DATA SHEET

1 FASTURTEC (POWDER FOR INFUSION)

Fasturtec 1.5mg powder for infusion
Fasturtec 7.5 mg powder for infusion*

* Not marketed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

After reconstitution, 1 mL of Fasturtec powder for infusion contains:

1.5 mg vials: 1.5 mg rasburicase rys.

7.5 mg vials: 7.5 mg rasburicase rys.

1 mg of rasburicase corresponds to 18.2 EAU. One enzyme activity unit (EAU) corresponds to the enzyme activity that converts 1µmol of uric acid into allantoin per minute under the operating conditions described: +30°C ± 1°C TEA pH 8.9 buffer.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for infusion.

Fasturtec is a sterile powder supplied in a stoppered clear glass vial, accompanied by a solvent in a clear glass ampoule. 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

Rasburicase is indicated for the treatment and prophylaxis of acute hyperuricaemia, in patients with haematological malignancy at risk of a rapid tumour lysis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

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

In patients who are not hyperuricemic at baseline, chemotherapy regimens should be started within 24 hours of first administration of rasburicase. In patients who are hyperuricemic at baseline, chemotherapy regimens should be started within 48 hours of first administration of rasburicase.

Children and adults

The recommended dose for rasburicase is 0.20 mg/kg/day. Rasburicase is administered as a once daily 30 minute intravenous infusion in 50 mL of a 0.9% sodium chloride solution. The duration of treatment with rasburicase may vary between 5 and 7 days. No dose adjustment is necessary for special populations (renally or hepatically impaired patients). Administration of rasburicase does not require any change in the timing or schedule of initiation of cytoressive chemotherapy.

Method of administration

Do not use an in-line filter. 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 agents infusion and rasburicase. Rasburicase should be administered under the supervision of a trained physician. It contains no antimicrobial agent. Rasburicase is for single use in one patient only. Discard any residue.

For instructions on reconstitution and dilution of rasburicase 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 rasburicase, other uricases or 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

Administration of rasburicase reduces the uric acid level 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. Rasburicase is not directly effective in the treatment of these abnormalities. Therefore, patients must be monitored closely.

Hypersensitivity

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

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

At the 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. In healthy volunteers, 53% subjects receiving rasburicase had anti-rasburicase antibodies one month post last dose. Most of the positive subjects were no longer positive at 1 year.

Methaemoglobinaemia has been reported in patients receiving rasburicase. It is not known whether patients with deficiency of methaemoglobin reductase or of other enzymes with antioxidant activity are at increased risk of methaemoglobinaemia. Rasburicase should be immediately and permanently discontinued in patients having developed methaemoglobinaemia, and appropriate measures initiated.

Haemolysis has been reported in patients receiving rasburicase. In such cases, treatment should be immediately and permanently discontinued and appropriate measures initiated.

Rasburicase has not been investigated in patients with hyperuricaemia in the context of myeloproliferative disorders.

There is no data available to recommend the sequential use of rasburicase and allopurinol.
4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

In vivo drug-drug interaction studies have not been conducted. In rats and baboons, rasburicase did not appear to induce or inhibit hepatic cytochrome P450 isoforms. In vitro, rasburicase did not metabolise 6-mercaptopurine, cyarabine or methotrexate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy (CATEGORY B2)

No clinical data on exposed pregnancies are available. 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 studies with respect to effects on parturition and postnatal development have not been performed. The potential risk for humans is unknown. Rasburicase should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether rasburicase is excreted in human milk, therefore it should not be used in breast-feeding women.

Fertility

No adverse effects on fertility were observed in male and female rats at intravenous doses up to 10 mg/kg/day at which systemic exposure (plasma AUC) was about 12 times greater than that in humans at the maximum recommended dose. The interpretation of the preclinical studies is hampered due to the presence of endogenous urate oxidase in standard animal models.

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

Because rasburicase is concomitantly administered as supportive care to cytoreductive chemotherapy of advanced malignancies, a significant burden of adverse events is expected from the underlying disease state and its treatment.

Undesirable effects possibly attributable to rasburicase reported in clinical trials involving 347 subjects:
Table 1

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Incidence in pooled studies (grade 3 or 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>6.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.7%</td>
</tr>
<tr>
<td>Uncommon:</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.9%</td>
</tr>
<tr>
<td>Headache</td>
<td>0.9%</td>
</tr>
<tr>
<td>Allergic reactions:</td>
<td></td>
</tr>
<tr>
<td>bronchospasm</td>
<td>1 grade 4</td>
</tr>
<tr>
<td>allergic reaction</td>
<td>1 grade 3</td>
</tr>
</tbody>
</table>

The most significant drug related adverse events were allergic reactions, mainly rashes (1.4%) and urticaria. Cases of rhinitis, hypotension, bronchospasm (<1%) and severe hypersensitivity reactions including anaphylaxis (<1%) have also been attributed to rasburicase.

Because the enzymatic conversion of uric acid to allantoin by rasburicase produces hydrogen peroxide, haemolytic anaemia and methaemoglobinaemia have been observed in certain at risk populations such as those with G6PD deficiency. In trials, 0.9% subjects developed haemolytic anaemia, one of these subjects was documented to have G6PD deficiency.

Post-marketing data

Adverse reactions reported during the post-marketing period are detailed below. These reactions are classified within body system categories using the following definitions:

- **very common**: $\geq 1/10$ ($\geq 10\%$)
- **common**: $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $<10\%$)
- **uncommon**: $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $<1.0\%$)
- **rare**: $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $<0.1\%$)
- **very rare**: $< 1/10,000$ ($< 0.01\%$)
- **not known**: frequency cannot be estimated from available data

**Nervous system disorders**

- **uncommon**: convulsion

*frequency not known*: muscle contractions involuntary
Blood and lymphatic system disorders

uncommon: haemolysis which could be related to G6PD deficiency, methemoglobinemia.

Immune system disorders

common: allergic reactions. These mainly include rash and urticaria.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Signs and Symptoms

In view of the mechanism of action of rasburicase, an overdose will lead to low or undetectable plasma uric acid concentrations and increased production of hydrogen peroxide.

Management

Thus patients suspected of receiving an overdose should be monitored for haemolysis, and general supportive measures should be initiated as no specific antidote for rasburicase has been identified.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

CAS registry number: 134774-45-1

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 degradation of renal function and renal failure which results from the precipitation of crystals of uric acid in renal tubules. Rasburicase is a potent uricolytic agent that catalyses enzymatic oxidation of uric acid into allantoin, a water soluble product, more easily excreted by the kidney in the urine. The enzymatic oxidation of uric acid leads to stoichiometric formation of hydrogen peroxide. The increase of hydrogen peroxide over ambient levels can be eliminated by endogenous antioxidants and the only increased risk for haemolysis is 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 rasburicase. This dose related decrease in plasma uric acid levels was seen within four hours post first dose and remained for up to 24 hours post last dose of rasburicase.

**Clinical efficacy and safety**

ACT2511 (n=107) and ACT2694 (n=131) were phase II, open-label, multicentre studies of rasburicase used as uricolytic therapy for the prophylaxis and treatment of hyperuricaemia in patients with leukemia or lymphoma. Patients in ACT2511 received 0.15 mg/kg, while those in ACT2694 received either 0.15 mg/kg (n=12) or 0.20 mg/kg (n=119). Primary endpoint was plasma uric acid concentrations over time. Overall, plasma uric acid fell rapidly after the first dose, and remained several-fold below the mean baseline value during rasburicase treatment. The mean percentage reduction (±SD) in uric acid four hours after the first dose was 88% ± 12% in ACT2511 and 84.9% ± 12.6% in ACT2694.

<table>
<thead>
<tr>
<th>Table 2 - Summary of efficacy results for the treatment indication</th>
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<tbody>
<tr>
<td><strong>Efficacy Criteria</strong></td>
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<tr>
<td>------------------------</td>
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<tr>
<td>Mean plasma UA concentration at baseline (T0h) (µmol/L)</td>
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<tr>
<td>[mg/dL]</td>
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<tr>
<td>Mean reduction in UA at 4 hours post first dose</td>
</tr>
<tr>
<td>Mean plasma UA concentration at 4 hours post first dose (µmol/L)</td>
</tr>
<tr>
<td>[mg/dL]</td>
</tr>
<tr>
<td>Mean time to first confirmation of control of UA²</td>
</tr>
<tr>
<td>(n=5)</td>
</tr>
<tr>
<td>No. of patients with uric acid rebound &gt;8 mg/dL following start of chemotherapy</td>
</tr>
<tr>
<td>Mean plasma uric acid AUC0-96 (µmol.hr/L)</td>
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<tr>
<td>[mg.hr/dL]</td>
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</tbody>
</table>
EFC2975 was a randomised, multicentre open-label phase III study, comparing rasburicase (n=27) 0.20 mg/kg versus allopurinol (n=25) for the treatment and prophylaxis of hyperuricaemic patients with leukemia and lymphoma. At 4 hours after the first dose, there was a significant difference (p<0.0001) in the mean percent reduction from baseline plasma uric acid concentration in the rasburicase group (86.0 ± 7.0%) compared to that for the allopurinol group (12.1 ± 13.3%). Time to first confirmation of normal levels of uric acid in hyperuricaemic patients is four hours for rasburicase and 24 hours for allopurinol. Rasburicase induced excretion of the serum phosphate load prevented further deterioration of renal function from calcium/phosphorus precipitation.

**Table 3 - Summary of efficacy results for the prophylaxis indication**

<table>
<thead>
<tr>
<th>Efficacy Criteria</th>
<th>EFC2975</th>
<th>ACT2511</th>
<th>ACT2694</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate</strong></td>
<td>100% (n=3)c</td>
<td>75% (n=8)c</td>
<td>100% (n=11)c</td>
</tr>
<tr>
<td><strong>Allopurinol</strong></td>
<td>n=16</td>
<td>n=17</td>
<td>n=95</td>
</tr>
<tr>
<td>Mean plasma UA concentration at baseline (T0h) (µmol/L) [mg/dL]</td>
<td>274 ± 54 [4.6 ± 0.9]</td>
<td>309 ± 71 [5.2 ± 1.2]</td>
<td>238 ± 83 [4.0 ± 1.4]</td>
</tr>
<tr>
<td>Mean reduction in UA at 4 hours post first dose</td>
<td>13.2%</td>
<td>85.1%</td>
<td>88.6%</td>
</tr>
<tr>
<td>Mean plasma UA concentration at 4 hours post first dose (µmol/L) [mg/dL]</td>
<td>234 ± 57 [3.93 ± 0.95]</td>
<td>46 ± 24 [0.78 ± 0.40]</td>
<td>26 ± 29 [0.44 ± 0.48]</td>
</tr>
<tr>
<td>No. of patients with uric acid rebound &gt;8 mg/dL following start of chemotherapy</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mean plasma uric acid AUC0-96 (µmol.hr/L) [mg.hr/L]</td>
<td>15816 [265.9]</td>
<td>6418 [107.9]</td>
<td>4800 [80.7]</td>
</tr>
<tr>
<td>Response rateb</td>
<td>91% (n=11)c</td>
<td>100% (n=15)c</td>
<td>99% (n=93)c</td>
</tr>
</tbody>
</table>

Page 8

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fasturtec-ccdsv5.1&6-dsv2-20sep18
In pivotal clinical studies, 246 paediatric patients (mean age 7 years, range 0 to 17) 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 to 17) 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 to 5 dosing.

**Distribution**

In patients, the volume of distribution ranged from 110 - 127 mL/kg in paediatric patients and from 75.8 to 138 mL/kg in adult patients, which is comparable to the physiological vascular volume.

**Biotransformation**

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, impaired liver function is not expected to affect the pharmacokinetics.

5.3 PRECLINICAL SAFETY DATA

Assays for gene mutations (histidine reversion in S. typhimurium and mouse lymphoma gene mutation assay), chromosomal damage (cytogenetics in human peripheral blood lymphocytes in vitro and micronucleus test in rats in vivo) and DNA damage (in vitro rat hepatocyte assay) did not provide any evidence of a genotoxic potential.

Long-term animal studies on carcinogenicity are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients contained in the Fasturtec 1.5 mg and 7.5 mg vials are: alanine, mannitol, disbasic sodium phosphate dihydrate, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dodecahydrate. The solvent contains poloxamer 188 and water for injections.

6.2 INCOMPATIBILITIES

Do not use any glucose intravenous infusion for dilution due to potential incompatibility.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.
6.3 SHELF LIFE

1.5 mg and 7.5 mg* Vials: 3 years

Solvent: 4 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.

* Not marketed

6.4 SPECIAL PRECAUTIONS FOR STORAGE

1.5 mg and 7.5 mg* Vials: Store at 2°C to 8°C (Refrigerate. Do not freeze).

Solvent: Store at or below 25°C.

* Not marketed

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

6.5 NATURE AND CONTENTS OF CONTAINER

1.5 mg Vials

Package size: 3 vials of rasburicase powder and 3 ampoules with 1 mL of solvent per box.

7.5 mg Vials*

Package size: 1 vial of rasburicase powder and 1 ampoule with 5 mL of solvent per box.

Not all pack sizes may be marketed.

* Not marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation

Rasburicase must be reconstituted with the solvent supplied and further diluted only in 0.9% sodium chloride injection. This product should not be mixed with other drugs for its infusion.
Reconstitution of the solution

1.5 mg Vials

Under controlled and validated aseptic conditions, add 1 mL of solvent to each vial containing 1.5 mg of rasburicase and mix by swirling very gently. Do not shake. Inspect visually prior to use. Only clear solutions without particles should be used. The solvent contains no preservative, therefore the solution should be reconstituted immediately prior to further dilution, and in no case be stored for longer than 24 hours at 2-8°C.

For single use only, any unused solution should be discarded.

7.5 mg Vials

Under controlled and validated aseptic conditions, add 5 mL of solvent to each vial containing 7.5 mg of rasburicase and mix by swirling very gently. Do not shake. Inspect visually prior to use. Only clear solutions without particles should be used. The solvent contains no preservative, therefore the solution should be reconstituted immediately prior to further dilution, and in no case be stored for longer than 24 hours at 2-8°C.

For single use only, any unused solution should be discarded.

Dilution before infusion

1.5 mg Vials

The required quantity of solution (according to the patient's body weight) is to be further diluted with 0.9% sodium chloride injection to make up a total volume of 50 mL. As the reconstituted solution contains no preservative the diluted solution should be infused immediately, and in no case be stored for longer than 24 hours at 2-8°C.

7.5 mg Vials

The required quantity of solution (according to the patient's body weight) is to be further diluted with 0.9% sodium chloride injection to make up a total volume of 50 mL. As the reconstituted solution contains no preservative the diluted solution should be infused immediately, and in no case be stored for longer than 24 hours at 2-8°C.

Rasburicase is for single use in one patient only. Discard any residue.

Infusion

The final solution should be infused over 30 minutes. Rasburicase solution should be infused through a different line from 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 agents infusions and rasburicase.
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 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street
Ellerslie, Auckland
New Zealand

9 DATE OF FIRST APPROVAL

14 August 2014

10 DATE OF REVISION OF THE TEXT

20 September 2018

Summary of changes

<table>
<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Align with the Medsafe data sheet format including minor additions of text to meet requirements</td>
</tr>
<tr>
<td>2</td>
<td>Editorial changes</td>
</tr>
<tr>
<td>4.3</td>
<td>Editorial changes</td>
</tr>
<tr>
<td>4.9</td>
<td>Removal Australian poison information</td>
</tr>
<tr>
<td>5.1</td>
<td>Addition of paediatric and long-term safety data</td>
</tr>
<tr>
<td>5.2</td>
<td>Addition of pharmacokinetic data</td>
</tr>
<tr>
<td>6.1</td>
<td>Revision of excipient names to align with INN</td>
</tr>
<tr>
<td>6.3</td>
<td>New section</td>
</tr>
<tr>
<td>6.4</td>
<td>Addition of diluent storage conditions</td>
</tr>
<tr>
<td>6.5</td>
<td>Editorial changes</td>
</tr>
<tr>
<td>Section changed</td>
<td>Summary of new information</td>
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<td>8</td>
<td>Remove Australian contact details</td>
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