SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oncaspar solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml solution for injection contain pegaspargase equivalent to 3750 I.U. L-asparaginase.

(One I.U. L-asparaginase is defined as the quantity of enzyme required to liberate 1 µmol ammonia per minute at pH 7.3 and 37 °C.)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oncaspar is indicated as a component of antineoplastic combination therapy for reinduction in acute lymphatic leukaemia (ALL) in children and adults in patients with known hypersensitivity to "native" L-asparaginases.

4.2 Posology and method of administration

Unless prescribed otherwise, the following dosage schedule applies:
The recommended dosage of Oncaspar is 2500 I.U. (equivalent to 3.3 ml Oncaspar)/m² body surface area every 2 weeks.

Children with a body surface area ≥ 0.6 m² receive 2500 I.U. (equivalent to 3.3 ml Oncaspar)/m² body surface area every 2 weeks.

Children with a body surface area < 0.6 m² receive 82.5 I.U. (equivalent to 0.1 ml Oncaspar)/kg body weight.

As a component of combination therapy, Oncaspar can be given either intravenously or intramuscularly for induction, consolidation, or maintenance therapy.

The preferred route of administration is intramuscular injection as the incidence of hepatotoxicity, coagulopathy, gastrointestinal disorders and renal impairment is lower compared to intravenous injection.

Intravenous injection of Oncaspar should be given over a period of 1-2 hours in 100 ml physiological saline or 5% dextrose solution together with an already running infusion.

When Oncaspar is given by intramuscular injection the volume injected at one site should not exceed two millilitres in children and three millilitres in adults. If more than two millilitres are given, the dose should be divided and given at several injection sites.

It is recommended that Oncaspar is used in combination schedules only by doctors who are familiar with the effects and risks of the respective schedule.

Oncaspar alone should be administered for induction in exceptional cases only, namely, when combination therapy with chemotherapeutic agents such as vincristine, methotrexate, cytarabine, daunorubicin or doxorubicin is not indicated because of toxicity or other patient-specific factors.

With the onset of remission appropriate maintenance therapy must be commenced. Oncaspar can be used as part of maintenance therapy.

4.3 Contraindications

- Oncaspar is contraindicated in presence of hypersensitivity to the active substance or to any of the excipients (in patients who have exhibited severe allergic reactions previously such as urticaria, bronchospasm, hypotension, laryngeal oedema or other severe side effects after administration of Oncaspar).

- Oncaspar is contraindicated in patients with pancreatitis (including a history of pancreatitis).

- It should not be used in patients who have had acute haemorrhagic reactions in association with previous L-asparaginase therapy.

4.4 Special warnings and precautions for use

Special precautions for use
In view of the unpredictability of adverse events, Oncaspar should only be given by a person experienced in the use of antineoplastic substances.

Hypersensitivity reactions to Oncaspar, e.g. life-threatening anaphylaxis, can occur during the therapy, particularly in patients with known hypersensitivity to the other forms of L-asparaginase. As a routine precautionary measure the patient should be monitored for an hour having resuscitation equipment and other means required for the treatment of anaphylaxis in readiness (epinephrine, oxygen, intravenous steroids etc.).

Patients who receive Oncaspar are at a higher risk than usual of bleeding disorders, particularly when other medicines with coagulation-inhibiting effects such as acetylsalicylic acid and nonsteroidal anti-inflammatory drugs are used simultaneously (see Interactions). Oncaspar can develop immunsuppressive activity. It is therefore possible that use of this medicine promotes infections in patients.

Combination therapy with Oncaspar can be followed by severe hepatic toxicity and toxicity in the central nervous system.

Caution is required when Oncaspar is given in combination with other hepatotoxic substances, especially if there is pre-existing hepatic dysfunction.

Information for the patient
Patients should be informed about possible hypersensitivity reactions to Oncaspar, including immediate anaphylaxis. Patients who receive Oncaspar are at an increased risk of bleeding disorders. It should be explained to patients that Oncaspar should not be given at the same time as other medicines associated with an increased risk of bleeding (see Interactions).

Laboratory tests
The decrease in the number of circulating cancer cells in the blood (lymphoblasts) is often quite marked, and normal or too low leukocyte counts are often seen in the first days after the start of therapy. This can be associated with a marked rise in the serum uric acid level. Uric acid nephropathy

may develop. To monitor the therapeutic effect, the concentrations of blood cells (peripheral blood count) and the patient's bone marrow should be monitored closely.

Enzyme measurements in the blood (blood amylase) should be carried out frequently to identify early signs of inflammation of the pancreas. If inflammation of the pancreas occurs, the treatment must be stopped and must not be resumed.

Blood sugar levels should be monitored during treatment with Oncaspar as they may rise.

If Oncaspar is used in association with hepatotoxic chemotherapy, the patients should be monitored for liver dysfunction.

Oncaspar can affect a range of serum proteins. Fibrinogen, PT and PTT should therefore be checked regularly.

4.5 Interaction with other medicinal products and other forms of interaction

The decrease in serum proteins caused by Oncaspar can increase the toxicity of other medicines that are bound to protein.

In addition, by inhibiting protein synthesis and cell division, Oncaspar can disturb the mechanism of action of other substances which require cell division for their effect, e.g. methotrexate.

Oncaspar can interfere with enzymatic detoxification of other medications, especially in the liver. The use of Oncaspar can lead to fluctuating coagulation factors. This can promote the tendency to bleeding and/or thrombosis.

Caution is therefore needed when anticoagulants such as coumarin, heparin, dipyridamole, acetylsalicylic acid or nonsteroidal anti-inflammatories are given at the same time.

Immediately preceding or simultaneous treatment with vincristine can increase its toxicity and increases the risk of anaphylactic reactions.

When prednisone and pegaspargase are given at the same time, alterations in coagulation parameters (e.g. fall in fibrinogen and ATIII) can be more pronounced.

Methotrexate and cytarabine can interfere differently: prior administration of these substances can increase the action of pegaspargase synergistically. If these substances are given subsequently, the effect of pegaspargase can be weakened antagonistically.

Pegaspargase can increase the toxicity of other medications by influencing liver function.

Simultaneous vaccination with live vaccines increases the risk of severe infections due to the overall situation and taking into account the underlying disease and the usually combined chemotherapy. Vaccination with live vaccines should therefore be given 3 months at the earliest after termination of the entire antileukaemic treatment.

4.6 Fertility, pregnancy and lactation

No reproduction studies in animals with Oncaspar were performed. It is therefore not known if Oncaspar in pregnant women can harm the foetus or influence the reproductive capacity. However, animal studies with the active substance asparaginase lead to malformations and embryolethal effects. Oncaspar must therefore not be used during pregnancy.

Effective contraception must be used during treatment.

It is not known if Oncaspar passes into breast milk. Since many medicines can pass into breast milk and since, as a consequence, there is a risk of serious adverse reactions to Oncasparfor the breast-fed infant, either breast-feeding should be stopped or the medicine discontinued, taking into account the importance of the medicine for the mother.

4.7 Effects on ability to drive and use machines

Even when used correctly, this medicine can alter the ability to react insofar (somnolence, fatigue and confusion) as the ability to drive or use machines is impaired. This applies to a greater degree in association with alcohol.

4.8 Undesirable effects

In addition to immunological reactions to the foreign protein, treatment with pegaspargase can lead to disturbances in organ systems which have a high level of protein synthesis (especially liver and pancreas). Since pegaspargase is used mainly in combination therapy, it is often difficult to distinguish these side effects from those of other medications.

The range of side effects of pegaspargase largely coincides with that of asparaginase. For safey reasons, therefore, there are also side effects listed which occurred in association with the use of asparaginase but have not hitherto been observed with pegaspargase.

The frequency of side effects is defined by the following convention:
Very common (≥ 1/10)
Common (≥ 1/100, ≤ 1/10)
Uncommon (≥ 1/1,000, ≤ 1/100)
Rare (≥ 1/10,000, ≤ 1/1,000)
Very rare (≤ 1/10,000)
Not known (cannot be estimated from the available data)

Organ system	**Frequency and symptom**
Infections and infestations	*Not known:* Infections.
Blood and lymphatic system disorders	*Common:* Mild to moderate myelosuppression of all three cell lines; coagulation disorders due to impaired protein synthesis; bleeding, disseminated intravascular coagulation (DIC) or thrombosis; with cerebral manifestation stroke, seizures, headache or loss of consciousness. *Very rare:* Haemolytic anaemia.
Immune system disorders	*Common:* Allergic reactions (local erythema, urticaria, pruritus, angioedema, pyrexia, myalgia, dyspnoea), bronchospasm, tachycardia, fall in blood pressure to the point of anaphylactic shock.
Endocrine disorders	*Common:* Alterations in endocrine pancreatic function with diabetic ketoacidosis, hyperosmolar hyperglycaemia. *Very rare:* Transient secondary hypothyroidism; decrease in thyroxine-binding globulin; hypoparathyroidism.
Metabolism and nutrition disorders	*Very common:* Changes in blood lipid values (e.g. an increase or decrease in cholesterol, increase in triglycerides, increase in the VLDL fraction and decrease in LDL, increased lipoprotein lipase activity), in most cases without clinical symptoms;

	Increase in blood urea by prerenal metabolic imbalance. *Uncommon:* Increased uric acid blood levels (hyperuricaemia), hyperammonaemia.
Nervous system disorders	*Common:* CNS dysfunction in the form of agitation, depression, hallucination, confusion and somnolence (mild impairment of consciousness); EEG changes (reduced alpha wave activity, increased theta and delta wave activity), possibly due to hyperammonaemia. *Rare:* Seizures and severe impairment of consciousness, including coma, may occur. Reversible Posterior Leukoencephalopathy Syndrome (RPLS) *Very rare:* mild tremor of the fingers
Gastrointestinal disorders	*Very common:* Mild to moderate gastrointestinal reactions such as loss of appetite, nausea, vomiting, abdominal cramps, diarrhoea and weight loss. *Common:* Acute pancreatitis, disorders of the exocrine pancreatic function with diarrhoea *Uncommon:* Parotitis *Rare:* Haemorrhagic or necrotising pancreatitis. *Very rare:* Pseudocysts of the pancreas, pancreatitis with fatal outcome, pancreatitis with simultaneous acute parotitis.
Hepatobiliary disorders	*Very common:* Alteration of liver parameters (e.g. alkaline phosphatase, serum transaminases, LDH, serum bilirubin), fatty liver, hypoalbuminaemia which may cause symptoms including oedemas *Rare:* Cholestasis, icterus, hepatocellular necrosis and hepatic failure with potentially fatal outcome.
Skin and subcutaneous tissue disorders	*Common:* Allergic skin reactions. *Very rare:* Toxic epidermal necrolysis (Lyell‘s syndrome).
Renal and urinary disorders	*Rare:* Acute renal failure.
General disorders and administration site conditions	*Very common:* pain at the injection site, oedema *Common:* Body temperature increased, pain (back pain, joint pain, abdominal pain) *Rare:* High fever which is life-threatening (hyperpyrexia).
Investigations	*Common:* increase in blood amylase

Infections and infestations
Infections may occur during treatment with pegaspargase-containing regimens. It cannot be determined whether these are caused by pegaspargase, the underlying disease or concomitant medications.

Blood and lymphatic system disorders
Pegaspargase can cause mild to moderate myelosuppression, and all three cell lines can be affected. There are usually no therapeutic consequences. Isolated cases of haemolytic anaemia have been observed in association with pegaspargase.

Coagulation abnormalities can occur as a result of the impairment of protein synthesis, and can be expressed as both as bleeding and as disseminated intravascular coagulation (DIC) or thrombosis; the risk of thrombosis appears to predominate with increasing time after discontinuing the therapy. However, simultaneous treatment with other myelosuppressive medications besides pegaspargase or the underlying illness itself can be for the cause of these side effects.

About half of all serious haemorrhages and thromboses affect cerebral vessels and can lead e.g. to stroke, seizures, headache or loss of consciousness.

In the ALL-BFM 95 study, an increased risk of thrombosis was described for children who presented factor V mutations, APC resistance or reduced serum levels of protein S, antithrombin III or protein C on native asparaginase. In these patients, the use of central venous catheters should be avoided if possible, as this can further increase the risk of thromboembolic complications. As part of induction therapy of ALL, central venous access should be placed only after termination of pegaspargase treatment, where possible.

The disturbances of coagulation and fibrinolysis can be apparent on blood testing e.g. as a fall in fibrinogen, factor IX, factor XI, antithrombin III, protein C and plasminogen and also as a rise in von Willebrand factor, plasminogen activator-1 inhibitor, prothrombin fragment 1 and 2 and fibrinogen splitting products (D-dimers).

Thrombocytopenia or sepsis increases the risk of bleeding.
Regular monitoring of the coagulation profile is necessary. Fibrinogen can be regarded as a parameter of the pro- and anticoagulatory system. When there is a marked drop in fibrinogen or ATIII, if any, targeted substitution appears conceivable. ATIII is given as an infusion in a dosage of 100 minus current value in % x kg body weight. Fibrinogen is given as fresh frozen plasma (FFP) in a dosage of 10 – 15 ml/kg body weight.

Immune system disorders
Specific antibodies to the foreign protein pegaspargase can be produced, which can lead uncommonly to clinical allergic reactions and which are also capable of inactivating the pegaspargase.
After administration of pegaspargase, allergic reactions are observed commonly and can manifest as local erythema, urticaria, pruritus, angioedema, pain at the injection site, pyrexia, myalgia, dyspnoea, bronchospasm, tachycardia, fall in blood pressure to the point of anaphylactic shock.

The likelihood of occurrence of allergic reactions increases with the number of doses administered, but in rare cases, allergic reactions can occur even with the first injection of pegaspargase.
Neutralising antibodies to pegaspargase can occur in some patients without clinical hypersensitivity symptoms being observed. However, these antibodies can lead to a more or less rapid inactivation and associated accelerated elimination of the pegaspargase (“silent inactivation“). Measurement of the asparaginase level is therefore recommended (for details, see Boos, J. et al.; Eur. J. Cancer 32A: 1544-50 (1996) or alternatively the product information on the medac Asparaginase Activity Test (MAAT)).
Prior intracutaneous testing does not exclude anaphylactic reactions.

If allergic symptoms occur, the medication must be stopped immediately. Depending on the severity of the symptoms, administration of antihistamines, steroids and possibly circulation-stabilising medication is indicated as countermeasure.

Endocrine disorders
Alterations in endocrine pancreatic function are observed commonly and are expressed mainly in the form of abnormal glucose metabolism. Both diabetic ketoacidosis and hyperosmolar hyperglycaemia have been described, which generally respond to administration of exogenous insulin.
Suggested cause is on the one hand, reduced insulin synthesis as a result of the inhibition of protein synthesis caused by pegaspargase and on the other hand disturbed insulin secretion or reduction in the number of insulin receptors.

Risk factors for hyperglycaemia are age > 10 years, overweight and Down's syndrome.
Regular monitoring of urine and blood sugar is therefore indicated during pegaspargase treatment.
Transient and secondary hypothyroidism and a fall in thyroxine-binding globulin after use of asparaginase have occurred in isolated cases. Hypoparathyroidism has also been reported.

Metabolism and nutrition disorders
An alteration in blood lipid levels (e.g. increase or decrease in cholesterol, increase in triglycerides, increase in the VLDL fraction and decrease in LDL, increased lipoprotein lipase activity) was observed, which in most cases is without clinical symptoms and does not require a change in treatment. The changes could also be associated with the simultaneous administration of steroids. If the levels are greatly increased (e.g. triglycerides > 2000 mg/dl) frequent measurements are advisable because of the increased risk of pancreatitis.

A rise in blood urea occurs regularly, is dose-independent and nearly always a sign of prerenal metabolic imbalance.
Increased blood levels of uric acid (hyperuricaemia) and hyperammonaemia can occur.

Nervous system disorders
Pegaspargase may cause CNS dysfunctions which commonly manifest itself in the form of agitation, depression, hallucination, confusion and somnolence (mildly impaired consciousness) and rarely in the form of seizures and severely impaired consciousness, including coma.
EEG changes may occur in the form of reduced alpha wave activity and increased theta and delta wave activity.

Hyperammonaemia should be ruled out as a possible cause.
In very rare cases, mild tremor in the fingers has been described.

In rare cases, a reversible posterior leukoencephalopathy syndrome (RPLS) may occur. This is characterised in MRI imaging by reversible (from a few days to months) lesions/oedema, primarily in the posterior region of the brain. Symptoms of RPLS essentially include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily cortical blindness or homonymous hemianopsia).

There have been reports of patients who developed an RPLS under a combined chemotherapy regimen which included pegaspargase. In these cases, it is unclear whether the RPLS was caused by pegaspargase, the concomitant medication or the underlying diseases. RPLS is treated symptomatically.

The primary measures in these cases are antihypertensive therapy and treatment of the seizures with antiepileptic drugs. Discontinuation or dose reduction of immunosuppressive medications is also recommended.

Gastrointestinal disorders
About half of the patients develop mild to moderate gastrointestinal reactions such as loss of appetite, nausea, vomiting, abdominal cramps, diarrhoea and weight loss.

Acute pancreatitis can occur commonly. There have been isolated reports of formation of pseudocysts (up to four months after the last treatment). Appropriate investigations (e.g. ultrasound) should

therefore be performed up to four months after termination of pegaspargase therapy. As the precise pathogenesis is unknown, only supportive measures can be recommended.

Haemorrhagic or necrotising pancreatitis occurs rarely. One case of pancreatitis with simultaneous acute parotitis has been described with asparaginase treatment. In single cases, haemorrhagic or necrotising pancreatitis with fatal outcome has been reported.

There are two case reports described in the literature of parotitis unrelated to pancreatitis. After L-asparaginase had been stopped, these resolved within days. In one study by Chan et al. (2002), four children developed parotitis after treatment using therapeutic protocols containing asparaginase.
Disturbances of exocrine pancreatic function can result in diarrhoea.
The blood amylase can rise during and also after the conclusion of the pegaspargase therapy. In these cases, treatment with pegaspargase should be discontinued.

Hepatobiliary disorders
Alterations of liver parameters are very common. A dose-independent rise in the alkaline phosphatase and serum transaminases, LDH and serum bilirubin is commonly observed.
A fatty liver can be observed very frequently. There have been rare reports of cholestasis, icterus, hepatic cell necrosis and hepatic failure with fatal outcome.

Impaired protein synthesis can lead to a fall in the serum proteins. There is a dose-independent fall in serum albumin in the majority of patients during the treatment. The α_2- nd β-fraction appears to be affected most often, while the α_1-fraction is unchanged. Since serum albumin is important in the binding and transport function of some medications, the serum albumin level should be monitored, especially when combination therapies are used. Oedema can occur as a result of hypoalbuminaemia.

An alteration in blood lipid levels (e.g. rise or fall in cholesterol, increase in triglycerides, rise in VLDL fraction and LDL reduction, increased lipoprotein lipase activity) has been observed, which is without clinical symptoms in most cases and does not require any change in treatment. The changes could also be associated with simultaneous administration of glucocorticoids.

If the levels are greatly raised (e.g. triglycerides > 2000 mg/100 ml), close monitoring is recommended because of the increased risk of pancreatitis.

Skin and subcutaneous tissue disorders
Allergic reactions can manifest in the skin. One case of toxic epidermal necrolysis (Lyell‘s syndrome) has been described in association with asparaginase.

Renal and urinary disorders
Acute renal failure may develop in rare cases during treatment with pegaspargase-containing regimens. In these cases, it is unclear whether the cause is pegaspargase, the concomitant medications or the underlying disease.

General disorders and administration side conditions
Increased body temperature can occur 2 - 5 hours after the injection, which usually subside spontaneously. Pain (joint pain, back pain and abdominal pain) has been commonly observed in connection with allergic reactions and pancreatitis. Life-threatening high temperature (hyperpyrexia) was observed rarely.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, Website: www.bfarm.de.

4.9 Overdose

There is no clinically relevant antidote. In the case of anaphylactic reactions, treatment must be given immediately with antihistamines, epinephrine, oxygen and intravenous steroids.

There has hitherto been experience with overdose in only three patients, all of whom received 10000 I.U./m² body surface area of Oncaspar as an intravenous infusion.

One patient developed a slight rise in liver enzymes and one developed a rash 10 minutes after the start of the infusion, which was controlled by giving an antihistamine and reducing the rate of the infusion. The third patient did not show any side effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents and immunomodulating agents
ATC-Code: L01XX24

In many patients with acute leukaemia, especially lymphatic leukaemia, the malignant cells depend on an exogenous source of L-asparagine to survive. Normal cells, in contrast, are capable of synthesising L-asparagine and are less affected by its rapid withdrawal during treatment with the enzyme L-asparaginase. This is a unique therapeutic approach on the basis of a metabolic defect in the L-asparagine synthesis of certain malignant cells.

5.2 Pharmacokinetic properties

In adults with leukaemia and lymphomas, the initial plasma concentrations of L-asparaginase after intravenous administration were proportional to the dose. The elimination half life from the plasma was between 315 and 588 hours (mean: t = 14.9 days); it appeared to be unaffected by the dosage, single and multiple doses, and was independent of age, sex, body surface area, renal and hepatic function, diagnosis and severity of the illness. The distribution volume was equal to the estimated plasma volume. Immediately after a one-hour intravenous infusion, asparagine was not found anymore and L-asparaginase was detected for at least 15 days after the first treatment with Oncaspar. The enzymewas not found in the urine.

Patients with newly diagnosed acute lymphatic leukaemia (ALL) received a single intramuscular injection of Oncaspar (2500 I.U./m² body surface area) or native asparaginase from *E. coli* (25000 I.U./m² body surface area) or from *Erwinia* (25000 I.U./m² body surface area). The plasma elimination half life of Oncaspar was statistically significantly longer (5.8 days) than the plasma elimination half lives of the native asparaginases from *E. coli* (1.4 days) and *Erwinia* (0.6 days). There were no differences in the distribution volume of the medications. The immediate cell death of leukaemic cells *in vivo*, measured by rhodamine fluorescence, was the same for all three L-asparaginase preparations.

ALL patients with several relapses were treated either with Oncaspar or with native asparaginase from *E. coli* as part of an induction therapy.

Oncaspar was given in a dose of 2500 I.U./m² body surface intramuscularly on days 1 and 15 of induction. The mean plasma half life of Oncaspar was 4.5 days in non-allergic patients (AUC 8.9 I.U./ml/day), and 2.3 days in allergic patients (AUC 5.8 I.U./ml/day).

5.3 Preclinical safety data

Acute toxicity
Only very high doses of Oncaspar given to mice intraperitoneally as a single dose (25000 - 100000 I.U./kg body weight) caused the death of 12% of the mice. Mild hepatotoxicity was observed with the

same dosages. Side effects were loss of body weight, piloerection and reduced activity. Reduced splenic weight might be a sign of potential immunosuppressant characteristics of the medication.

Toxicity with repeated doses
A four-week study in rats with a dosage of 400 I.U./kg/day i.p. resulted in a fall in feed intake and body weight compared to the control group.
A three-month study of Oncaspar in a dose of 500 I.U./kg i.v. or i.m. in mice resulted in slight hepatocellular changes.
A temporarily diminished increase in body weight and a slight temporary reduction in the total leukocyte count was observed in dogs which were treated intravenously or intramuscularly with 1200 I.U./kg weekly for 2 weeks. Increased SGPT activity also occurred in one of four dogs.

Reproductive toxicity
No studies of reproductive toxicity were conducted with Oncaspar.
Embryotoxicity studies with the active substance asparaginase have given evidence of teratogenic potential in rats, mice and rabbits. Multiple malformations and embryolethal effects were observed with doses in the therapeutic range. Investigations of the effect on fertility and peri- and postnatal development were not conducted.
There is no experience of use during pregnancy and lactation in humans.

Carcinogenicity, mutagenicity, impairment of fertility
Long-term investigations of carcinogenicity or studies of the effect on fertility in animals were not conducted with Oncaspar. Oncaspar did not prove to be mutagenic in the Ames test using *Salmonella typhimurium* strains.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogenphosphate $1H_2O$, Sodium monohydrogenphosphate $7H_2O$, Sodium chloride, Water for injections

6.2 Incompatibilities

None known so far.

6.3 Shelf life

2 years.

Do not use if the solution is cloudy or a precipitate has formed.
Do not use if stored at room temperature for more than 48 hours.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

DO NOT SHAKE!
Discard residue.

The medicinal product must not be used after the expiry date stated on the container and outer packaging.

6.5 Nature and contents of container

Oncaspar is available in packs with
1 vial (type I glass) containing 5 ml ready-to-use solution for injection [N1] (Geman labelling) or
1 vial (type I glass) containing 5 ml ready-to-use solution for injection [N1] (Geman-English labelling).

Not all pack sizes may be marketed.

1 bottle contains 3750 I.U. pegaspargase (equivalent to 750 I.U./ml), in a clear colourless phosphate-buffered sodrium chloride solution, pH 7.3.

6.6 Special precautions for disposal and other handling

This medication can cause irritation on contact. The solution must therefore be handled and administered with particular caution. Inhalation of the vapour and contact with the skin and mucoous membranes, especially the eyes, must be avoided. In case of contact, irrigate with plenty of water for at least 15 minutes.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

30204.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07.11.1994
Date of latest renewal: 27.03.2001

10. DATE OF REVISION OF THE TEXT

06.2014

11. PRESCRIPTION/LEGAL CATEGORY

Prescription only