 times the human dose.

Local tolerance

Rasburicase was well tolerated by the intravenous, intra-arterial and perivenous routes. In addition, rasburicase was found to be non-irritating to rabbit skin and eyes.

Hemolytic potential

Rasburicase was non-hemolytic in whole human blood.

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