SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fasturtec 1.5 mg/ml powder and solvent for concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fasturtec is a recombinant urate-oxidase enzyme produced by genetically modified *Saccharomyces cerevisiae* strain. Rasburicase is a tetrameric protein with identical subunits of a molecular mass of about 34 kDa.

After reconstitution, 1 ml of Fasturtec concentrate contains 1.5 mg rasburicase.

1 mg corresponds to 18.2 EAU*.

*One enzyme activity unit (EAU) corresponds to the enzyme activity that converts 1 µmol of uric acid into allantoin per minute under the operating conditions described: +30 °C ± 1 °C TEA pH 8.9 buffer.

Excipient(s) with known effect:
Each 1.5 mg/ml vial contains 0.091 mmol of sodium, which is 2.1 mg of sodium and 7.5 mg/5 ml vial contains 0.457 mmol of sodium, which is 10.5 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion (powder for sterile concentrate).

The powder is an entire or broken white to off white pellet.
The solvent is a colourless and clear liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of acute hyperuricaemia, in order to prevent acute renal failure, in 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.

4.2 Posology and method of administration

Posology
Fasturtec is to be used immediately prior to and during the initiation of chemotherapy only, as at the present, there is insufficient data to recommend multiple treatment courses.

The recommended dose for Fasturtec is 0.20 mg/kg/day. Fasturtec is administered as a once daily 30 minute intravenous infusion in 50 ml of a sodium chloride 9 mg/ml (0.9%) solution (see section 6.6).

The duration of treatment with Fasturtec may be up to 7 days, the exact duration should be based upon adequate monitoring of uric acid levels in plasma and clinical judgment.

Paediatric population
As no adjustment is necessary, the recommended dose is 0.20 mg/kg/day.

Special populations
Renally or hepatically impaired patients: No dose adjustment is necessary.

Method of Administration
Fasturtec should be administered under the supervision of a physician trained in chemotherapy of haematological malignancies.

Administration of rasburicase does not require any change in the timing or schedule of initiation of cytoreductive chemotherapy.
Rasburicase solution should be infused over 30 minutes. Rasburicase solution should be infused through a different line than that used for infusion of chemotherapeutic agents to prevent any possible drug incompatibility. If use of a separate line is not possible, the line should be flushed out with saline solution between infusion of chemotherapeutic agents and rasburicase. For instructions on reconstitution and dilution of the medicinal product before

administration, see section 6.6.

Because rasburicase may degrade uric acid *in vitro*, special precautions must be used during sample handling for plasma uric acid measurements, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia. Hydrogen peroxide is a by-product of the conversion of uric acid to allantoin. In order to prevent possible haemolytic anaemia induced by hydrogen peroxide, rasburicase is contraindicated in patients with these disorders.

4.4 Special warnings and precautions for use

Rasburicase like other proteins, has the potential to induce allergic responses in humans, such as anaphylaxis, including anaphylactic shock, with potential fatal outcome**.** Clinical experience with Fasturtec demonstrates that patients should be closely monitored for the onset of allergic-type undesirable effects, especially severe hypersensitivity reactions including anaphylaxis (see section 4.8). In case of severe allergic reaction, treatment should immediately and permanently be discontinued and appropriate therapy initiated.

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

At present, there is insufficient data available on patients being retreated to recommend multiple treatment courses. Anti-rasburicase antibodies have been detected in treated patients and healthy volunteers administered rasburicase.

Methaemoglobinaemia has been reported in patients receiving Fasturtec. Fasturtec should immediately and permanently be discontinued in patients having developed methaemoglobinaemia, and appropriate measures initiated (see section 4.8).

Haemolysis has been reported in patients receiving Fasturtec. In such case, treatment should immediately and permanently be discontinued and appropriate measures initiated (see section 4.8).

Administration of Fasturtec reduces the uric acid levels to below normal levels

and by this mechanism reduces the chance of development of renal failure due to precipitation of uric acid crystals in renal tubules as a consequence of hyperuricaemia. Tumour lysis can also result in hyperphosphataemia, hyperkalaemia and hypocalcaemia. Fasturtec is not directly effective in the treatment of these abnormalities. Therefore, patients must be monitored closely.

Fasturtec has not been investigated in the patients with hyperuricemia in the context of myeloproliferative disorders.

To ensure accurate measurement of uric acid plasma level during treatment with Fasturtec, a strict sample handling procedure must be followed (see section 6.6).

This medicinal product contains up to 10.5 mg sodium per vial, equivalent to 0.53 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Rasburicase being an enzyme itself, it would be an unlikely candidate for drug-drug interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of rasburicase in pregnant women. Results from animal studies could not be interpreted due to the presence of endogenous urate oxidase in standard animal models. Because teratogenic effects of rasburicase cannot be ruled out, Fasturtec should only be used during pregnancy if strictly necessary. Fasturtec is not recommended in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether rasburicase is excreted in human milk. As a protein the dose for the infant is expected to be very low. During treatment with Fasturtec, the advantage of breastfeeding should be weighed against the potential risk for the infant.

Fertility
There are no data regarding the effect of rasburicase on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile
Fasturtec is concomitantly administered as supportive care to cytoreductive chemotherapy of advanced malignancies, the causality of adverse events is therefore difficult to assess due to the significant burden of adverse events expected from the underlying disease and its treatment.

The most commonly reported adverse reactions were nausea, vomiting, headache, fever, and diarrhoea.

In clinical trials, haematological disorders such as haemolysis, haemolytic anaemia and methaemoglobinaemia are uncommonly caused by Fasturtec. The enzymatic digestion of uric acid to allantoin by rasburicase produces hydrogen peroxide and haemolytic anaemia or methaemoglobinaemia have been observed in certain at risk populations such as those with G6PD deficiency.

Adverse reactions possibly attributable to Fasturtec and reported in the clinical trials, are listed below, by system organ class and by frequency. Frequencies are defined using the following MedDRA convention as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

MedDRA Organ system classes	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			- Haemolysis - Haemolytic anaemia - Methaemoglobinaemia		
Immune system disorders		- Allergy/ allergic reactions (rashes and urticaria)	- Severe hypersensitivity reactions	- Anaphylaxis	- Anaphylactic shock*
Nervous system disorders	- Headache +		- Convulsion**		- Muscle contraction involuntary **
Vascular disorders			- Hypotension		
Respiratory, thoracic and mediastinal disorders			- Bronchospasm	- Rhinitis	
Gastrointestinal disorders	- Diarrhoea + - Vomiting++ - Nausea++				
General disorders and administration site conditions	- Fever++				

* Anaphylactic shock including potential fatal outcome
** From post-marketing experience
\+ Uncommon G3/4
++ Common G3/4

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In view of the mechanism of action of Fasturtec, an overdose will lead to low or undetectable plasma uric acid concentrations and increased production of hydrogen peroxide. Thus patients suspected of receiving an overdose should be monitored for haemolysis, and general supportive measures should be initiated as no specific antidote for Fasturtec has been identified.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment, ATC code: V03AF07.

Mechanism of action
In humans, uric acid is the final step in the catabolic pathway of purines. The acute increase in plasma levels of uric acid subsequent to the lysis of large numbers of malignant cells and during cytoreductive chemotherapy may lead to impairment of renal function and renal failure resulting from the precipitation of crystals of uric acid in renal tubules. Rasburicase is a highly potent uricolytic agent that catalyses enzymatic oxidation of uric acid into allantoin, a water soluble product, easily excreted by the kidneys in the urine. The enzymatic oxidation of uric acid leads to stoichiometric formation of hydrogen peroxide. The increased of hydrogen peroxide over ambient levels can be eliminated by endogenous antioxidants and the only increased risk is for haemolysis in G6PD deficient and inherited anaemia patients.

In healthy volunteers, a marked dose-related decrease in plasma uric acid levels was observed across the dose range 0.05 mg/kg to 0.20 mg/kg of Fasturtec.

Clinical efficacy and safety

In a randomised comparative phase III study, performed in 52 paediatric patients, 27 patients were treated with rasburicase at 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%).

Time to first confirmation of normal levels of uric acid in hyperuricaemic patients is four hours for Fasturtec and 24 hours for allopurinol. In addition this rapid control of uric acid in this population is accompanied by improvements in renal function. In turn, this allows efficient excretion of the serum phosphate load preventing further deterioration of renal function from calcium/phosphorus precipitation.

In a randomized (1:1:1), multi-center, open-label study, 275 adult patients with leukemia and lymphoma at risk for hyperuricemia and tumour lysis syndrome (TLS) were treated with either rasburicase at a dose of 0.2 mg/kg/day, intravenously, for 5 days (arm A: n=92), rasburicase at a dose of 0.2 mg/kg/day, intravenously, from day 1 through day 3 followed by oral allopurinol at a dose of 300 mg once a day from day 3 through day 5 (overlap on day 3: rasburicase and allopurinol administered approximately 12 hours apart) (arm B: n=92), or oral allopurinol at a dose of 300 mg once a day for 5 days (arm C: n=91). The uric acid response rate (proportion of patients with plasma uric acid levels ≤7.5 mg/dl from day 3 to day 7 after initiation of antihyperuricemic treatment) was 87% in arm A, 78% in arm B, and 66% in arm C. The response rate in arm A was significantly greater than in arm C ($p=0.0009$); the response rate was higher for arm B compared to arm C although this difference was not statistically significant. Uric acid levels were ≤2 mg/dl in 96% of patients in the two arms containing rasburicase and 5% of patients in the allopurinol arm at 4 hours of the day 1 dose. The safety results of patients treated with Fasturtec in Study EFC4978 were consistent with the adverse events profile observed in previous clinical studies with predominantly paediatric patients.

In pivotal clinical studies, 246 paediatric patients (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 (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.

5.2 Pharmacokinetic properties

The pharmacokinetics of rasburicase were evaluated in both paediatric and adult patients with leukaemia, lymphoma or other haematological malignancies.

Absorption
After infusion of rasburicase at a dose of 0.20 mg/kg/day, steady state is achieved at day 2 - 3. Minimal accumulation of rasburicase (<1.3 fold) was observed between days 1 and 5 of dosing.

Distribution
The mean volume of distribution ranged from 110 - 127 ml/kg in paediatric patients and from 75.8 to 138 ml/kg in adult patients, respectively, which is comparable to the physiological vascular volume.

Metabolism
Rasburicase is a protein, and therefore: 1) not expected to bind to proteins, 2) expected that metabolic degradation will follow the pathways of other proteins, i.e. peptide hydrolysis, 3) unlikely to be candidate for drug-drug interactions.

Elimination
Clearance of rasburicase was ca. 3.5 ml/h/kg. The mean terminal half-life was similar between paediatric and adult patients and ranged from 15.7 to 22.5 hours. Clearance is increased (ca. 35%) in children and adolescents compared to adults, resulting in a lower systemic exposure. Renal elimination of rasburicase is considered to be a minor pathway for rasburicase clearance.

Special patient populations
In adults (≥ the age of 18 years), age, gender, baseline liver enzymes and creatinine clearance did not impact the pharmacokinetics of rasburicase. A cross-study comparison revealed that after administration of rasburicase at 0.15 or 0.20 mg/kg, the geometric mean values of body-weight normalized clearance were approximately 40% lower in Japanese (n=20) than that in Caucasians (n=26).

As metabolism is expected to occur by peptide hydrolysis, an impaired liver function is not expected to affect the pharmacokinetics.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional

studies of safety pharmacology, repeated dose toxicity and genotoxicity. The interpretation of the non-clinical studies is hampered due to the presence of endogenous urate oxidase in standard animal models.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
alanine
mannitol
disodium phosphate dodecahydrate
disodium phosphate dihydrate
sodium dihydrogen phosphate dihydrate

Solvent:
poloxamer 188
water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Rasburicase solution should be infused through a different line than that used for infusion of chemotherapeutic agents to prevent any possible drug incompatibility. If use of a separate line is not possible, the line should be flushed out with saline solution between chemotherapeutic agent infusions and rasburicase.
No filter should be used for infusion.
Do not use any glucose solution for dilution due to potential incompatibility.

6.3 Shelf life

3 years.

After reconstitution or dilution an immediate use is recommended. However,

the in-use stability has been demonstrated for 24 hours between +2°C and 8°C.

6.4 Special precautions for storage

Powder in vial: store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Fasturtec is supplied as a pack of:

3 vials of 1.5 mg rasburicase and 3 ampoules of 1 ml solvent. The powder is supplied in 2 ml or 3 ml clear glass (type I) vial with a rubber stopper and the solvent in a 2 ml clear glass (type I) ampoule.

1 vial of 7.5 mg rasburicase and 1 ampoule of 5 ml solvent. The powder is supplied in 10 ml clear glass (type I) vial with a rubber stopper and the solvent in a 5 ml clear glass (type I) ampoule.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Rasburicase must be reconstituted with the entire volume of the supplied solvent ampoule (1.5 mg rasburicase vial to be reconstituted with the 1 ml solvent ampoule; 7.5 mg rasburicase vial to be reconstituted with the 5 ml solvent ampoule). Reconstitution results in a solution with a concentration of 1.5 mg/ml rasburicase to be further diluted with sodium chloride 9 mg/ml (0.9%) intravenous solution.

<u>Reconstitution of the solution:</u>
Add the content of one ampoule of solvent to one vial containing rasburicase and mix by swirling very gently under controlled and validated aseptic conditions.
Do not shake.

Inspect visually prior to use. Only clear and colourless solutions without particles should be used.
For single-use only, any unused solution should be discarded.
The solvent contains no preservative. Therefore the reconstituted solution should be diluted under controlled and validated aseptic conditions.

Dilution before infusion:
The required volume of the reconstituted solution depends on the patient's body weight. The use of several vials may be necessary to obtain the quantity of rasburicase required for one administration. The required volume of the reconstituted solution, taken from one or more vials, is to be further diluted with sodium chloride 9 mg/ml (0.9%) solution to make a total volume of 50 ml. The concentration of rasburicase in the final solution for infusion depends on the patient's body weight.

The reconstituted solution contains no preservative. Therefore the diluted solution should be infused immediately.

Infusion:
The final solution should be infused over 30 minutes.

Sample handling:
If it is necessary to monitor a patient’s uric acid level, a strict sample-handling procedure must be followed to minimise *ex vivo* degradation of the analyte. Blood must be collected into pre-chilled tubes containing heparin anticoagulant. Samples must be immersed in an ice/water bath. Plasma samples should immediately be prepared by centrifugation in a pre-cooled centrifuge (4°C). Finally, plasma must be maintained in an ice/water bath and analysed for uric acid within 4 hours.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
410 Thames Valley Park Drive
Reading
Berkshire
RG6 1PT
UK

Trading as:

Sanofi
410 Thames Valley Park Drive
Reading
Berkshire
RG6 1PT
UK

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