SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Spectrila 10,000 U powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 10,000 units of asparaginase*.
After reconstitution, each ml of solution contains 2,500 units of asparaginase.

One unit (U) is defined as the quantity of enzyme required to liberate one µmol ammonia per minute at pH 7.3 and 37 °C.

*Produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spectrila is indicated as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults.

4.2 Posology and method of administration

Spectrila should be prescribed and administered by physicians and healthcare personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available.

Posology

Spectrila is usually employed as part of combination chemotherapy protocols with other antineoplastic agents (see also section 4.5).

Adults and children older than 1 year
The recommended intravenous dose of asparaginase is 5,000 units per square metre (U/m²) body surface area (BSA) given every third day.

Treatment may be monitored based on the trough serum asparaginase activity measured three days after administration of Spectrila. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered (see section 4.4).

Children 0 – 12 months old
Based on limited data, the recommended dose in infants is as follows:
- age less than 6 months: 6,700 U/m² BSA,
- age 6 – 12 months: 7,500 U/m² BSA.

Data on efficacy and safety of Spectrila in adults are limited.

Data on efficacy and safety of Spectrila in the post-induction treatment phases are very limited.

Special populations

Renal impairment
No dose adjustment is necessary in patients with renal impairment.

Hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment. However, Spectrila should not be used in patients with severe hepatic impairment (see section 4.3).

Elderly
Limited data are available for the treatment of patients older than 65 years of age.

Method of administration

Spectrila is for administration by intravenous infusion only.

The daily amount of Spectrila needed per patient can be diluted in a final volume of 50-250 ml sodium chloride 9 mg/ml (0.9%) solution for infusion. The diluted solution of asparaginase may be infused over 0.5 to 2 hours.

Asparaginase must not be administered as a bolus dose.

4.3 Contraindications

- Hypersensitivity to the active substance, any native (non-pegylated) E. coli-asparaginase preparation or to any of the excipients listed in section 6.1.
- Pancreatitis.
- Severe hepatic impairment (bilirubin > 3 times upper limit of normal [ULN]; transaminases > 10 times ULN).
- Pre-existing known coagulopathy (e.g. haemophilia).
- History of pancreatitis, serious haemorrhage or serious thrombosis with prior asparaginase therapy.

4.4 Special warnings and precautions for use

Traceability

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

General information and monitoring

The following life-threatening situations may arise during asparaginase treatment in patients of all age groups:
- acute pancreatitis,
- hepatotoxicity,
- anaphylaxis,
- coagulation disorders including symptomatic thrombosis related to the use of central venous catheters,
- hyperglycaemic conditions.

Before initiating therapy bilirubin, hepatic transaminases and coagulation parameters (e.g. partial thromboplastin time [PTT], prothrombin time [PT], antithrombin III and fibrinogen) should be determined.
After administration of any asparaginase preparation, close monitoring of bilirubin, hepatic transaminases, blood/urinary glucose, coagulation parameters (e.g. PTT, PT, antithrombin III, fibrinogen and D-dimer), amylase, lipase, triglycerides and cholesterol is recommended.

Acute pancreatitis

Treatment with asparaginase should be discontinued in patients developing acute pancreatitis. Acute pancreatitis has developed in less than 10% of patients. In rare cases, haemorrhagic or necrotising pancreatitis occurs. There have been isolated reports of fatal outcomes. Clinical symptoms include abdominal pain, nausea, vomiting and anorexia. Serum amylase and lipase are usually elevated, although in some patients they can be normal due to impaired protein synthesis. Patients with severe hypertriglyceridaemia are at increased risk of developing acute pancreatitis.
These patients should no longer be treated with any asparaginase preparation (see also sections 4.3 and 4.8).

Hepatotoxicity

In rare cases severe liver impairment has been described, including cholestasis, icterus, hepatic necrosis and hepatic failure with fatal outcome (see sections 4.8 and 4.5). Liver parameters should be monitored closely before and during treatment with asparaginase.
Treatment with asparaginase should be interrupted if patients develop severe hepatic impairment (bilirubin > 3 times the upper limit of normal [ULN]; transaminases > 10 times ULN), severe hypertriglyceridaemia, hyperglycaemia or coagulation disorder (e.g. sinus vein thrombosis, severe bleeding).

Allergy and anaphylaxis

Because of the risk of severe anaphylactic reactions asparaginase should not be administered as a bolus intravenous injection.
A previous intracutaneous test or a small intravenous test dose can be used. Both procedures, however, do not allow for predicting accurately which patients will experience an allergic reaction.
If allergic symptoms occur, administration of asparaginase must be discontinued immediately and appropriate treatment given, which may include antihistamines and corticosteroids.

Coagulation disorders

Due to the inhibition of protein synthesis (decreased synthesis of factors II, V, VII, VIII, and IX, proteins C and S, antithrombin III [AT III]) caused by asparaginase, coagulation disorders can occur which can manifest either as thrombosis, disseminated intravascular coagulation (DIC), or bleeding. The risk of thrombosis seems to be higher than the risk of bleeding. Symptomatic thromboses related to the use of central venous catheters have been described, too.
Approximately half of the thrombotic events is localised in cerebral vessels. Sinus vein thrombosis can occur. Ischaemic strokes are rare.
Acquired or genetically decreased physiologic coagulation inhibitors (protein C, protein S, antithrombin) are also described in relation to vascular complications.
Frequent evaluation of coagulation parameters is important before and during asparaginase treatment. Expert advice should be sought in cases where AT III is decreased.

Hyperglycaemic conditions

Asparaginase may induce hyperglycaemia as a consequence of decreased insulin production. Additionally it may decrease insulin secretion from pancreatic β-cells and impair insulin receptor function. The syndrome is generally self-limiting. However, in rare cases it can result in diabetic ketoacidosis. Concomitant treatment with corticosteroids contributes to this effect. Serum and urine glucose levels should be regularly monitored and managed as clinically indicated.

Antineoplastic agents

Asparaginase-induced tumour cell destruction may release large amounts of uric acid, resulting in hyperuricaemia. Co-administration of other antineoplastic medicinal products contributes to this effect. Aggressive alkalinisation of the urine and use of allopurinol can prevent urate nephropathy.

Glucocorticoids

A higher risk of thrombosis during induction therapy with asparaginase and prednisone was seen in children with a genetic prothrombotic risk factor (factor V G1691A-mutations, prothrombin G20210A-variation, methylenetetrahydrofolate reductase [MTHFR] T677T-genotype, increased lipoprotein A, hyperhomocysteinaemia).

Contraceptives

Women of childbearing potential should use effective contraceptive measures while being treated with asparaginase and for 7 months following completion of treatment. Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation (see section 4.6).

Philadelphia chromosome-positive patients

Efficacy and safety of Spectrila have not been established in Philadelphia chromosome-positive patients.

Recommended control examinations for patients of all age groups

Asparaginase activity
Measurement of the asparaginase activity level in serum or plasma may be undertaken in order to rule out accelerated reduction of asparaginase activity. Preferably, levels should be measured three days after the last asparaginase administration, i.e. usually directly before the next dose of asparaginase is given. Low asparaginase activity levels are often accompanied by the appearance of anti-asparaginase antibodies. In such cases, a switch to a different asparaginase preparation should be considered. Expert advice should first be sought.

Hypoalbuminaemia
As a result of impaired protein synthesis, the serum protein level (especially albumin) decreases very commonly in patients treated with asparaginase. Since serum protein is important for the binding and transport function of some active substances, the serum protein level should be monitored regularly.

Hyperammonaemia
Plasma ammonia levels should be determined in all patients with unexplained neurologic symptoms or severe and prolonged vomiting. In case of hyperammonaemia with severe clinical symptoms, therapeutic and pharmacological measures that rapidly reduce plasma ammonia levels (e.g. protein restriction and haemodialysis), reverse catabolic states and increase removal of nitrogen wastes should be initiated and expert advice sought.

Reversible posterior leukoencephalopathy syndrome
Reversible posterior leukoencephalopathy syndrome (RPLS) may occur rarely during treatment with any asparaginase (see section 4.8). This syndrome is characterised in magnetic resonance imaging (MRI) 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). It is unclear whether the RPLS is caused by asparaginase, concomitant treatment or the underlying diseases.
RPLS is treated symptomatically, including measures to treat any seizures. Discontinuation or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary. Expert advice should be sought.

4.5 Interaction with other medicinal products and other forms of interaction

General

Asparaginase may increase the toxicity of other medicinal products through its effect on liver function, e.g. increased hepatotoxicity with potentially hepatotoxic medicinal products, increased toxicity of medicinal products metabolised by the liver or bound to plasma proteins and altered pharmacokinetics and pharmacodynamics of medicinal product bound to plasma proteins. Therefore, caution should be exercised in patients receiving other medicinal products metabolised by the liver.
Hepatic parameters should be monitored when potentially hepatotoxic medicinal products are given concomitantly with asparaginase (see sections 4.4 and 4.8).

Myelosuppressive agents

During treatment with asparaginase-containing regimens, myelosuppression, potentially affecting all three myeloid cell lineages (erythrocytes, leukocytes, thrombocytes), and infections can occur. Concomitant treatment with myelosuppressive medicinal products and those known to cause infections are major contributing factors and patients should be carefully monitored for signs and symptoms of myelosuppression and infection (see section 4.8).

Vincristine

The toxicity of vincristine may be additive with that of asparaginase if both agents are administered concomitantly. Therefore, vincristine should be given 3 to 24 hours before administration of asparaginase in order to minimise toxicity.

Glucocorticoids and/or anticoagulants

Concomitant use of glucocorticoids and/ or anticoagulants with asparaginase may increase the risk of a change in coagulation parameters (see section 4.4).
This can promote tendency to bleeding (anticoagulants) or thrombosis (glucocorticoids). Caution is therefore needed when anticoagulants (e.g. coumarin, heparin, dipyridamole, acetylsalicylic acid or nonsteroidal anti-inflammatory medicinal products) or glucocorticoids are given at the same time.

Methotrexate (MTX)

Inhibition of protein synthesis secondary to the asparaginase-induced depletion of asparagine has been shown to attenuate the cytotoxic effect of MTX which requires cell replication for its antineoplastic activity. This antagonism is observed if asparaginase is administered prior to or concurrently with methotrexate. Conversely, the antitumour effects of methotrexate are enhanced when asparaginase is administered 24 hours following methotrexate treatment. This regimen has been shown to reduce the gastrointestinal and haematological effects of methotrexate.

Cytarabine

Laboratory *in vitro* and *in vivo* data indicate that the efficacy of high-dose cytarabine is reduced by prior administration of asparaginase. However, when asparaginase was given after cytarabine a synergistic effect was observed. This effect was most prominent with a treatment interval of about 120 hours.

Vaccination

Concomitant vaccination with live vaccines increases the risk of serious infection. Immunisation with live vaccines should therefore take place at the earliest 3 months after completion of the course of antileukaemic treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential have to use effective contraception and avoid becoming pregnant while being treated with asparaginase-containing chemotherapy and for 7 months following completion of treatment. Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral contraceptives should be used in women of childbearing potential (see section 4.4).
Men should use effective contraceptive measures and be advised to not father a child while receiving asparaginase and for 4 months following completion of treatment.

Pregnancy

There are no data on the use of asparaginase in pregnant women. No reproduction studies in animals with asparaginase were performed but studies with asparaginase preparations in mice, rats, chicken and rabbits have shown embryotoxic and teratogenic effects (see section 5.3). Based on results from animal studies and its mechanism of action, Spectrila should not be used during pregnancy unless the clinical condition of the woman requires treatment with asparaginase.

Breast-feeding

It is unknown whether asparaginase is excreted into human breast milk. Because potential serious adverse reactions may occur in breast-feeding infants, Spectrila should be discontinued during breast-feeding.

Fertility

No human data on the effect of asparaginase on fertility are available.

4.7 Effects on ability to drive and use machines

Spectrila has moderate influence on the ability to drive and use machines, especially through its potential effects on the nervous and gastrointestinal systems (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The primary toxicity of asparaginase results from immunologic reactions caused by exposure to the bacterial protein. Hypersensitivity reactions range from transient flushing or rash and urticaria to bronchospasm, angioedema and anaphylaxis.

In addition, treatment with asparaginase can result in disturbances in organ systems which exhibit a high level of protein synthesis. Decreased protein synthesis can predominantly lead to liver impairment, acute pancreatitis, decreased insulin production with hyperglycaemia, decreased production of clotting factors (especially fibrinogen and antithrombin III) leading to coagulation disorders (thrombosis, bleeding), and decreased production of lipoproteins resulting in hypertriglyceridaemia.

Most serious adverse reactions of Spectrila include severe hypersensitivity reactions such as anaphylactic shock (rare), thromboembolic events (common), acute pancreatitis (common), and severe hepatotoxicity, e.g. jaundice, hepatic necrosis, hepatic failure (rare).

Most frequently (very common) observed adverse reactions of Spectrila include hypersensitivity reactions, hyperglycaemia, hypoalbuminaemia, nausea, vomiting, diarrhoea, abdominal pain, oedema, fatigue, and change in laboratory parameters (e.g. transaminases, bilirubin, blood lipids, coagulation parameters).
Since Spectrila is usually used in combination therapy with other antineoplastic agents, the demarcation from undesirable effects of other medicinal products is often difficult.

Tabulated list of adverse reactions

The following adverse reactions, listed in table 1, have been accumulated from clinical trials with Spectrila in 125 children with newly diagnosed acute lymphoblastic leukaemia as well as post-marketing experience with other *E. coli*-derived asparaginase preparations in children and adults. Adverse reactions are ranked under headings of frequency, the most frequent first. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Frequencies in this table are defined using the following convention:
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).

Table 1

System organ class	**Frequency and adverse reaction**
Infections and infestations	**Not known** Infections
Blood and lymphatic system disorders	**Common** Disseminated intravascular coagulation (DIC), anaemia, leukopenia, thrombocytopenia
Immune system disorders	**Very common** Hypersensitivity including flushing, rash, hypotension, oedema/angioedema, urticaria, dyspnoea **Common** Hypersensitivity including bronchospasm

	Rare Anaphylactic shock
Endocrine disorders	**Very rare** Secondary hypothyroidism, hypoparathyroidism
Metabolism and nutrition disorders	**Very common** Hyperglycaemia, hypoalbuminaemia **Common** Hypoglycaemia, decreased appetite, weight loss **Uncommon** Hyperuricaemia, hyperammonaemia **Rare** Diabetic ketoacidosis
Psychiatric disorders	**Common** Depression, hallucination, confusion
Nervous system disorders	**Common** Neurological signs and symptoms including agitation, dizziness and somnolence **Uncommon** Headaches **Rare** Ischaemic stroke, reversible posterior leukoencephalopathy syndrome (RPLS), convulsion, disturbances in consciousness including coma **Very rare** Tremor
Vascular disorders	**Common** Thrombosis especially cavernous sinus thrombosis or deep vein thrombosis, haemorrhage
Gastrointestinal disorders	**Very common** Diarrhoea, nausea, vomiting, abdominal pain **Common** Acute pancreatitis **Rare** Haemorrhagic pancreatitis, necrotising pancreatitis, parotitis **Very rare** Pancreatitis with fatal outcome, pancreatic pseudocyst
Hepatobiliary disorders	**Rare** Hepatic failure with potentially fatal outcome, hepatic necrosis, cholestasis, jaundice **Not known** Hepatic steatosis
General disorders and administration site conditions	**Very common** Oedema, fatigue **Common** Pain (back pain, joint pain)

Investigations	**Very common** Increase in transaminases, blood bilirubin, blood alkaline phosphatase, blood cholesterol, blood triglyceride, very low density lipoprotein (VLDL), lipoprotein lipase activity, blood urea, ammonia, blood lactate dehydrogenase (LDH), Decrease in antithrombin III, blood fibrinogen, blood cholesterol, low density lipoprotein (LDL), total protein **Common** Increase in amylase, lipase, abnormal electroencephalogram (EEG) (reduced alpha wave activity, increased theta and delta wave activity)

Description of selected adverse reactions

Immune system disorders
Spectrila can induce antibodies of different immunoglobulin classes (IgG, IgM, IgE). These antibodies may induce clinical allergic reactions, inactivate the enzymatic activity or accelerate the elimination of asparaginase.
Allergic reactions can manifest as flushing, rash, pain (joint pain, back pain and abdominal pain), hypotension, oedema/angioedema, urticaria, dyspnoea, bronchospasm up to anaphylactic shock.
The probability of the occurrence of allergic reactions increases with the number of administered doses; however, in very rare cases reactions can occur at the first dose of asparaginase. Most hypersensitivity reactions to asparaginase are observed during subsequent treatment phases (re-induction treatment, delayed intensification).

In a clinical trial in children with newly diagnosed ALL (study MC-ASP.5/ALL), the following frequencies of allergic events were observed (table 2).

Table 2: Frequency of patients with allergic reactions (MC-ASP.5/ALL; Safety analysis set)

Treatment group	**Spectrila**	**Reference asparaginase**
Number of patients	97	101
Allergic reactions within 12 hours after asparaginase infusion during induction treatment	2 (2.1%)	5 (5.0%)
Any allergic event* within 24 hours after asparaginase infusion during induction treatment	16 (16%)	24 (24%)
**Including all allergic reactions within 12 hours after asparaginase infusion and all adverse events with CTCAE terms syncope (fainting), hypotension, rash, flushing, pruritus, dyspnoea, injection site reaction or airway obstruction within 24 hours after asparaginase infusion*		

No allergic reactions were observed in any of the 12 infants < 1 year of age during treatment with Spectrila (study MC-ASP.6/INF).
In case of occurrence of allergic symptoms, administration of Spectrila should be discontinued immediately (see section 4.4).

Immunogenicity
In the study in children/adolescents aged 1–18 years with *de novo* ALL (study MC-ASP.5/ALL), by day 33 of induction treatment 10 patients in the Spectrila group (10.3%) and 9 in the reference group (8.9%) were measured positive for anti-asparaginase antibodies at least at one time point.

A comparable proportion of patients in both groups developed anti-asparaginase antibodies before the start of the post-induction treatment phase (Spectrila 54.6% vs. reference *E. coli*-asparaginase 52.5%). The majority of anti-asparaginase antibodies developed in the time gap between the last asparaginase infusion on day 33 and start of post-induction treatment at day 79.
No anti-asparaginase antibodies were detected in any of the 12 infants < 1 year of age during treatment with Spectrila (study MC-ASP.6/INF).

Hypothyroidism
There have been reports of transitory secondary hypothyroidism probably caused by a decrease in the serum thyroxin-binding globulin due to asparaginase-induced protein synthesis inhibition.

Hypoalbuminaemia
As a result of impaired protein synthesis, the serum protein level (especially albumin) decreases very commonly in patients treated with asparaginase (see section 4.4). As a consequence of hypoalbuminaemia oedema can occur.

Dyslipidemia
Mild to moderate changes in blood lipid values (e.g. increased or decreased cholesterol, increased triglyceride, increased VLDL fraction and decreased LDL, increased lipoprotein lipase activity) are very commonly observed in patients treated with asparaginase, which in most cases present without clinical symptoms. Concomitant administration of glucocorticoids may be a contributing factor. However, in rare cases severe hypertriglyceridaemia (triglycerides > 1,000 mg/dl) has been reported which increases the risk of development of acute pancreatitis. Asparaginase-associated hyperlipidaemia should be treated depending on its severity and on clinical symptoms.

Hyperammonaemia
Hyperammonaemia has been reported uncommonly in patients treated with asparaginase-containing therapy protocols, especially if patients suffer additionally from hepatic impairment. In very rare cases, severe hyperammonaemia has been reported which may induce neurologic disorders such as seizures and coma.

Hyperglycaemia and hypoglycaemia
Changes in endocrine pancreatic function are observed very commonly during treatment with asparaginase and manifest predominantly as hyperglycaemia. These events are usually transient.
In rare cases, diabetic ketoacidosis has been reported.
Hypoglycaemia mostly without clinical symptoms has been commonly observed in patients treated with asparaginase. The mechanism leading to this reaction is unknown.

Nervous system disorders
Adverse central nervous system reactions observed in patients treated with asparaginase-containing therapy protocols include changes in EEG, seizures, dizziness, somnolence, coma and headache. The causes of these nervous system disorders are unclear. Hyperammonaemia and sinus vein thrombosis may need to be excluded.
In rare cases, RPLS has been observed during therapy with asparaginase-containing regimens.

Gastrointestinal disorders
Nausea/vomiting are very commonly observed in patients treated with asparaginase-containing treatment regimens but are usually mild. Anorexia, loss of appetite, abdominal cramps, diarrhoea and weight loss have also been reported.
Acute pancreatitis has developed in less than 10% of patients. In rare cases, haemorrhagic or necrotising pancreatitis occurs. There have been isolated reports of fatal outcomes. A few cases of asparaginase-induced parotitis have been reported in the literature.

<u>Paediatric population</u>

Data on safety of Spectrila in infants < 1 year of age is limited.

Adults and other special populations

Qualitatively, the same asparaginase-induced adverse drug reactions are observed in adults and children; however, some of these undesirable effects (e.g. thromboembolic events) are known to occur with a higher frequency in adult patients compared to the paediatric population.

Because of a higher frequency of comorbidities such as liver and/or renal impairment, patients > 55 years of age usually tolerate asparaginase treatment worse than paediatric patients.

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 (see details below).

United Kingdom
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

No case of asparaginase overdose with clinical symptoms has been reported. There is no specific antidote. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX02

Mechanism of action

Asparaginase hydrolyses asparagine to aspartic acid and ammonia. In contrast to normal cells, lymphoblastic tumour cells have a very limited capacity for synthesising asparagine because of a significantly reduced expression of asparagine synthetase. Therefore, they require asparagine which diffuses from the extracellular environment. As a result of asparaginase-induced asparagine depletion in serum, protein synthesis in lymphoblastic tumour cells is disturbed while sparing most normal cells. Asparaginase may also be toxic to normal cells that divide rapidly and are dependent to some degree on exogenous asparagine supply.
Due to the asparagine concentration gradient between the extra- and intravascular space, asparagine levels are subsequently also reduced in the extravascular spaces, e.g. the cerebrospinal fluid.

Pharmacodynamic effects

In a clinical trial in children with *de novo* ALL (study MC-ASP.4/ALL) it was shown that immediately after the end of infusion of asparaginase mean asparagine concentrations in serum dropped from the pre-dose concentrations of about 40 µM to below the lower limit of quantification of the bioanalytical method (< 0.5 µM). The mean asparagine concentrations in serum remained below 0.5 µM from immediately after the end of first infusion of asparaginase until at least three days after the last infusion. Thereafter, asparagine serum levels increased again and returned to normal values within 1–3 weeks.

In addition to asparagine, asparaginase is also able to cleave the amino acid glutamine to glutamic acid and ammonia, however with much less efficiency. Clinical trials with asparaginase have shown that glutamine levels are only moderately affected with a very high interindividual variability. Immediately after the end of infusion of asparaginase, serum levels of glutamine declined by a maximum of 50% from pre-dose levels of about 400 µM but rapidly returned to normal values within a few hours.

Clinical efficacy and safety

Study in children/adolescents aged 1–18 years with de novo ALL
Efficacy and safety of Spectrila was compared to a native *E. coli*-asparaginase (reference medicinal product) in a randomised double-blinded clinical trial (study MC-ASP.5/ALL; based on ALL treatment protocol DCOG ALL10) in 199 children/adolescents aged 1–18 years with *de novo* ALL. Patients received 5,000 U/m² asparaginase (Spectrila versus a reference *E.coli*- asparaginase) at days 12, 15, 18, 21, 24, 27, 30, and 33 of induction treatment. After induction treatment, patients continued treatment with chemotherapy regimens which included further treatment with asparaginases.
The primary endpoint was the rate of patients with complete asparagine depletion in serum (defined as asparagine serum levels below the lower limit of quantification (< 0.5 µM) at all time points measured from day 12 up to day 33) during induction treatment. The objective of the study was to demonstrate the non-inferiority of Spectrila to the reference *E. coli*-asparaginase with regard to the primary endpoint.

Results of this study are summarised in table 3:

Table 3: Efficacy results (MC-ASP.5/ALL; Full analysis set)

Treatment group	**Spectrila**	**Reference asparaginase**
Number of patients	98	101
Complete asparagine depletion in serum		
Yes	93 (94.9%)	95 (94.1%)
No	2 (2.0%)	2 (2.0%)
Not evaluable	3 (3.1%)	4 (4.0%)
Difference (95% CI[a]); P value[b]	0.8% (-6.25%; 8.04%); P = 0.0028	
Complete asparagine depletion in CSF		
Yes[c]	82 (83.7%)	88 (87.1%)
No	1 (1.0%)	6 (5.9%)
Not evaluable	15 (15.3%)	7 (6.9%)
Difference (95% CI[a])	-3.5% (-13.67%; 6.58%)	
Complete remission rate at end of induction treatment		
Yes	90 (91.8%)	97 (96.0%)
No	2 (2.0%)	2 (2.0%)
Not evaluable / not known	6 (6.1%)	2 (2.0%)
Difference (95% CI[a])	-4.2% (-11.90%; 2.81%)	
MRD status at end of induction treatment		
MRD negative	29 (29.6%)	32 (31.7%)
MRD positive	63 (64.3%)	60 (59.4%)
Not evaluable / not known	6 (6.1%)	9 (8.9%)
Difference (95% CI[a])	-2.1% (-14.97%; 10.84%)	

Treatment group	Spectrila	Reference asparaginase
CI = confidence interval; CSF = cerebrospinal fluid; MRD = minimal residual disease *[a] Unconditional exact confidence interval based on Chan and Zhang* *[b] Unconditional exact test of non-inferiority for binomial differences based on restricted maximum likelihood estimates* *[c] Patients were considered as responders if asparagine values in CSF on protocol day 33 were below the lower limit of quantification.*		

During induction treatment, asparaginase-typical adverse drug reactions like elevated liver enzymes/bilirubin (≥ CTCAE Grade III: 44.3% *vs.* 39.6%), haemorrhage or thromboembolism (≥ CTCAE Grade II: 2.1% *vs.* 4.0%), and neurotoxicity (≥ CTCAE Grade III: 4.1% *vs.* 5.9%) were observed in comparable frequencies in both groups (Spectrila *versus* reference).

Study in infants with de novo ALL
In an uncontrolled clinical trial (study MC-ASP.6/INF), 12 infants (median age [range] at time of first infusion: 6 months [0.5–12.2 months]) with *de novo* ALL were treated with Spectrila within the INTERFANT-06 protocol. Patients received asparaginase at a dose of 10,000 U/m², adjusted to the current age of the patient at the time of administration (< 6 months: 6,700 U/m²; 6–12 months: 7,500 U/m²; > 12 months: 10,000 U/m²) on days 15, 18, 22, 25, 29, and 33 of induction treatment. Asparagine depletion in serum was complete in 11 of 12 patients (92%). All 12 patients (100%) were in CR after induction treatment.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of Spectrila were determined in 7 adult patients after intravenous infusion of 5,000 U/m².

Absorption

Asparaginase is not absorbed by the gastrointestinal tract, thus Spectrila must be given intravenously.

Distribution

Asparaginase is distributed mainly within the intravascular space. The mean (Standard Deviation, SD) of the volume of distribution at steady state (V_{dss}) was 2.47 l (0.45 l).
Asparaginase does not seem to penetrate the blood-brain barrier in measurable amounts.
Median (range) maximum serum concentrations of asparaginase activity were 2,324 U/l (1,625-4,819 U/l). Peak (C_{max}) of asparaginase activity in serum was reached with a delay of approximately 2 hours after the end of the infusion.
After repeated administration of asparaginase at a dose of 5,000 U/m² every third day, trough asparaginase activity levels in serum ranged from 108 to 510 U/l.

Biotransformation

The metabolism of asparaginase is not known but thought to occur via degradation within the reticulo-histiocytic system and by serum proteases.

Elimination

The mean ± SD terminal half-life (elimination half-life) of asparaginase activity in serum was 25.8 ± 9.9 h, with a range between 14.2 and 44.2 h.

Pharmacokinetic/pharmacodynamic relationships

In clinical trials with asparaginase, trough asparaginase serum activity levels greater than 100 U/l were achieved in the majority of patients which nearly always correlated with a complete depletion of asparagine in serum and cerebrospinal fluid (CSF). Even those few patients with trough asparaginase serum activity levels of 10–100 U/l usually experienced complete asparagine depletion in serum and CSF.

Paediatric population
Pharmacokinetic parameters after administration of 5,000 U/m² of Spectrila were determined in 14 children/adolescents (age 2–14 years) with *de novo* ALL (study MC-ASP.4/ALL). Results are shown in table 4.

Table 4: Pharmacokinetic parameters of Spectrila in 14 children/adolescents

Parameter	**Median (range)**
Area under the curve (AUC_{0-72h})	60,165 (38,627–80,764) U*h/l
Maximum serum concentration (C_{max})	3,527 (2,231–4,526) U/l
Time to C_{max}	0 (0–2) h
Half-life	17.33 (12.54–22.91) h
Total clearance	0.053 (0.043–0.178) l/h
Volume of distribution	0.948 (0.691–2.770) l

Median trough serum asparaginase activities were measured in 81 children/adolescents with *de novo* ALL three days after infusion of asparaginase (just before the next dose had to be given) during induction treatment and ranged from 168 to 184 U/l (study MC-ASP.5/ALL).

Trough serum activity levels were measured in 12 infants (age from birth to 1 year) with *de novo* ALL (study MC-ASP.6/INF). Median (range) serum trough asparaginase activities on days 18, 25, and 33 were 209 (42–330) U/l, 130 (6–424) U/l, and 32 (1–129) U/l, respectively. The lower median activity level on day 33 compared to the former two measurements was in part due to the fact that this last serum sample was taken 4 days after the last infusion of asparaginase instead of three days on the other occasions.

5.3 Preclinical safety data

Non-clinical repeat-dose toxicity and safety pharmacology studies in rats revealed no special hazard for humans, except a slight but significant saluretic effect at doses below the recommended dose for ALL patients. Additionally, the urinary pH value and the relative weight of kidneys were increased at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Evidence from published data with asparaginase renders the mutagenic, clastogenic and carcinogenic potential of asparaginase negligible.

Asparaginase caused an increase in the incidence of malformations (including those of the central nervous system, heart and skeletal system) and foetal death at doses that are similar to or in excess of those proposed clinically (on a U/m² basis) in a number of species including the mouse, rat and/or rabbit.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
4 years

Reconstituted and diluted solution
Chemical and physical in-use stability has been demonstrated for 2 days at 2 °C–8 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C–8 °C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C–8 °C).
Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Colourless 20 ml glass vial (Type I glass) closed with butylrubber stopper, aluminium seal and plastic flip-off cap, containing 10,000 units of asparaginase.

Each pack contains either 1 or 5 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

To dissolve the powder, 3.7 ml of water for injections are carefully squirted against the inner wall of the vial with an injection syringe (do not squirt directly on or into the powder). Dissolution of the contents is achieved by slow turning (avoid froth formation due to shaking). The reconstituted solution may exhibit a slight opalescence.

The calculated quantity of asparaginase is dissolved further in 50 to 250 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion.

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

7. MARKETING AUTHORISATION HOLDER

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