PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**FASTURTEC®**

Rasburicase for Injection

Powder for Injection

Professed

1.5 mg/vial

(1.5 mg/mL/vial)

Uricolytic Agent

ATC Code: V03AF07

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.3 Reconstitution	07/2023
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	07/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FASTURTEC (Rasburicase for injection) is indicated for:

- the treatment and prophylaxis of hyperuricemia in pediatric and adult cancer patients.

1.1 Pediatrics

Pediatrics (1 month – 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Fasturtec in pediatric patients have been established. Therefore, Health Canada has authorized an indication for pediatric use.

2 CONTRAINDICATIONS

Fasturtec (rasburicase for injection) should not be administered to patients with a known history of:

- anaphylactic reactions or hypersensitivity reactions to Fasturtec or any of the excipients. Studies have not been conducted in patients with severe allergies or asthma.

- glucose-6-phosphate dehydrogenase deficiency (G6PD) or other cellular metabolic disorders known to cause hemolytic anemia [See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, 10 CLINICAL PHARMACOLOGY].

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypersensitivity Reactions: Fasturtec can cause serious and fatal hypersensitivity reactions including anaphylaxis. Immediately and permanently discontinue Fasturtec if a serious hypersensitivity reaction occurs (see 7 WARNINGS AND PRECAUTIONS, General)
- Hemolysis: Do not administer Fasturtec to patients with glucose-6phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue Fasturtec if hemolysis occurs. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Fasturtec therapy (see 7 WARNINGS AND PRECAUTIONS, Hematologic).
- Methemoglobinemia: Fasturtec can result in methemoglobinemia in some patients. Immediately and permanently discontinue Fasturtec if methemoglobinemia occurs (see 7 WARNINGS AND PRECAUTIONS, Hematologic).
- Interference with uric acid measurements: Fasturtec enzymatically degrades uric acid in blood samples left at room temperature. Collect blood samples in pre-chilled tubes containing heparin and immediately immerse and maintain sample in an ice water bath. Assay plasma samples within 4 hours of collection (see 9 DRUG INTERACTIONS, 9.7 Drug-Laboratory Test Interactions).

4 DOSAGE AND ADMINISTRATION

4.2 Dosing Considerations

- Fasturtec (rasburicase for injection) 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.

4.3 Reconstitution

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.

Table 1 - Reconstitution

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

4.4 Administration

Caution: Fasturtec (rasburicase for injection) should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

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.

5 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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Powder for Injection • 1.5 mg/vial	Powder: Disodium phosphate dodecahydrate, L-alanine, mannitol Sterile solution: poloxamer 188, sterile water for injection, USP

1.5 mg/mL/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 disodium phosphate dodecahydrate.

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).

Description

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

Fasturtec is supplied as a pack of:

- 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.
- 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 2 mL colourless glass vial with a rubber stopper and the solvent in a 2 mL clear glass ampoule.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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.

Carcinogenesis and Mutagenesis

Only animal data see 16 NON-CLINICAL TOXICOLOGY

Hematologic

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.

Leukapheresis/Exchange Transfusions

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

Immune

Hypersensitivity/Allergic Reactions

Clinical experience with Fasturtec (rasburicase for injection) demonstrates that Fasturtec, like other proteins, can cause severe allergic reaction, including anaphylaxis and/or anaphylactic shock with potential fatal outcome. Clinical experience with Fasturtec demonstrates that patients should be closely monitored for the onset of allergic-type adverse events, especially bronchospasm, chest pain and tightness, dyspnea, hypoxia, hypotension, shock and urticaria. If any serious allergic or anaphylactic reaction occurs, Fasturtec therapy should be immediately and permanently discontinued, and appropriate therapy initiated.

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

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.

Antibody detection

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 5-7day 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 3).

Renal

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

7.1 Special Populations

7.1.1 Pregnant Women

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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Fasturtec has been shown to be safe and effective in children over the age of one month.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 for injection).

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 is presented in the table below.

Table 3 - Incidence of Adverse Events

	Comparator Study				**Non-Comparator**	
	Allopurinol (N=25)		Fasturtec (N=27)		Fasturtec (N=320)	
Adverse Event	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 >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.

8.5 Post-Market Adverse Reactions

Hematologic:

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

Immune system disorders:

Allergic reactions, mainly including rash and urticarial have been reported.

Cases of rhinitis, bronchospasm, and hypotension have been reported. Cases of anaphylaxis and/or anaphylactic shock with potential fatal outcome have been reported.

Nervous system disorders:

Cases of convulsions and involuntary muscle contraction have been reported.

9 DRUG INTERACTIONS

9.4 Drug-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 administration 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 or inhibition potential. Clinically relevant P450-mediated drug-drug interactions are therefore not anticipated in patients based on the dosing schedule recommended.

9.7 Drug-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.

10 CLINICAL PHARMACOLOGY

10.2 Mechanism of Action

Fasturtec is a highly potent uricolytic 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.

Fasturtec (rasburicase for injection) 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.

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

10.3 Pharmacokinetics

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

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 or acute myelogenous leukemia.
Rasburicase exposure, as measured by AUC_{0-24} 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 rasburicase were achieved on Day 2 in patients. The plasma concentrations declined slowly; the mean elimination half-life was approximately 17 to 21 hours. Because rasburicase is a protein, peptide hydrolysis is the expected metabolic degradation pathway. Clearance of rasburicase is low (4.6 - 5.0 mL/h/kg in patients). Rasburicase 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 4 - Pharmacokinetic Parameters

	Pediatric and Adult Patients (Dose=0.20 mg/kg on Day 5)		
Parameter	**N**	**Mean**	**SD**
C_{max} (µg/mL)	15	4.5	1.15
AUC_{0-24} (µg·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

Special Populations and Conditions

- **Renal Insufficiency:** No dose adjustment is necessary for renally impaired patients.
- **Allergy:** Rasburicase, 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, rasburicase is contraindicated in patients exhibiting allergic or anaphylactic reactions to rasburicase or any of the excipients.

11 STORAGE, STABILITY AND DISPOSAL

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Rasburicase

Chemical name: Urate Oxidase

Molecular formula and molecular mass: C_{1523} H_{2383} N_{417} O_{462} S_7 / Monomer: Approximately 34 kDa.

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	DEKTGVQTVY	EMTVCVLLEG	EIETSYTKAD
NSVIVATDSI	KNTIYITAKQ	NPVTPPELFG	SILGTHFIEK	YNHIHAAHVN
IVCHRWTRMD	IDGKPHPHSF	IRDSEEKRNV	QVDVVEGKGI	DIKSSLSGLT
VLKSTNSQFW	GFLRDEYTTL	KETWDRILST	DVDATWQWKN	FSGLQEVRSH
VPKFDATWAT	AREVTLKTFA	EDNSASVQAT	MYKMAEQILA	RQQLIETVEY
SLPNKHYFEI	DLSWHKGLQN	TGKNAEVFAP	QSDPNGLIKC	TVGRSSLKSKL

Physicochemical properties: Colourless to slightly yellow liquid, clear to slightly opalescent

Pharmaceutical standard: Professed

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The Treatment and Prophylaxis of Hyperuricemia in Pediatric and Adult Cancer Patients

Table 5 – Summary of patient demographics for clinical trials

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ACT2694 (Study 1)	Open-label, multicenter trial Dose-validation phase followed by accrual phase	30-minute IV infusion: 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) *	130 pediatric, 1 adult	<13 years (76%)	M: 67% F: 33%
ACT2511 (Study 2)	Open-label, multicenter trial Dose-validation phase followed by accrual phase	30-minute IV infusion: 0.15 mg/kg/day (n=105) 0.3-0.4 mg/kg/day divided dose (n=2) *	89 pediatric, 18 adult	<13 years (76%)	M: 61% F: 39%
EFC2975 (Study 3)	Open-label, randomized, multicenter comparator trial of rasburicase vs. allopurinol	30-minute IV infusion: 0.2 mg/kg/day (n=26) 0.3-0.4 mg/kg/day divided dose (n=1) *	52 (27: Fasturtec, 25: allopurinol)	Fasturtec: <13 years (82%) Allopurinol: <13 years (76%)	M: 82% F: 18%
Pooled Data (Study 1, 2 & 3)	N/A	30-minute IV infusion: 0.15 mg/kg/day (n=116) 0.20 mg/kg/day (n=135) 0.30-0.40 mg/kg/day divided dose (n=14) *	265 pediatric and adult (note: 4 patients did not have baseline plasma uric acid samples)	<13 years (77%)	M: 64% F: 36%

*Note safety and efficacy of divided doses has not been established.

Table 6- Results of study 1, 2, 3 and pooled data in prophylaxis of hyperuricemia in pediatric and adult cancer patients

Primary Endpoints	ACT2694 (Study 1)	ACT2511 (Study 2)	EFC2975 (Study 3)	Pooled Data (Study 1, 2 & 3)	
% Reduction in Uric Acid at 4 hours post first dose	85%	88%	86%: Fasturtec 12%: alopurinol	Pre-treatment uric acid < 8mg/dL (n=200)	Pre-treatment hyperuricemic patients ≥ 8mg/dL (n=61)
				98%	72%
Uric Acid Maintenance at 48 hours * * patients)	92% at 0.15 mg/kg/day 95% at 0.20 mg/kg/day	99%	96%: Fasturtec 96%: alopurinol	99%	92%

* * Uric Acid Maintenance at 48 hours defined as 1) uric acid concentrations of $\leq$ 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 2) control of uric acid level without the need for allopurinol or other agents

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).

ACT2694 (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).

ACT2511 (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).

EFC2975 (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 μmol/L and ≥ 472 μmol/L][1]).

The primary study objective was to demonstrate a greater reduction in uric acid concentration over 96 hours ($AUC_{0\text{-}96\ hr}$) in the Fasturtec group as compared to the allopurinol group. Uric acid $AUC_{0\text{-}96\ hr}$ 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 $AUC_{0\text{-}96\ hr}$ 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 $AUC_{0\text{-}96\ hr}$ was significantly lower in the Fasturtec group (128 ± s.e. 14 mg•hr/dL) as compared to the allopurinol group (328 ± s.e. 26 mg•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 (Study 1, 2 and 3)

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

[1] Results are reported in mg/dL. To convert to SI units of μmol/L, multiply mg/dL by conversion factor 59 (i.e. 8 mg/dL x 59 = 472 μmol/L)

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 (see14.1 Clinical Trials by Indication, 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).

14.3 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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

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.

Genotoxicity: Fasturtec was non-genotoxic in the Ames, unscheduled DNA synthesis, chromosome analysis, mouse lymphoma, and micronucleus tests.

Reproductive and Developmental Toxicology: Fasturtec did not affect reproductive performance or fertility in male or female rats

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.

Animal Pharmacology:

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

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 or 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr FASTURTEC®

Rasburicase, Powder for Injection

Read this carefully before you start taking **Fasturtec** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Fasturtec**

Serious Warnings and Precautions

- Allergic reactions: Fasturtec can cause serious allergic reactions, which may be fatal. If allergic reactions develop, your doctor will immediately and permanently discontinue treatment with Fasturtec.
- You should not be given Fasturtec if you have a disease called glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency). Your doctor will decide if you should be tested before treatment.
- You should not be given Fasturtec if you have a history of hemolysis (disorder of the blood in which red blood cells are abnormally broken down). If hemolysis or methemoglobinemia (disease caused by abnormal blood pigment levels) develop during treatment, your doctor will immediately and permanently discontinue Fasturtec.

What is Fasturtec used for?

- To treat or prevent high blood levels of uric acid from occurring in adults and children with cancer who are about to receive or are receiving chemotherapy treatment.

How does Fasturtec work?

When chemotherapy is given, cancer cells are destroyed, releasing large amounts of uric acid into the bloodstream.

Fasturtec works by allowing uric acid to be more easily removed from the body by the kidneys

What are the ingredients in Fasturtec?

Medicinal ingredients: rasburicase

Non-medicinal ingredients: disodium phosphate dodecahydrate, L-alanine, mannitol

The solvent for rasburicase powder contains sterile water for injection and poloxamer 188.

Fasturtec comes in the following dosage forms:

Fasturtec comes as a clear glass vial with a rubber stop containing a white to off-white powder, along with an ampoule containing a clear and colorless liquid to dissolve the powder.

Fasturtec is provided in a box containing:

- 3 vials of 1.5 mg rasburicase and 3 ampoules of 1 ml solvent.

Do not use Fasturtec if:

- you are allergic (hypersensitive) to rasburicase, to other uricases or to any of the other ingredients of this medicine (see section above: What are the ingredients in Fasturtec?)
- you have a disease called glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency), also known as favism
- you have a history of hemolytic anemia (an illness caused by red blood cells being abnormally broken down).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Fasturtec. Talk about any health conditions or problems you may have, including if you:

- have a history of any kind of allergy. Tell your doctor if you have ever had any allergic type reactions due to other medicines, as Fasturtec can cause allergic-type reactions, including severe cases. It is not known whether the chance of developing an allergic reaction is increased if treatment with Fasturtec is repeated.
- are, or think you may be pregnant
- are breastfeeding, or intend to breastfeed.

Other warnings you should know about:

During treatment with Fasturtec, your doctor will carry out blood tests to check the levels of uric acid and decide how long you will be treated for.

Your doctor may also test your blood to make sure that you do not develop any blood disorders.

In case disorders of the blood in which red blood cells are abnormally broken down (hemolysis) or abnormal blood pigment levels occur (methemoglobinemia), your doctor will immediately and permanently discontinue treatment with Fasturtec.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Fasturtec:

- Fasturtec is to be given to you before or during the start of your course of chemotherapy.
- Fasturtec is injected slowly into a vein, which should take about 30 minutes.

Usual dose:

- Your dose will be calculated according to your body weight.

- The recommended dose is 0.20 mg per kg of body weight per day in both children and adults.
- It will be given once a day, for up to 7 days.

Overdose:

If an overdose does occur, your doctor will closely monitor the effects on your red blood cells and treat any symptoms that follow.

If you have any further questions on the use of this medicine, ask your doctor, nurse or hospital pharmacist.

If you think you, or a person you are caring for, have taken too much [Brand name], contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Fasturtec?

These are not all the possible side effects you may have when taking Fasturtec. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, this medicine can cause side effects, although not everybody gets them. Fasturtec will be administered at the same time as other medicines that may also cause side effects.

These are not all the possible side effects you may feel when taking Fasturtec. If you experience any side effects not listed here, contact your healthcare professional.

Tell your doctor, nurse or hospital pharmacist immediately if you suddenly notice the following symptoms, as these may be signs of a serious allergic reaction (anaphylaxis):

- a swelling of the face, lips, tongue or other part of your body
- a shortness of breath, wheezing or breathing problems
- a rash, itching or hives.

Very common side effects (may affect more than 1 in 10 people):

- diarrhea
- vomiting
- nausea
- headache
- fever
- allergic reactions, mainly rashes and urticaria.

Frequency not known (frequency cannot be estimated from the available data):

- severe hypersensitivity reactions, including anaphylaxis
- low blood pressure (hypotension)
- wheezing or difficulty in breathing (bronchospasm)
- runny or blocked nose, sneezing, facial pressure or pain (rhinitis)

- blood disorders such as a disorder of the blood in which red blood cells are abnormally broken down (hemolytic anemia), or disorders with abnormal blood pigment levels (methemoglobinemia)
- involuntary muscle movements/contraction
- convulsions.

If you notice any of these, tell your doctor, nurse or hospital pharmacist.

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	Only if severe	In all cases	
RARE Severe hypersensitivity reactions, with symptoms such as: swelling of the face, lips, tongue or other part of your body; shortness of breath, wheezing or breathing problems; rash, itching or hives.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton.

This medicine should be stored in a refrigerator (2°C – 8°C). Do not freeze.

Store in the original package in order to protect from light.

Do not use this medicine if you notice that the solution is unclear and/or contains particles.

If you want more information about Fasturtec:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofi.ca, or by calling 1-800- 265-7927

This leaflet was prepared by Sanofi-aventis Canada Inc.

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